CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

ANDA 076477Orig1s000

Name: Atorvastatin Calcium Tablets
10 mg, 20 mg, 40 mg, and 80 mg

Sponsor: Ranbaxy, Inc.

Approval Date: November 30, 2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076477

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 076477

Ranbaxy Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Scott D. Tomsky
Senior Manager, Regulatory Affairs
600 College Road East
Princeton, NJ 08540

Dear Sir:

This is in reference to your abbreviated new drug application (ANDA) dated August 19, 2002, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act), for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base).

Reference is also made to your amendments dated December 4, and December 9, 2009; November 12, and November 16, 2010; and June 2, June 3, June 7, July 18, July 25, July 27, August 26, September 1, September 19, and October 5, 2011.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is approved, effective on the date of this letter. The Division of Bioequivalence has determined your Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base), to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Lipitor Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base), respectively, of Pfizer, Inc. (Pfizer). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your ANDA.

The RLD upon which you have based your ANDA, Pfizer's Lipitor Tablets, is subject to periods of patent protection. The following unexpired patents and their expiration dates (with pediatric exclusivity added) are currently listed in the

agency's publication titled Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") for this drug product:

U.S. Patent Number	Expiration Date
5,686,104 (the '104 patent)	May 11, 2015
5,969,156 (the '156 patent)	January 8, 2017
6,126,971 (the '971 patent)	July 19, 2013

With respect to all three patents, your ANDA contains paragraph IV certifications under section 505(j)(2)(A)(vii)(IV) of the Act stating that each patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base), under this ANDA. You have notified the agency that Ranbaxy Laboratories Limited (Ranbaxy) complied with the requirements of section 505(j)(2)(B) of the Act, and that no action for infringement of any of these patents was brought against Ranbaxy.

With regard to 180-day generic drug exclusivity, we note that Ranbaxy was the first ANDA applicant to submit a substantially complete ANDA for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base), with paragraph IV certifications to the '104, '156, and '971 patents. Therefore, with this approval, Ranbaxy is eligible for 180 days of generic drug exclusivity for Atorvastatin Calcium Tablets, 10 mg (base), 20 mg (base), 40 mg (base), and 80 mg (base). This exclusivity, which is provided for under section 505(j)(5)(B)(iv) of the Act, will begin to run from the earlier of the commercial marketing or court decision dates identified in section 505(j)(5)(B)(iv).[1] Please submit correspondence to this ANDA informing the agency of the date the exclusivity begins to run.

Under section 506A of the Act, certain changes in the conditions described in this ANDA require an approved supplemental application before the change may be made.

[1] Because your ANDA was filed before the date of enactment of the Medicare Prescription Drug, Improvement and Modernization Act (MMA) (Public Law 108-173) on December 8, 2003, this reference to the 180-day exclusivity provision is to the section of the Act as in effect prior to December 8, 2003. See MMA § 1102(b)(1).

Please note that if FDA requires a Risk Evaluation & Mitigation Strategy (REMS) for a listed drug, an ANDA citing that listed drug also will be required to have a REMS. See section 505-1(i) of the Act.

Postmarketing reporting requirements for this ANDA are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

Promotional materials may be submitted to FDA for comment prior to publication or dissemination. Please note that these submissions are voluntary. If you desire comments on proposed launch promotional materials with respect to compliance with applicable regulatory requirements, we recommend you submit, in draft or mock-up form, two copies of both the promotional materials and package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion
5901-B Ammendale Road
Beltsville, MD 20705

We call your attention to 21 CFR 314.81(b)(3) which requires that all promotional materials be submitted to the Office of Prescription Drug Promotion with a completed Form FDA 2253 at the time of their initial use.

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/U_CM072392.pdf.

The SPL will be accessible via publicly available labeling repositories.

Sincerely yours,

Keith Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

11/30/2011

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT L WEST

11/30/2011

Deputy Director, Office of Generic Drugs
for Keith Webber, Ph.D.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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LABELING

ATORVASTATIN
CALCIUM TABLETS

0000000

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use atorvastatin calcium tablets safely and effectively. See full prescribing information for atorvastatin calcium tablets.

Atorvastatin calcium tablets for oral administration

Initial U.S. Approval: 1996

INDICATIONS AND USAGE

Atorvastatin calcium tablets are an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct herapy to diet to:

- Reduce he risk of MI, st oke, revascularization p ocedures, and angina in patients wi hout CHD, but wi h multiple risk factors (1.1).
- Reduce he risk of MI and st oke in patients wi h type 2 diabetes wi hout CHD, but wi h multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal st oke, revascularization p ocedures, hospitalization for CHF, and angina in patients wi h CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients wi h primary hyperlipidemia (hete ozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipop oteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholeste olemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, wi h hete ozygous familial hypercholeste olemia after failing an adequate trial of diet herapy (1.2).

Limitations of Use

Atorvastatin calcium tablets have not been studied in *Fredrickson* Types I and V dyslipidemias.

DOSAGE AND ADMINISTRATION

Dose range: 10 to 80 mg once daily (2.1).

Recommended start dose: 10 or 20 mg once daily (2.1).

Patients requiring large LDL-C reduction (> 45%) may start at 40 mg once daily (2.1).

Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

DOSAGE FORMS AND STRENGTHS

10, 20, 40, and 80 mg tablets (3).

CONTRAINDICATIONS

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).

Women who are pregnant or may become pregnant (4.3).

Nursing mothers (4.4).

Hypersensitivity to any component of his medication (4.2).

WARNINGS AND PRECAUTIONS

Skeletal muscle effects (e.g., myopathy and habdomyolysis): Risks increase when higher doses are used concomitantly wi h cyclosporine, fibrates, and st ong CYP3A4 inhibitors (e.g., clari h omycin, itraconazole, HIV p otease inhibitors). Predisposing factors include advanced age (> 65), uncont olled hypo hy oidism, and renal impairment. Rare cases of habdomyolysis wi h acute renal failure secondary to myoglobinuria have been reported. In cases of myopa hy or habdomyolysis, therapy should be temporarily withheld or discontinued (5.1).

Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminases can occur. Monitor liver enzymes before and during treatment (5.2).

A higher incidence of hemor hagic st oke was seen in patients without CHD but wi h st oke or TIA wi hin he previous 6 mon hs in he atorvastatin calcium 80 mg g oup vs. placebo (5.5).

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin calcium in placebo-cont olled trials regardless of causality were: nasopharyngitis, arthralgia, diar hea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Ranbaxy Pharmaceuticals Inc. at (1-888-Ranbaxy(726-2299)) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Drug Interactions Associated wi h Increased Risk of Myopa hy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine	Do not exceed 10 mg atorvastatin daily
Clari h omycin, itraconazole, HIV p otease inhibitors (ritonavir plus saquinavir or lopinavir plus ritonavir)	Caution when exceeding doses > 20 mg atorvastatin daily. The lowest dose necessary should be used.

- Digoxin: Patients should be monitored app opriately (7.5).
- Oral Contraceptives: Values for nore hind one and e hinyl estradiol may be increased (7.6).
- Rifampin should be simultaneously co-administered with atorvastatin calcium (7.4).

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Plasma concentrations markedly increased in patients wi h ch onic alcoholic liver disease (12.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: [05/2011]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted f om he full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy wi h lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for a he oscle otic vascular disease due to hypercholeste olemia. Drug herapy is recommended as an adjunct to diet when he response to a diet restricted in saturated fat and choleste ol and o her nonpharmacologic measures alone has been inadequate. In patients wi h CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously wi h diet.

1.1 Prevention of Cardiovascular Disease

In adult patients wi hout clinically evident co onary heart disease, but wi h multiple risk factors for co onary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early co onary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce he risk of myocardial infarction
- Reduce he risk of st oke
- Reduce he risk for revascularization p ocedures and angina

In patients with type 2 diabetes, and wi hout clinically evident co onary heart disease, but wi h multiple risk factors for co onary heart disease such as retinopa hy, albuminuria, smoking, or hypertension, atorvastatin calcium tablets are indicated to:

- Reduce he risk of myocardial infarction
- Reduce he risk of st oke

In patients wi h clinically evident co onary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce he risk of non-fatal myocardial infarction
- Reduce he risk of fatal and non-fatal st oke
- Reduce he risk for revascularization p ocedures
- Reduce he risk of hospitalization for CHF
- Reduce he risk of angina

1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients wi h primary hypercholeste olemia (hete ozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb);
- As an adjunct to diet for he treatment of patients wi h elevated serum TG levels *(Fredrickson* Type IV);
- For he treatment of patients wi h primary dysbetalipop oteinemia *(Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients wi h homozygous familial hypercholeste olemia as an adjunct to o her lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with hete ozygous familial hypercholeste olemia if after an adequate trial of diet herapy the following findings are present:

  a. LDL-C remains ≥ 190 mg/dL or

  b. LDL-C remains ≥ 160 mg/dL and:

  - here is a positive family history of premature cardiovascular disease or
  - two or more other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

Atorvastatin calcium tablets have not been studied in conditions where the major lipop otein abnormality is elevation of chylomic ons *(Fredrickson* Types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

The recommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of he day, wi h or without food. The starting dose and maintenance doses of atorvastatin calcium tablets should be individualized according to patient characteristics such as goal of herapy and response (see current *NCEP Guidelines*). After initiation and/or upon titration of atorvastatin calcium tablets, lipid levels should be analyzed wi hin 2 to 4 weeks and dosage adjusted accordingly.

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age)

The recommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in his patient population). Doses should be individualized according to the recommended goal of herapy [see current *NCEP Pediatric Panel Guidelines*, *Clinical Pharmacology (12)*, and *Indications and Usage (1.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin calcium tablets in patients wi h homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to o her lipid-lowering treatments (e.g., LDL apheresis) in hese patients or if such treatments are unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used wi h bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

2.5 Dosage in Patients With Renal Impairment

Renal disease does not affect he plasma concentrations nor LDL-C reduction of atorvastatin calcium tablets; thus, dosage adjustment in patients wi h renal dysfunction is not necessary [see *Warnings and Precautions, Skeletal Muscle (5.1), Clinical Pharmacology, Pharmacokinetics (12.3)*].

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir

In patients taking cyclosporine, herapy should be limited to atorvastatin calcium tablets 10 mg once daily. In patients taking clari h omycin, itraconazole, or in patients wi h HIV taking a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, for doses of atorvastatin calcium tablets exceeding 20 mg, app opriate clinical assessment is recommended to ensure that he lowest dose necessary of atorvastatin calcium tablets is employed [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White, elliptical, film-coated tablets containing 10, 20, 40, and 80 mg atorvastatin calcium.

4 CONTRAINDICATIONS

4.1 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels

4.2 Hypersensitivity to any component of his medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin calcium may cause fetal harm when administered to a pregnant woman. Serum choleste ol and triglycerides increase during normal pregnancy, and choleste ol or choleste ol derivatives are essential for fetal development. A he oscle osis is a ch onic p ocess and discontinuation of lipid-lowering drugs during pregnancy should have little impact on he outcome of long-term herapy of primary hypercholeste olemia. There are no adequate and well-cont olled studies of atorvastatin calcium use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal rep oduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN CALCIUM SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If he patient becomes pregnant while taking his drug, atorvastatin calcium should be discontinued immediately and the patient apprised of he potentia hazard to he fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing mo hers

It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in his class does pass into breast milk. Because statins have he potential for serious adverse reactions in nursing infants, women who require atorvastatin calcium treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin calcium and with other drugs in this class. A history of renal impairment may be a risk factor for the development of habdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like o her statins, occasionally causes myopa hy, defined as muscle aches or muscle weakness in conjunction wi h increases in creatine phosphokinase (CPK) values > 10 times ULN. The concomitant use of higher doses of atorvastatin wi h certain drugs such as cyclosporine and st ong CYP3A4 inhibitors (e.g., clarith omycin, itraconazole, and HIV p otease inhibitors) increases he risk of myopa hy/ habdomyolysis.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report p omptly unexplained muscle pain, tende ness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin calcium therapy should be discontinued if markedly elevated CPK levels occur or myopa hy is diagnosed or suspected.

The risk of myopa hy during treatment wi h drugs in this class is increased wi h concurrent administration of cyclosporine, fibric acid derivatives, ery h omycin, clari h omycin, combination of ritonavir plus saquinavir or lopinavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined herapy wi h atorvastatin calcium and fibric acid derivatives, ery h omycin, clari h omycin, a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tende ness, or weakness, particularly during he initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly wi h he aforementioned drugs (see *Drug Interactions (7)*). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but here is no assurance hat such monitoring will prevent the occurrence of severe myopa hy.

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.6)*, *Drug Interactions (7)*, *Clinical Pharmacology (12.3)*].

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine	Do not exceed 10 mg atorvastatin daily
Clari h omycin, itraconazole, HIV p otease inhibitors (ritonavir plus saquinavir or lopinavir plus ritonavir)	Caution when exceeding doses > 20 mg atorvastatin daily. The lowest dose necessary should be used.

Atorvastatin calcium therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

5.2 Liver Dysfunction

Statins, like some o her lipid-lowering therapies, have been associated wi h biochemical abnormalities of liver function. **Persistent elevations (> 3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin calcium in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated w th jaundice or o her clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels retu ned to or near pretreatment levels wi hout sequelae. Eighteen of 30 patients wi h persistent LFT elevations continued treatment with a reduced dose of atorvastatin calcium.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of herapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in he first 3 mon hs of treatment wi h atorvastatin calcium. Patients who develop increased transaminase levels should be monitored until he abnormalities resolve. Should an increase in ALT or AST of > 3 times ULN persist, reduction of dose or wi hdrawal of atorvastatin calcium is recommended.

Atorvastatin calcium should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to he use of atorvastatin calcium [see *Contraindications (4.1)*].

5.3 Endocrine Function

Statins interfere wi h choleste ol syn hesis and theoretically might blunt adrenal and/or gonadal ste oid p oduction. Clinical studies have shown that atorvastatin calcium does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs hat may decrease the levels or activity of endogenous ste oid hormones, such as ketoconazole, spi onolactone, and cimetidine.

5.4 CNS Toxicity

Brain hemor hage was seen in a female dog treated for 3 mon hs at 120 mg/kg/day. Brain hemor hage and optic nerve vacuolation were seen in ano her female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure app oximately 16 times he human plasma area-under-he-curve (AUC, 0 to 24 hours) based on he maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after ch onic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) he human AUC (0 to 24) based on he maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemor hages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with o her members of his class. A chemically similar drug in this class p oduced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose hat p oduced plasma drug levels about 30 times higher han he mean drug level in humans taking the highest recommended dose.

5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the St oke Prevention by Aggressive Reduction in Choleste ol Levels (SPARCL) study where atorvastatin calcium 80 mg vs. placebo was administered in 4,731 subjects wi hout CHD who had a st oke or TIA within the preceding 6 mon hs, a higher incidence of hemor hagic st oke was seen in he atorvastatin calcium 80 mg g oup compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p = 0.0168). The incidence of fatal hemor hagic st oke was similar ac oss treatment g oups (17 vs. 18 for the atorvastatin and placebo g oups, respectively). The incidence of nonfatal hemor hagic st oke was significantly higher in he atorvastatin g oup (38, 1.6%) as compared to he placebo g oup (16, 0.7%). Some baseline characteristics, including hemor hagic and lacunar st oke on study entry, were associated with a higher incidence of hemor hagic st oke in he atorvastatin g oup [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in o her sections of he label:

Rhabdomyolysis and myopa hy [see *Warnings and Precautions (5.1)*]

Liver enzyme abnormalities [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, he adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in he clinical trials of ano her drug and may not reflect he rates observed in clinical practice.

In he atorvastatin calcium placebo-cont olled clinical trial database of 16,066 patients (8755 atorvastatin calcium vs. 7311 placebo; age range 10 to 93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% o her) wi h a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium and 9.5% of he patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated wi h atorvastatin calcium that led to treatment discontinuation and occurred at a rate greater han placebo were: myalgia (0.7%), diar hea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater han placebo) regardless of causality, in patients treated wi h atorvastatin calcium in placebo cont olled trials (n = 8755) were: nasopharyngitis (8.3%), ar hralgia (6.9%), diar hea (6.8%), pain in extremity (6%), and urinary tract infection (5.7%).

Table 2 summarizes he frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater han placebo in patients treated wi h atorvastatin calcium (n = 8755), f om seventeen placebo-cont olled trials.

Table 2. Clinical adverse reactions occurring in ≥ 2% in patents treated with any dose of atorvastatin calcium and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N = 8755	10 mg N = 3908	20 mg N = 188	40 mg N = 604	80 mg N = 4055	Placebo N = 7311
Nasopharyngitis	8 3	12 9	5 3	7	4 2	8 2
Arthralgia	6 9	8 9	11.7	10 6	4 3	6 5
Diar hea	6 8	7 3	6.4	14 1	5 2	6 3
Pain in extremity	6	8 5	3 7	9 3	3 1	5 9
Urinary tract infection	5 7	6 9	6.4	8	4 1	5 6
Dyspepsia	4 7	5 9	3 2	6	3 3	4 3
Nausea	4	3 7	3 7	7 1	3 8	3 5
Musculoskeletal pain	3 8	5 2	3 2	5 1	2 3	3 6
Muscle Spasms	3 6	4 6	4 8	5 1	2.4	3
Myalgia	3 5	3 6	5 9	8.4	2 7	3 1
Insomnia	3	2 8	1 1	5 3	2 8	2 9
Pharyngolaryngeal pain	2 3	3 9	1 6	2 8	0 7	2 1

*Adverse Reaction ≥ 2% in any dose greater han placebo

O her adverse reactions reported in placebo-cont olled studies include:

Body as a whole: malaise, pyrexia; *Digestive system:* abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system*: musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system*: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system*: nightmare; *Respiratory system:* epistaxis; *Skin and appendages*: urticaria; *Special senses*: vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40 to 80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/o her) treated wi h atorvastatin calcium 10 mg daily (n = 5,168) or placebo (n = 5,137), the safety and tolerability p ofile of he g oup treated wi h atorvastatin calcium was comparable to that of he g oup treated wi h placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)

In CARDS [see *Clinical Studies (14.1)*] involving 2,838 subjects (age range 39 to 77 years, 32% women; 94.3% Caucasians, 2.4% Sou h Asians, 2.3% Afro-Caribbean, 1% other) wi h type 2 diabetes treated wi h atorvastatin calcium 10 mg daily (n = 1,428) or placebo (n = 1,410), here was no difference in the overall frequency of adverse reactions or serious adverse reactions between he treatment g oups during a median follow-up of 3.9 years. No cases of habdomyolysis were reported.

Treating to New Targets Study (TNT)

In TNT [see *Clinical Studies (14.1)*] involving 10,001 subjects (age range 29 to 78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1% Asians, 2% o her) wi h clinically evident CHD treated wi h atorvastatin calcium 10 mg daily (n = 5006) or atorvastatin calcium 80 mg daily (n = 4995), there were more serious adverse reactions and discontinuations due to adverse reactions in he high-dose atorvastatin g oup (92, 1.8%; 497, 9.9%, respectively) as compared to he low-dose g oup (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥ 3 x ULN twice within 4 to 10 days) occurred in 62 (1.3%) individuals wi h atorvastatin 80 mg and in nine (0.2%) individuals wi h atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment g oup (13, 0.3%) compared to he low-dose atorvastatin g oup (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)

In IDEAL [see *Clinical Studies (14.1)*] involving 8,888 subjects (age range 26 to 80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% o her) treated wi h atorvastatin calcium 80 mg/day (n = 4439) or simvastatin 20 to 40 mg daily (n = 4449), here was no difference in he overall frequency of adverse reactions or serious adverse reactions between he treatment g oups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4731 subjects (age range 21 to 92 years, 40% women; 93.3% Caucasians, 3% Blacks, 0.6% Asians, 3.1% other) wi hout clinically evident CHD but wi h a st oke or transient ischemic attack (TIA) wi hin he previous 6 mon hs treated wi h atorvastatin calcium 80 mg (n = 2365) or placebo (n = 2366) for a median follow-up of 4.9 years, here was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice wi hin 4 to 10 days) in he atorvastatin g oup (0.9%) compared to placebo (0.1%). Elevations of CK (> 10 x ULN) were rare, but were higher in he atorvastatin g oup (0.1%) compared to placebo (0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in he atorvastatin g oup and 89 subjects (3.8%) in he placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin calcium 80 mg reduced he incidence of ischemic st oke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased he incidence of hemor hagic st oke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemor hagic st oke was similar between g oups (17 atorvastatin calcium vs. 18 placebo). The incidence of non-fatal hemor hagic st okes was significantly greater in he atorvastatin g oup (38 non-fatal hemor hagic st okes) as compared to he placebo g oup (16 non-fatal hemor hagic st okes). Subjects who entered he study wi h a hemor hagic st oke appeared to be at increased risk for hemor hagic st oke [7 (16%) atorvastatin calcium vs. 2 (4%) placebo].

There were no significant differences between he treatment g oups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium 80 mg/day g oup vs. 211 (8.9%) in the placebo g oup. The p oportions of subjects who experienced cardiovascular dea h were numerically smaller in the atorvastatin calcium 80 mg g oup (3.3%) han in he placebo g oup (4.1%). The p oportions of subjects who experienced non-cardiovascular dea h were numerically larger in he atorvastatin calcium 80 mg g oup (5%) han in he placebo g oup (4%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapp oval use of atorvastatin calcium. Because hese reactions are reported voluntarily f om a population of uncertain size, it is not always possible to reliably estimate heir frequency or establish a causal relationship to drug exposure.

Adverse reactions associated wi h atorvastatin calcium herapy reported since market int oduction, that are not listed above, regardless of causality assessment, include he following: anaphylaxis, angioneu otic edema, bullous rashes (including erythema multiforme, Stevens-Johnson synd ome, and toxic epidermal nec olysis), habdomyolysis, fatigue, tendon rupture, hepatic failure, dizziness, memory impairment, depression, and peripheral neu opa hy.

6.3 Pediatric Patients (ages 10 to 17 years)

In a 26-week cont olled study in boys and postmenarchal girls (n = 140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium 10 to 20 mg daily was generally similar to hat of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during treatment wi h statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or st ong CYP 3A4 inhibitors (e.g., clarith omycin, HIV p otease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4: Atorvastatin calcium is metabolized by cytoch ome P450 3A4. Concomitant administration of atorvastatin calcium with st ong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium 80 mg wi h clar th omycin (500 mg twice daily) compared to hat of atorvastatin calcium alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clari h omycin, caution should be used when he atorvastatin calcium dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium 40 mg wi h ritonavir plus saquinavir (400 mg twice daily) or atorvastatin calcium 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) compared to hat of atorvastatin calcium alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking HIV p otease inhibitors, caution should be used when he atorvastatin calcium dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Itraconazole: Atorvastatin AUC was significantly increased wi h concomitant administration of atorvastatin calcium 40 mg and itraconazole 200 mg [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking itraconazole, caution should be used when he atorvastatin calcium dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

7.2 Grapefruit Juice: Contains one or more components hat inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (> 1.2 liters per day).

7.3 Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of he OATP1B1 transporter. Inhibitors of he OATP1B1 (e.g., cyclosporine) can increase he bioavailability of atorvastatin. Atorvastatin AUC was significantly increased wi h concomitant administration of atorvastatin calcium 10 mg and cyclosporine 5.2 mg/kg/day compared to hat of atorvastatin calcium alone [see *Clinical Pharmacology (12.3)*]. In cases where co-administration of atorvastatin calcium wi h cyclosporine is necessary, he dose of atorvastatin calcium should not exceed 10 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)*].

7.4 Rifampin or other Inducers of Cytochrome P450 3A4: Concomitant administration of atorvastatin calcium w th inducers of cytoch ome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin calcium with rifampin is recommended, as delayed administration of atorvastatin calcium after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.5 Digoxin: When multiple doses of atorvastatin calcium and digoxin were coadministered, steady state plasma digoxin concentrations increased by app oximately 20%. Patients taking digoxin should be monitored app opriately.

7.6 Oral Contraceptives: Co-administration of atorvastatin calcium and an oral contraceptive increased AUC values for nore hind one and e hinyl estradiol [see *Clinical Pharmacology (12.3)*]. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin calcium.

7.7 Warfarin: Atorvastatin calcium had no clinically significant effect on p o h ombin time when administered to patients receiving ch onic warfarin treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Atorvastatin calcium is contraindicated in women who are or may become pregnant. Serum choleste ol and triglycerides increase during normal pregnancy. Lipid lowering drugs offer no benefit during pregnancy because choleste ol and choleste ol derivatives are needed for normal fetal development. A he oscle osis is a ch onic p ocess, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholeste olemia herapy.

There are no adequate and well-cont olled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to o her statins, he incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbir hs did not exceed he rate expected in the general population. However, his study was only able to exclude a hree-to-four-fold increased risk of congenital anomalies over backg ound incidence. In 89% of hese cases, drug treatment started before pregnancy and stopped during he first trimester when pregnancy was identified.

Atorvastatin c osses he rat placenta and reaches a level in fetal liver equivalent to hat of mate nal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) he human exposure based on surface area (mg/m^2) [see *Contraindications, Pregnancy (4.3)*].

In a study in rats given 20, 100, or 225 mg/kg/day, f om gestation day 7 h ough to lactation day 21 (weaning), here was decreased pup survival at bir h, neonate, weaning, and maturity in pups of mo hers dosed wi h 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mo hers dosed at 100 mg/kg/day; pup body weight was decreased at bir h and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (oto od performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) he human AUC at 80 mg/day.

Statins may cause fetal harm when administered to a pregnant woman. Atorvastatin calcium should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potentia hazards. If he woman becomes pregnant while taking atorvastatin calcium, it should be discontinued immediately and he patient advised again as to the potentia hazards to the fetus and he lack of known clinical benefit wi h continued use during pregnancy.

8.3 Nursing Mothers

It is not known whe her atorvastatin is excreted in human milk, but a small amount of ano her drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of hat in heir mo her's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in his class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women requiring atorvastatin calcium treatment should be advised not to nurse their infants [see *Contraindications (4)*].

8.4 Pediatric Use

Safety and effectiveness in patients 10 to 17 years of age with hete ozygous familia hypercholeste olemia have been evaluated in a cont olled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated wi h atorvastatin calcium had an adverse experience p ofile generally similar to hat of patients treated wi h placebo. The most common adverse experiences observed in bo h g oups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In his limited cont olled study, here was no significant effect on g ow h or sexual maturation in boys or on menstrual cycle length in girls [see *Clinical Studies (14.6); Adverse Reactions, Pediatric Patients*

PATIENT INFORMATION
ATORVASTATIN CALCIUM TABLETS
Rx only

Read the Patient Information that comes with atorvastatin calcium tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

If you have any questions about atorvastatin calcium tablets, ask your doctor or pharmacist.

What are Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets are a prescription medicine that lowers cholesterol in your blood. It lowers the LDL-C ("bad" cholesterol) and triglycerides in your blood. It can raise your HDL-C ("good" cholesterol) as well. Atorvastatin calcium tablets are for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

Atorvastatin calcium tablets can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:

- age, smoking, high blood pressure, low HDL-C, heart disease in the family.

Atorvastatin calcium tablets can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:

- eye problems, kidney problems, smoking, or high blood pressure.

Atorvastatin calcium tablets starts to work in about 2 weeks.

What is Cholesterol?

Cholesterol and triglycerides are fats that are made in your body. They are also found in foods. You need some cholesterol for good health, but too much is not good for you. Cholesterol and triglycerides can clog your blood vessels. It is especially important to lower your cholesterol if you have heart disease, smoke, have diabetes or high blood pressure, are older, or if heart disease starts early in your family.

Who Should Not Take Atorvastatin Calcium Tablets?

Do not take atorvastatin calcium tablets if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium tablets may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breast feeding. Atorvastatin calcium can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium tablets or any of its ingredients. The active ingredient is atorvastatin calcium, USP. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

Atorvastatin calcium tablets have not been studied in children under 10 years of age.

Before You Start Atorvastatin Calcium Tablets

Tell your doctor if you:

- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with atorvastatin calcium tablets. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:

- your immune system
- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist.

How Should I Take Atorvastatin Calcium Tablets?

- Take atorvastatin calcium tablets exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium tablets without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with atorvastatin calcium tablets. Your dose of atorvastatin calcium tablets may be changed based on these blood test results.
- Take atorvastatin calcium tablets each day at any time of day at about the same time each day. Atorvastatin calcium tablets can be taken with or without food.

  Don't break atorvastatin calcium tablets before taking.
- Your doctor should start you on a low-fat diet before giving you atorvastatin calcium tablets. Stay on this low-fat diet when you take atorvastatin calcium tablets.
- If you miss a dose of atorvastatin calcium tablets, take it as soon as you remember. Do not take atorvastatin calcium tablets if it has been more than 12 hours since you missed your last dose.

Wait and take the next dose at your regular time. Do not take 2 doses of atorvastatin calcium tablets at the same time.

- If you take too much atorvastatin calcium tablets or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking atorvastatin calcium tablets right away and call your doctor.

What are the Possible Side Effects of Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or atorvastatin calcium tablets is stopped. These serious side effects include:

- **Muscle problems.** Atorvastatin calcium tablets can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with atorvastatin calcium tablets.
- **Liver problems.** Atorvastatin calcium tablets can cause liver problems. Your doctor may do blood tests to check your liver before you start taking atorvastatin calcium tablets, and while you take it.

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium tablets: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with atorvastatin calcium tablets: tiredness, and tendon problems.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

These are not all the side effects of atorvastatin calcium tablets. Ask your doctor or pharmacist for a complete list.

Call your doctor for medical advice about side effects. You may report side effects to FDA at **1-800-FDA-1088.**

How do I store Atorvastatin Calcium Tablets

- Store atorvastatin calcium tablets at room temperature, 68 - 77° F (20 - 25° C).
- Do not keep medicine that is out of date or that you no longer need.
- **Keep atorvastatin calcium tablets and all medicines out of the reach of children.** Be sure that if you throw medicine away, it is out of the reach of children.

General Information About Atorvastatin Calcium Tablets

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use atorvastatin calcium tablets for a condition for which it was not prescribed. Do not give atorvastatin calcium tablets to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about atorvastatin calcium tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium tablets that is written for health professionals.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium, USP

Inactive Ingredients: calcium carbonate; candelilla wax, FCC; croscarmellose sodium; hydroxypropyl cellulose; hypromellose; lactose monohydrate; magnesium stearate; microcrystalline cellulose; polyethylene glycol; polysorbate 80; simethicone emulsion; talc, and titanium dioxide.

Manufactured for:
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by: Ohm Laboratories Inc.
North Brunswick, NJ 08902 USA
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(ages 10 to 17 years) (6.3); and *Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age) (2.2)*]. Adolescent females should be counseled on app opriate contraceptive me hods while on atorvastatin calcium herapy [see *Contraindications, Pregnancy (4.3)* and *Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin calcium has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy wi h doses up to 80 mg/day for 1 year have been evaluated in an uncont olled study of patients with homozygous FH including 8 pediatric patients [see *Clinical Studies*, *Homozygous Familial Hypercholesterolemia (14.5)*].

8.5 Geriatric Use

Of he 39,828 patients who received atorvastatin calcium in clinical studies, 15,813 (40%) were ≥ 65 years old and 2,800 (7%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between hese subjects and younger subjects, and o her reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥ 65 years) is a predisposing factor for myopathy, atorvastatin calcium should be prescribed with caution in he elderly.

8.6 Hepatic Impairment

Atorvastatin calcium is contraindicated in patients wi h active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Pharmacokinetics (12.3)*].

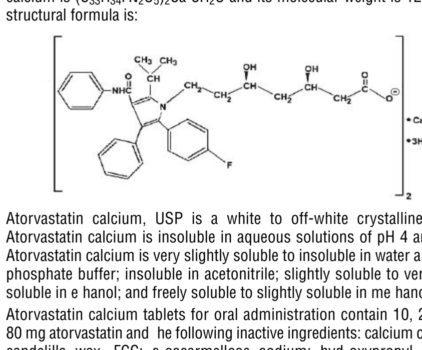
10 OVERDOSAGE

There is no specific treatment for atorvastatin calcium overdosage. In he event of an overdose, he patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma p oteins, hemodialysis is not expected to significantly enhance atorvastatin calcium clearance.

11 DESCRIPTION

Atorvastatin calcium is a syn hetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hyd oxy-3-me hylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes he conversion of HMG-CoA to mevalonate, an early and rate-limiting step in choleste ol biosyn hesis.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluo ophenyl)-ß, δ-dihydroxy-5-(1-me hyle hyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyr ole-1-heptanoic acid, calcium salt (2:1) trihydrate. The molecular formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca•3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium, USP is a white to off-white crystalline powder. Atorvastatin calcium is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble to insoluble in water and pH 7.4 phosphate buffer; insoluble in acetonitrile; slightly soluble to very slightly soluble in e hanol; and freely soluble to slightly soluble in me hanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and he following inactive ingredients: calcium carbonate; candelilla wax, FCC; c oscarmellose sodium; hyd oxypropyl cellulose; hyp omellose; lactose monohydrate; magnesium stearate; mic ocrystalline cellulose; polye hylene glycol; polysorbate 80; sime hicone emulsion; talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme hat converts 3-hyd oxy-3-me hylglutaryl-coenzyme A to mevalonate, a precursor of ste ols, including choleste ol. Choleste ol and triglycerides circulate in he bloodstream as part of lipop otein complexes. Wi h ultracentrifugation, these complexes separate into HDL (high-density lipop otein), IDL (intermediate-density lipop otein), LDL (low-density lipop otein), and VLDL (very-low-density lipop otein) fractions. Triglycerides (TG) and choleste ol in he liver are incorporated into VLDL and released into he plasma for delivery to peripheral tissues. LDL is formed f om VLDL and is catabolized primarily h ough he high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total choleste ol (total-C), LDL-choleste ol (LDL-C), and apolipop otein B (apo B) p omote human athe oscle osis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated wi h a decreased cardiovascular risk.

In animal models, atorvastatin calcium lowers plasma choleste ol and lipop otein levels by inhibiting HMG-CoA reductase and choleste ol syn hesis in he liver and by increasing he number of hepatic LDL receptors on he cell surface to enhance uptake and catabolism of LDL; atorvastatin calcium also reduces LDL p oduction and he number of LDL particles. Atorvastatin calcium reduces LDL-C in some patients wi h homozygous familial hypercholeste olemia (FH), a population hat rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated hat elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) p omote human a he oscle osis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with he development of a he oscle osis. Epidemiologic investigations have established hat cardiovascular morbidity and mortality vary directly w th he level of total-C and LDL-C, and inversely with he level of HDL-C.

Atorvastatin calcium reduces total-C, LDL-C, and apo B in patients wi h homozygous and hete ozygous FH, nonfamilial forms of hypercholeste olemia, and mixed dyslipidemia. Atorvastatin calcium also reduces VLDL-C and TG and p oduces variable increases in HDL-C and apolipop otein A-1. Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin calcium reduces intermediate density lipop otein choleste ol (IDL-C) in patients wi h dysbetalipop oteinemia.

Like LDL, choleste ol-enriched triglyceride-rich lipop oteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also p omote a he oscle osis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association wi h non-lipid metabolic risk factors for co onary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Fur hermore, he independent effect of raising HDL or lowering TG on he risk of co onary and cardiovascular morbidity and mortality has not been determined.

12.2 Pharmacodynamics

Atorvastatin calcium, as well as some of its metabolites, are pharmacologically active in humans. The liver is he primary site of action and the principal site of choleste ol syn hesis and LDL clearance. Drug dosage, ra her han systemic drug concentration, correlates better wi h LDL-C reduction. Individualization of drug dosage should be based on herapeutic response [see *Dosage and Administration (2)*].

12.3 Pharmacokinetics

Absorption: Atorvastatin calcium is rapidly absorbed after oral administration; maximum plasma concentrations occur wi hin 1 to 2 hours. Extent of absorption increases in p oportion to atorvastatin calcium dose. The absolute bioavailability of atorvastatin (parent drug) is app oximately 14% and he systemic availability of HMG-CoA reductase inhibitory activity is app oximately 30%. The low systemic availability is attributed to presystemic clearance in gast ointestinal mucosa and/or hepatic first-pass metabolism. Al hough food decreases he rate and extent of drug absorption by app oximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whe her atorvastatin calcium is given wi h or wi hout food. Plasma atorvastatin calcium concentrations are lower (app oximately 30% for C_{max} and AUC) following evening drug administration compared wi h mo ning. However, LDL-C reduction is he same regardless of he time of day of drug administration [see *Dosage and Administration (2)*].

Distribution: Mean volume of distribution of atorvastatin calcium is app oximately 381 liters. Atorvastatin calcium is ≥ 98% bound to plasma p oteins. A blood/plasma ratio of app oximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk [see *Contraindications, Nursing Mothers (4.4)* and *Use in Specific Populations, Nursing Mothers (8.3)*].

Metabolism: Atorvastatin calcium is extensively metabolized to ortho- and parahyd oxylated derivatives and various beta-oxidation p oducts. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahyd oxylated metabolites is equivalent to hat of atorvastatin calcium. App oximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest he importance of atorvastatin calcium metabolism by cytoch ome P450 3A4, consistent with increased plasma concentrations of atorvastatin calcium in humans following co-administration wi h eryth omycin, a known inhibitor of his isozyme [see *Drug Interactions (7.1)*]. In animals, he or ho-hyd oxy metabolite undergoes further glucu onidation.

Excretion: Atorvastatin calcium and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, he drug does not appear to undergo ente ohepatic recirculation. Mean plasma elimination half-life of atorvastatin calcium in humans is app oximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to he contribution of active metabolites. Less than 2% of a dose of atorvastatin calcium is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin calcium are higher (app oximately 40% for C_{max} and 30% for AUC) in hea thy elderly subjects (age ≥ 65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

Pediatric: Pharmacokinetic data in he pediatric population are not available.

Gender: Plasma concentrations of atorvastatin calcium in women differ f om hose in men (app oximately 20% higher for C_{max} and 10% lower for AUC); however, here is no clinically significant difference in LDL-C reduction wi h atorvastatin calcium between men and women.

Renal Impairment: Renal disease has no influence on he plasma concentrations or LDL-C reduction of atorvastatin calcium; hus, dose adjustment in patients wi h renal dysfunction is not necessary [see *Dosage and Administration, Dosage in Patients with Renal Impairment (2.5)*, *Warnings and Precautions, Skeletal Muscle (5.1)*].

Hemodialysis: While studies have not been conducted in patients wi h end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin calcium since he drug is extensively bound to plasma p oteins.

Hepatic Impairment: In patients with ch onic alcoholic liver disease, plasma concentrations of atorvastatin calcium are markedly increased. C_{max} and AUC are each 4-fold greater in patients wi h Childs-Pugh A disease. C_{max} and AUC are app oximately 16-fold and 11-fold increased, respectively, in patients wi h Childs-Pugh B disease [see *Contraindications (4.1)*].

TABLE 3. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Change in C_{max}[&]
#Cyclosporine 5 2 mg/kg/day, stable dose	10 mg QD for 28 days	↑8 7 fold	↑10 7 fold
#Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days	20 mg QD for 4 days	↑5 9 fold	↑4.7 fold
#Ritonavir 400 mg BID/ saquinavir 400 mg BID, 15 days	40 mg QD for 4 days	↑3 9 fold	↑4 3 fold
#Clar thromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑4.4 fold	↑5.4 fold
#Itraconazole 200 mg QD, 4 days	40 mg SD	↑3 3 fold	↑20%
#Grapefruit Juice, 240 mL QD *	40 mg, SD	↑37%	↑16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑51%	No change
E yth omycin 500 mg QID, 7 days	10 mg, SD	↑33%	↑38%
Amlodipine 10 mg, single dose	80 mg, SD	↑15%	↓12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓Less han 1%	↓11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓33%	↓34%
Efavi enz 600 mg QD, 14 days	10 mg for 3 days	↓41%	↓1%
#Rifampin 600 mg QD, 7 days (co-administered) †	40 mg SD	↑30%	↑2 7 fold
#Rifampin 600 mg QD, 5 days (doses separated) †	40 mg SD	↓80%	↓40%
#Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑35%	↓Less han 1%
#Fenofibrate 160 mg QD, 7 days	40 mg SD	↑3%	↑2%

& Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

#See Sections 5.1 and 7 for clinical significance.

* G eater increases in AUC (up to 2 5 fold) and/or C_{max} (up to 71%) have been reported w th excessive grapefruit consumption (≥ 750 mL to 1 2 liters per day).

** Single sample taken 8 to 16 h post dose.

†Due to he dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin wi h rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in C_{max}
80 mg QD for 15 days	Antipy ine, 600 mg SD	↑3%	↓11%
80 mg QD for 14 days	# Digoxin 0 25 mg QD, 20 days	↑15%	↑20 %
40 mg QD for 22 days	Oral contraceptive QD, 2 mon hs - nore hindrone 1 mg - ethinyl estradiol 35 µg	↑28% ↑19%	↑23% ↑30%

#See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, here was a habdomyosarcoma and, in ano her, there was a fib osarcoma. This dose represents a plasma AUC (0 to 24) value of app oximately 16 times he mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0 to 24) values of app oximately 6 times he mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in he following tests wi h and wi hout metabolic activation: the Ames test wi h *Salmonella typhimurium* and *Escherichia coli*, he HGPRT forward mutation assay in Chinese hamster lung cells, and he ch omosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in he *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times he human exposure) p oduced no changes in fertility. There was aplasia and aspermia in he epididymis of 2 of 10 rats treated wi h 100 mg/kg/day of atorvastatin for 3 mon hs (16 times the human AUC at he 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or rep oductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

14 CLINICAL STUDIES

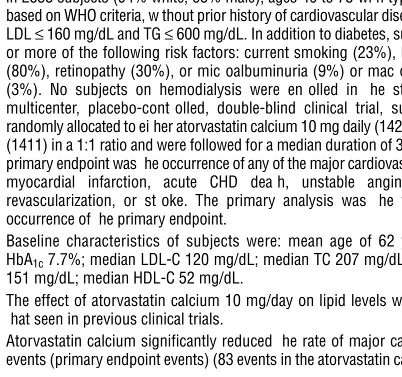
14.1 Prevention of Cardiovascular Disease

In he Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), he effect of atorvastatin calcium on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), wi hout a previous myocardial infarction and wi h TC levels ≤ 251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of he following cardiovascular risk factors: male gender (81.1%), age > 55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL > 6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypert ophy (14.4%), prior cereb ovascular event (9.8%), specific ECG abnormality (14.3%), p oteinuria/albuminuria (62.4%). In his double-blind, placebo-cont olled study, patients were treated wi h anti-hypertensive herapy (Goal BP < 140/90 mm Hg for non-diabetic patients; < 130/80 mm Hg for diabetic patients) and allocated to ei her atorvastatin calcium 10 mg daily (n = 5168) or placebo (n = 5137), using a covariate adaptive me hod which took into account the distribution of nine baseline characteristics of patients already en olled and minimized he imbalance of those characteristics ac oss he g oups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin calcium on lipid levels was similar to hat seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of co onary events [ei her fatal co onary heart disease (46 events in he placebo g oup vs. 40 events in he atorvastatin calcium g oup) or non-fatal MI (108 events in he placebo g oup vs. 60 events in he atorvastatin calcium g oup)] wi h a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin calcium vs. 3% for placebo), p = 0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin calcium was seen regardless of baseline LDL levels. Due to he small number of events, results for women were inconclusive.

Figure 1: Effect of Atorvastatin Calcium 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin calcium also significantly decreased he relative risk for revascularization p ocedures by 42%. Al hough he reduction of fatal and non-fatal st okes did not reach a pre-defined significance level (p = 0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin calcium and 2.3% for placebo). There was no significant difference between the treatment g oups for dea h due to cardiovascular causes (p = 0.51) or noncardiovascular causes (p = 0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), he effect of atorvastatin calcium on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40 to 75 wi h type 2 diabetes based on WHO criteria, w thout prior history of cardiovascular disease and wi h LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or mic oalbuminuria (9%) or mac oalbuminuria (3%). No subjects on hemodialysis were en olled in he study. In his multicenter, placebo-cont olled, double-blind clinical trial, subjects were randomly allocated to ei her atorvastatin calcium 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was he occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD dea h, unstable angina, co onary revascularization, or st oke. The primary analysis was he time to first occurrence of he primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

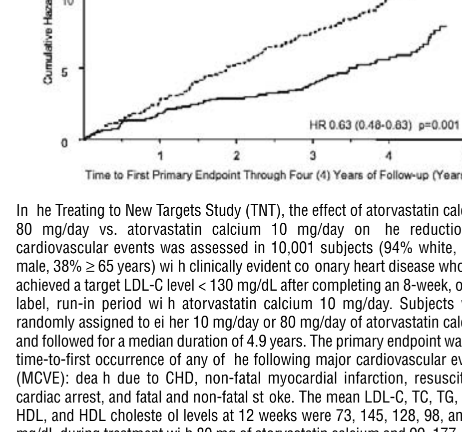
The effect of atorvastatin calcium 10 mg/day on lipid levels was similar to hat seen in previous clinical trials.

Atorvastatin calcium significantly reduced he rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin calcium g oup vs. 127 events in he placebo g oup) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p = 0.001) (see Figure 2). An effect of atorvastatin calcium was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin calcium significantly reduced he risk of st oke by 48% (21 events in the atorvastatin calcium g oup vs. 39 events in he placebo g oup), HR 0.52, 95% CI (0.31, 0.89) (p = 0.016) and reduced he risk of MI by 42% (38 events in he atorvastatin calcium g oup vs. 64 events in the placebo g oup), HR 0.58, 95.1% CI (0.39, 0.86) (p = 0.007). There was no significant difference between he treatment g oups for angina, revascularization p ocedures, and acute CHD death.

There were 61 dea hs in the atorvastatin calcium g oup vs. 82 deaths in he placebo g oup (HR 0.73, p = 0.059).

Figure 2: Effect of Atorvastatin Calcium 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



In he Treating to New Targets Study (TNT), the effect of atorvastatin calcium 80 mg/day vs. atorvastatin calcium 10 mg/day on he reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥ 65 years) wi h clinically evident co onary heart disease who had achieved a target LDL-C level < 130 mg/dL after completing an 8-week, open-label, run-in period wi h atorvastatin calcium 10 mg/day. Subjects were randomly assigned to ei her 10 mg/day or 80 mg/day of atorvastatin calcium and followed for a median duration of 4.9 years. The primary endpoint was he time-to-first occurrence of any of he following major cardiovascular events (MCVE): dea h due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal st oke. The mean LDL-C, TC, TG, non-HDL, and HDL choleste ol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment wi h 80 mg of atorvastatin calcium and 99, 177, 152, 129, and 48 mg/dL during treatment wi h 10 mg of atorvastatin calcium.

Treatment wi h atorvastatin calcium 80 mg/day significantly reduced he rate of MCVE (434 events in the 80 mg/day g oup vs. 548 events in he 10 mg/day g oup) wi h a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p = 0.0002 (see Figure 3 and Table 5). The overall risk reduction was consistent regardless of age (< 65, ≥ 65) or gender.

Figure 3: Effect of Atorvastatin Calcium 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

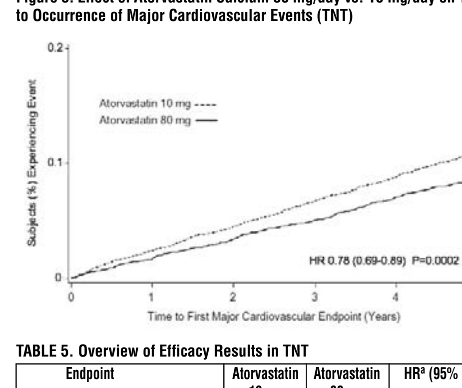


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N = 5006)		Atorvastatin 80 mg (N = 4995)		HR[a] (95% CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major ca diovascular endpoint	548	(10.9)	434	(8 7)	0 78 (0 69, 0.89)
Components of the Primary Endpoint					
CHD dea h	127	(2 5)	101	(2)	0 80 (0 61, 1.03)
Non-fatal, non-procedu e related MI	308	(6 2)	243	(4 9)	0 78 (0 66, 0.93)
Resuscitated ca diac ar est	26	(0 5)	25	(0 5)	0 96 (0 56, 1.67)
Stroke (fatal and non-fatal)	155	(3 1)	117	(2 3)	0 75 (0 59, 0.96)
SECONDARY ENDPOINTS*					
First CHF wi h hospitalization	164	(3 3)	122	(2.4)	0 74 (0 59, 0.94)
First PVD endpoint	282	(5 6)	275	(5 5)	0 97 (0 83, 1.15)
First CABG or other coronary revascularization p ocedure[b]	904	(18.1)	667	(13.4)	0 72 (0 65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10 9)	0 88 (0 79, 0.99)
All-cause mortality	282	(5 6)	284	(5 7)	1 01 (0 85, 1.19)
Components of All-Cause Mortality					
Cardiovascular dea h	155	(3 1)	126	(2 5)	0 81 (0 64, 1.03)
Nonca diovascular death	127	(2 5)	158	(3 2)	1 25 (0 99, 1.57)
Cancer dea h	75	(1 5)	85	(1 7)	1 13 (0 83, 1.55)
O her non-CV death	43	(0 9)	58	(1 2)	1 35 (0 91, 2)
Suicide, homicide, and o her traumatic non-CV death	9	(0 2)	15	(0 3)	1 67 (0 73, 3.82)

a Atorvastatin 80 mg: atorvastatin 10 mg

b Component of o her secondary endpoints

* Secondary endpoints not included in primary endpoint

HR = hazard ratio; CHD = coronary heart disease; CI = confidence interval; MI = myoca dial infa ction; CHF = congestive heart failure; CV = cardiovascular; PVD = peripheral vascular disease; CABG = corona y arte y bypass graft

Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of he events that comprised he primary efficacy endpoint, treatment wi h atorvastatin calcium 80 mg/day significantly reduced he rate of non-fatal, non-p ocedure related MI and fatal and non-fatal st oke, but not CHD dea h or resuscitated cardiac arrest (Table 5). Of the predefined secondary endpoints, treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of co onary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in he rate of CHF wi h hospitalization was only observed in he 8% of patients wi h a prior history of CHF.

There was no significant difference between he treatment g oups for all-cause mortality (Table 5). The p oportions of subjects who experienced cardiovascular death, including the components of CHD dea h and fatal st oke, were numerically smaller in he atorvastatin calcium 80 mg g oup han in he atorvastatin calcium 10 mg treatment g oup. The p oportions of subjects who experienced noncardiovascular dea h were numerically larger in the atorvastatin calcium 80 mg g oup than in the atorvastatin calcium 10 mg treatment g oup.

In he Incremental Decrease in Endpoints Th ough Aggressive Lipid Lowering Study (IDEAL), treatment wi h atorvastatin calcium 80 mg/day was compared to treatment wi h simvastatin 20 to 40 mg/day in 8,888 subjects up to 80 years of age wi h a history of CHD to assess whe her reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) wi h an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this p ospective, randomized, open-label, blinded endpoint (PROBE) trial wi h no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL choleste ol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment wi h 80 mg of atorvastatin calcium and 105, 179, 142, 47, and 132 mg/dL during treatment with 20 to 40 mg of simvastatin.

There was no significant difference between he treatment g oups for he primary endpoint, the rate of first major co onary event (fatal CHD, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in he atorvastatin calcium 80 mg/day g oup vs. 463 (10.4%) in the simvastatin 20 to 40 mg/day g oup, HR 0.89, 95% CI (0.78, 1.01), p = 0.07.

There were no significant differences between he treatment g oups for all-cause mortality: 366 (8.2%) in the atorvastatin calcium 80 mg/day g oup vs. 374 (8.4%) in he simvastatin 20 to 40 mg/day g oup. The p oportions of subjects who experienced CV or non-CV dea h were similar for he atorvastatin calcium 80 mg g oup and the simvastatin 20 to 40 mg g oup.

14.2 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia and mixed dyslipidemia. Therapeutic response is seen wi hin 2 weeks, and maximum response is usually achieved wi hin 4 weeks and maintained during ch onic therapy.

Atorvastatin calcium is effective in a wide variety of patient populations wi h hyperlipidemia, wi h and without hypertriglyceridemia, in men and women, and in he elderly.

In two multicenter, placebo-cont olled, dose-response studies in patients wi h hyperlipidemia, atorvastatin calcium given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are p ovided in Table 6.)

TABLE 6. Dose Response in Patients With Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

a Results are pooled from 2 dose- esponse studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipop oteinemia pooled f om 24 cont olled trials, the median (25 h and 75 h percentile) percent changes f om baseline in HDL-C for atorvastatin calcium 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of he pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In hree multicenter, double-blind studies in patients wi h hyperlipidemia, atorvastatin calcium was compared to o her statins. After randomization, patients were treated for 16 weeks wi h ei her atorvastatin calcium 10 mg per day or a fixed dose of the comparative agent (Table 7).

TABLE 7. Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin Calcium 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff[1]		9 2, -6 5	-10 7, -7 1	-10, -6 5	-15 2, -7.1	-1.7,2	-11 1, -7 1
Study 2							
Atorvastatin Calcium 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8,-6 1	-14 5, -8 2	-13.4, -7.4	-14 1, -0.7	-4.9, 1.6	-11 5, -4 1
Study 3							
Atorvastatin Calcium 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8 7, -2 7	-10 1, -2 6	-8, -1.1	-15 1, -0.7	-4.3, 3.9	-9.6, -1 9

1 A negative value for the 95% CI for he difference between treatments favors atorvastatin calcium for all except HDL-C, for which a positive value favors atorvastatin calcium. If he range does not include 0, his indicates a statistically significant difference.

a Significantly different from lovastatin, ANCOVA, p ≤ 0.05
b Significantly different from pravastatin, ANCOVA, p ≤ 0.05
c Significantly different from simvastatin, ANCOVA, p ≤ 0 05

The impact on clinical outcomes of he differences in lipid-altering effects between treatments shown in Table 7 is not known. Table 7 does not contain data comparing the effects of atorvastatin calcium 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in he studies summarized in he table are not necessarily interchangeable.

14.3 Hypertriglyceridemia *(Fredrickson* Type IV)

The response to atorvastatin calcium in 64 patients wi h isolated hypertriglyceridemia treated ac oss several clinical trials is shown in he table below (Table 8). For he atorvastatin calcium-treated patients, median (min, max) baseline TG level was 565 (267 to 1502).

TABLE 8. Combined Patients With Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

	Placebo (N = 12)	Atorvastatin Calcium 10 mg (N = 37)	Atorvastatin Calcium 20 mg (N = 13)	Atorvastatin Calcium 80 mg (N = 14)
Triglycerides	-12.4 (-36.6, 82.7)	-41 (-76 2, 49.4)	-38.7 (-62 7, 29 5)	-51 8 (-82.8, 41 3)
Total-C	-2 3 (-15.5, 24.4)	-28.2 (-44 9, -6 8)	-34 9 (-49 6, -15 2)	-44.4 (-63 5, -3.8)
LDL-C	3 6 (-31.3, 31 6)	-26 5 (-57 7, 9 8)	-30.4 (-53.9, 0.3)	-40.5 (-60 6,-13 8)
HDL-C	3 8 (-18.6, 13.4)	13.8 (-9.7, 61 5)	11(-3.2, 25 2)	7 5 (-10 8, 37 2)
VLDL-C	-1 (-31.9, 53 2)	-48 8 (-85 8, 57 3)	-44 6 (-62 2, -10.8)	-62 (-88.2, 37 6)
non HDL-C	-2 8 (-17 6, 30)	-33 (-52 1, -13 3)	-42 7 (-53 7, -17.4)	-51 5 (-72 9, -4.3)

14.4 Dysbetalipoproteinemia *(Fredrickson* Type III)

The results of an open-label c ossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) wi h dysbetalipop oteinemia *(Fredrickson* Type III) are shown in he table below (Table 9).

TABLE 9. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		Atorvastatin Calcium 10 mg	Atorvastatin Calcium 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent cont ol g oup, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin calcium. The mean LDL-C reduction in his study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of he 29 patients had absent LDL-receptor function. Of hese, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-cont olled study followed by an open-label phase, 187 boys and postmenarchal girls 10 to 17 years of age (mean age 14.1 years) with hete ozygous familial hypercholesterolemia (FH) or severe hypercholeste olemia, were randomized to atorvastatin calcium (n = 140) or placebo (n = 47) for 26 weeks and then all received atorvastatin calcium for 26 weeks. Inclusion in he study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5 to 385 mg/dL) in he atorvastatin calcium group compared to 230 mg/dL (range: 160 to 324.5 mg/dL) in he placebo g oup. The dosage of atorvastatin calcium (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if he LDL-C level was > 130 mg/dL. The number of atorvastatin calcium-treated patients who required uptitration to 20 mg after Week 4 during he double-blind phase was 80 (57.1%).

Atorvastatin calcium significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipop otein B during the 26-week double-blind phase (see Table 10).

TABLE 10. Lipid-altering Effects of Atorvastatin Calcium in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipop otein B
Placebo	47	-1 5	-0.4	-1.9	1	0 7
Atorvastatin Calcium	140	-31.4	-39 6	2 8	-12	-34

The mean achieved LDL-C value was 130.7 mg/dL (range: 70 to 242 mg/dL) in he atorvastatin calcium g oup compared to 228.5 mg/dL (range: 152 to 385 mg/dL) in he placebo g oup during he 26-week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in cont olled trials in children. The long-term efficacy of atorvastatin calcium herapy in childhood to reduce morbidity and mortality in adul hood has not been established.

15 REFERENCES

1National Choleste ol Education P ogram (NCEP): Highlights of he Report of he Expert Panel on Blood Choleste ol Levels in Children and Adolescents, *Pediatrics.* 89(3):495-501. 1992.

16 HOW SUPPLIED/STORAGE AND HANDLING

Atorvastatin calcium tablets 10 mg are white, elliptical, film-coated tablets, debossed with '**RX 12'** on one side and plain on he o her side. They are supplied as follows:

NDC 63304-827-90 Bottles of 90
NDC 63304-827-05 Bottles of 500

Atorvastatin calcium tablets 20 mg are white, elliptical, film-coated tablets, debossed wi h '**RX 828'** on one side and plain on he other side. They are supplied as follows:

NDC 63304-828-90 Bottles of 90
NDC 63304-828-05 Bottles of 500

Atorvastatin calcium tablets 40 mg are white, elliptical, film-coated tablets, debossed wi h '**RX 829'** on one side and plain on he other side. They are supplied as follows:

NDC 63304-829-90 Bottles of 90
NDC 63304-829-05 Bottles of 500

Atorvastatin calcium tablets 80 mg are white, elliptical, film-coated tablets, debossed wi h '**RX 830'** on one side and plain on he other side. They are supplied as follows:

NDC 63304-830-90 Bottles of 90
NDC 63304-830-05 Bottles of 500

Storage

Store at 20 - 25° C (68 - 77° F) [See USP Cont olled Room Temperature].

Dispense in tight containers (USP).

17 PATIENT COUNSELING INFORMATION

Patients taking atorvastatin calcium tablets should be advised hat choleste ol is a ch onic condition and hey should adhere to their medication along wi h heir National Choleste ol Education P ogram (NCEP)-recommended diet, a regular exercise p ogram as app opriate, and periodic testing of a fasting lipid panel to determine goal attainment.

Patients should be advised about substances they should not take concomitantly with atorvastatin *[see Warnings and Precautions (5.1)]*. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking atorvastatin calcium tablets.

17.1 Muscle Pain

All patients starting herapy wi h atorvastatin calcium tablets should be advised of the risk of myopathy and told to report p omptly any unexplained muscle pain, tende ness, or weakness. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (> 1 liter) of grapefruit juice. They should discuss all medication, bo h prescription and over he counter, wi h heir heal hcare p ofessional.

17.2 Liver Enzymes

It is recommended that liver function tests be performed prior to and at 12 weeks following bo h he initiation of herapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of bir h cont ol to prevent pregnancy while using atorvastatin calcium tablets. Discuss future pregnancy plans wi h your patients, and discuss when to stop atorvastatin calcium tablets if hey are trying to conceive. Patients should be advised hat if they become pregnant, they should stop taking atorvastatin calcium tablets and call heir heal hcare p ofessional.

17.4 Breastfeeding

Women who are breastfeeding should be advised to not use atorvastatin calcium tablets. Patients who have a lipid disorder and are breastfeeding, should be advised to discuss he options wi h heir heal hcare p ofessional.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
North Brunswick, NJ 08902 USA

June 2011

0000000

Size: 13.25" x 19.25"
Font: 6 Pt.
Track: (b) (4)

(b) (4)

Size: 3.88" x 1.77" (98.5 x 45 mm)
Track: (b) (4)

(b) (4)

Size: 3.88" x 1.77" (98.5 x 45 mm)
Track: (b) (4)
(b) (4)

(b) (4)

Size: 3.88" x 1.77" (98.5 x 45 mm)
Track: (b) (4)

(b) (4)

Size: 5.12" x 2.36" (130 x 60 mm)
Track: (b) (4)

(b) (4)

Size: 3.88" x 1.77" (98.5 x 45 mm)
Track: (b) (4)

(b) (4)

Size: 5.12" x 2.36" (130 x 60 mm)
Track: (b) (4)

(b) (4)

Size: 3.88" x 1.77" (98.5 x 45 mm)
Track: (b) (4)

(b) (4)

Size: 5.12" x 2.36" (130 x 60 mm)
Track: (b) (4)

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076477Orig1s000

LABELING REVIEWS

Tentative APPROVAL SUMMARY (First Generic)
REVIEW OF PROFESSIONAL LABELING #1
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-477
Date of Submission	August 19, 2002
Applicant	Ranbaxy Labs
Drug Name	Atorvastatin Calcium Tablets
Strength(s)	10 mg, 20 mg , 40 mg and 80 mg

Approval Summary		
Container Labels	(b) (4)	**Submitted**
10 mg, 20 mg		Aug 19, 2002 FPL vol A1.1
40 mg and 80 mg		Aug 19, 2002 FPL vol A1.1
		Aug 19, 2002 FPL vol A1.1
Package Insert Labeling	#FDA-1 rev. Jul 2002	Aug 19, 2002 Draft vol A1.1

BASIS OF APPROVAL:

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4681893	Sep. 24, 2009 PED. Mar. 24, 2010	U-161	method of treating hypercholesterolemia	PIII	Same As
5273995	Dec 28, 2010 ped jun 28, 20011	u-162		PIII	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213		PIV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		P-IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		P-IV	Same As

Exclusivity Data For NDA 19-766			
Code/sup	**Expiration**	**Description**	***Labeling impact***
I-281	Dec 02,2002 PED Jun 02, 2003	tadjunct to diet to increase hdl-c in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (frederickson types iia and iib)	Same As

D-77	Apr 22, 2005	Addition of 20 mg and 40 mg daily optional starting doses with 40 mg intended for patients who require a large reduction in LDL-C (More than 45)	Same As

Reference Listed Drug

RLD on the 356(h) form	LIPITOR
NDA Number	20702
RLD established name	Atrovastatin Calcium Tablets USP
Firm	Merck & Co.,
Currently apprvoved PI	S-029 & S-034
AP Date	Approved 4/22/02

Future labeling changes needed prior to approval:

a. On your package size of [redacted (b) (4)]. You may delete "dispense in tight container".

b. We note, we cannot consider [redacted (b) (4)]

c. Commit to revising the storage temperature from [redacted (b) (4)] To store at 20-25 C(deg F). See USP CRT.

d. Mr/Ms Abha Pant 1-609-720-5666.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.	X (b) (4)		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	
Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert		X	

labeling? Note: Chemist should confirm the data has been adequately supported.			
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	x		

NOTE TO THE CHEMIST: Please confirm the accuracy of my comment with regards to revising the storage statement to store at 20-25C (deg F). See USP CRT). (b) (4)

FOR THE RECORD:

1. MODEL LABELING

   Review based on the labeling of Lipitor (NDA 20-702/S-029 & 034; Merck & Co., Approved April 22, 2002). The firm submitted an excellent account of the RLD labeling.

2. PATENTS/EXCLUSIVITIES - See above

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
   Ranbaxy Laboratories Limited, Paonta Sahib, district Sirmour Himachal Pradesh, India.. page 3851-3856 red vol. 1.2. No outside firms are used. Manufactured for Ranbaxy Pharmaceutical in

Princeton NJ

4. CONTAINER/CLOSURE
   High density, white round opaque bottle. Page 7500 to 7509 vol A1.1 date Oct.9, 2002.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
   NDA - (b) (4)
   ANDA – (b) (4)
   A reivsed accelerated stability data storage conditions from 25 C +/- 2C/60% +/ - 5% RH to 40 deg +/- 2 deg/75 =_ 5% RH. Came in on Oct 9, 2002 vol 1.1A
   USP - none

6. DISPENSING STATEMENTS COMPARISON
   NDA – none
   ANDA – dispense in tight containers
   USP – Preserve in tight containers

7. Scoring:
   NDA - unscored
   ANDA - unscored
   USP -none

8. PACKAGING CONFIGURATIONS

   Product Line:
   RLD: The **innovator** markets their product in 10 mg (90s, 5000s, 100s u/d); 20 mg (90s, u/d 100s 10x10; 40 mg (90s), 80 mg (90s)

   ANDA: The **applicant** proposes to market their product in bottle of **10 mg, 20 mg, 40 mg and 80 mg** (b) (4) & (b) (4)). The (b) (4) count will be change to delete (b) (4) Page 7500 - 7509 volA. 1.1

9. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).7500 -7509 vol A 1.1 dated Oct 9, 2002

10. INACTIVE INGREDIENTS
    The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 6090 (Volume A1.14).

11. BIOAVAILABILITY/BIOEQUIVALENCE: Bio pending

Date of Review: 12/6/02 Date of Submission: Aug 19, 2002 & Oct 9, 2002

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cc:

ANDA: 76-477
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsnz\ranbaxy\ltrs&rev\76477TA.Lab Review

APayne 12/09/02
John J. Grace 12/13/2002

APPROVAL SUMMARY (mrnd)
REVIEW OF PROFESSIONAL LABELING #2
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number	76-477
Date of Submission	January 28, 2004
Applicant	Ranbaxy Labs
Drug Name	Atorvastatin Calcium Tablets
Strength(s)	10 mg, 20 mg , 40 mg and 80 mg (base)

Approval Summary

Container Labels		**Submitted**
10 mg, 20 mg	(b) (4)	Jan. 28, 2004 FPL vol A3.1
40 mg and 80 mg		Jan. 28, 2004 FPL vol A3.1
		Jan. 28, 2004 FPL vol A3.1
Package Insert Labeling	#FDA-3 rev. Jan 2004	Jan. 28, 2004 FPL vol A3.1

BASIS OF APPROVAL:

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
4681893	Sep. 24, 2009 PED. Mar. 24, 2010	U-161	method of treating hypercholesterolemia METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS IN A PATIENT	PIII	Same As
5273995	Dec 28, 2010 ped jun 28, 20011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	PIII	Same As
5686104	Nov 11, 20014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	PIV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		P-IV	Same As
6126971	Jan 19, 2013 ped July 19, 2013	—		P-IV	Same As

Exclusivity Data For NDA 20702			
Code/sup	**Expiration**	**Description**	***Labeling impact***
I-281	Dec 02,2002 PED Jun 02, 2003	adjunct to diet to increase hdl-c in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia (frederickson types iia and iib)	Same As
D-77	Apr 22, 2005	Addition of 20 mg and 40 mg daily optional starting doses with 40 mg intended for patients who require a large reduction in LDL-C (More than 45)	Same As
I-350/S-035	Oct 18, 2005 ped Apr 18, 2006	TREATMENT OF HETEROZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA IN ADOLESCENT BOYS AND GIRLS AT LEAST ONE YEAR POSTMENARCHAL, AGES 10 TO 17 YEARS, WITH A RECOMMENDED DOSING RANGE OF 10 TO 40MG ONCE DAILY	Same As

Reference Listed Drug

RLD on the 356(h) form	LIPITOR
NDA Number	20702
RLD established name	Atrovastatin Calcium Tablets USP
Firm	Merck & Co.,
Currently approved PI	S-035
AP Date	Approved 5/12/03

Note: Mr/Ms Abha Pant 1-609-720-5666. The chemist says that you are using (b) (4) form while the RLD has the trihydrate form. And that your product is not crystalline but amorphous. Please comment on the discrepancies and revise accordingly.
There are several pending supplements, firm will need to revise prior to the plan market date 2010.

REVIEW OF PROFESSIONAL LABELING CHECKLIST

Applicant's Established Name	Yes	No	N.A.
Different name than on acceptance to file letter?		x	
Is this product a USP item? If so, USP supplement in which verification was assured. **USP 24**		X	
Is this name different than that used in the Orange Book?		x	
If not USP, has the product name been proposed in the PF?			x
Error Prevention Analysis			
Has the firm proposed a proprietary name? If yes, complete this subsection.		x	
Do you find the name objectionable? List reasons in FTR, if so. Consider: Misleading? Sounds or looks like another name? USAN stem present? Prefix or Suffix present?			x
Has the name been forwarded to the Labeling and Nomenclature Committee? If so, what were the recommendations? If the name was unacceptable, has the firm been notified?			x
PACKAGING -See applicant's packaging configuration in FTR			
Is this a new packaging configuration, never been approved by an ANDA or NDA for this drug product? If yes, describe in FTR.	X (b) (4)		
Is this package size mismatched with the recommended dosage? If yes, the Poison Prevention Act may require a CRC. [see FTR]		X	
Does the package proposed have any safety and/or regulatory concerns?		X	
If IV product packaged in syringe, could there be adverse patient outcome if given by direct IV injection?			x
Conflict between the DOSAGE AND ADMINISTRATION and INDICATIONS sections and the packaging configuration?		X	
Is the strength and/or concentration of the product unsupported by the insert labeling?		X	
Is the color of the container (i.e. the color of the cap of a mydriatic ophthalmic) or cap incorrect?			x
Individual cartons required? Issues for FTR: Innovator individually cartoned? Light sensitive product which might require cartoning? Must the package insert accompany the product?		X	
Are there any other safety concerns?		X	
LABELING			
Is the name of the drug unclear in print or lacking in prominence? (Name should be the most prominent information on the label).		X	
Has applicant failed to clearly differentiate multiple product strengths?		x	
Is the corporate logo larger than 1/3 container label? (No regulation - see ASHP guidelines)		X	
Does RLD make special differentiation for this label? (i.e., Pediatric strength vs Adult; Oral Solution vs Concentrate, Warning Statements that might be in red for the NDA)		X	

Is the Manufactured by/Distributor statement incorrect or falsely inconsistent between labels and labeling? Is "Jointly Manufactured by...", statement needed?		X	
Failure to describe solid oral dosage form identifying markings in HOW SUPPLIED?		x	
Has the firm failed to adequately support compatibility or stability claims which appear in the insert labeling? Note: Chemist should confirm the data has been adequately supported.		X	
Scoring: Describe scoring configuration of RLD and applicant (p. #) in the FTR			
Is the scoring configuration different than the RLD?		x	
Has the firm failed to describe the scoring in the HOW SUPPLIED section?		x	
Inactive Ingredients: (FTR: List p. # in application where inactives are listed)			
Does the product contain alcohol? If so, has the accuracy of the statement been confirmed?		X	
Do any of the inactives differ in concentration for this route of administration?			X
Any adverse effects anticipated from inactives (i.e., benzyl alcohol in neonates)?			x
Is there a discrepancy in inactives between DESCRIPTION and the composition statement?		X	
Has the term "other ingredients" been used to protect a trade secret? If so, is claim supported?		x	
Failure to list the coloring agents if the composition statement lists e.g., Opacode, Opaspray?		x	
Failure to list gelatin, coloring agents, antimicrobials for capsules in DESCRIPTION?		X	
Failure to list dyes in imprinting inks? (Coloring agents e.g., iron oxides need not be listed)		X	
USP Issues: (FTR: List USP/NDA/ANDA dispensing/storage recommendations)			
Do container recommendations fail to meet or exceed USP/NDA recommendations? If so, are the recommendations supported and is the difference acceptable?[see FTR]		X	
Does USP have labeling recommendations? If any, does ANDA meet them?		X	
Is the product light sensitive? If so, is NDA and/or ANDA in a light resistant container?	X		
Failure of DESCRIPTION to meet USP Description and Solubility information? If so, USP information should be used. However, only include solvents appearing in innovator labeling.		X	
Bioequivalence Issues: (Compare bioequivalency values: insert to study. List Cmax, Tmax, T 1/2 and date study acceptable)			
Insert labeling references a food effect or a no-effect? If so, was a food study done?	X		
Has CLINICAL PHARMACOLOGY been modified? If so, briefly detail where/why.		X	
Patent/Exclusivity Issues: FTR: Check the Orange Book edition or cumulative supplement for verification of the latest Patent or Exclusivity. List expiration date for all patents, exclusivities, etc. or if none, please state.	x		

NOTE TO THE CHEMIST: The issue in the description section is whether we can approve a product where the RLD is a trihydrate product and a crystalline powder and the generic is (b) (4) and amorphous powder.

FOR THE RECORD:

1. MODEL LABELING

Review based on the labeling of Lipitor (NDA 20-702/S-035; Merck & Co., Approved 5/12/03).

2. PATENTS/EXCLUSIVITIES - See above

3. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM
Ranbaxy Laboratories Limited, Paonta Sahib, district Sirmour Himachal Pradesh, India.. page 3851-3856 red vol. 1.2. No outside firms are used. Manufactured for Ranbaxy Pharmaceutical in Princeton NJ

4. CONTAINER/CLOSURE
High density, white round opaque bottle. Page 7500 to 7509 vol A1.1 date Oct.9, 2002.

5. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
NDA - (b) (4)
ANDA – (b) (4)
A reivsed accelerated stability data storage conditions from 25 C +/- 2C/60% +/ - 5% RH to 40 deg +/- 2 deg/75 =_ 5% RH. Came in on Oct 9, 2002 vol 1.1A
USP - none

6. DISPENSING STATEMENTS COMPARISON
NDA – none
ANDA – dispense in tight containers
USP – Preserve in tight containers

7. Scoring:
NDA - unscored
ANDA - unscored
USP -none

8. PACKAGING CONFIGURATIONS

Product Line:
RLD: The **innovator** markets their product in 10 mg (90s, 5000s, 100s u/d); 20 mg (90s, u/d 100s 10x10; 40 mg (90s), 80 mg (90s)

ANDA: The **applicant** proposes to market their product in bottle of **10 mg, 20 mg, 40 mg and 80 mg** (b) (4) & (b) (4)). (b) (4) . Page 7500 - 7509 volA. 1.1

9. The tablet/capsule imprint(ings)/embossing(s)/ debossing(s) has/have been accurately described in the HOW SUPPLIED section as required by 21 CFR 206,et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule, effective 9/13/95).7500 -7509 vol A 1.1 dated Oct 9, 2002

10. INACTIVE INGREDIENTS
The listing of inactive ingredients in the DESCRIPTION section of the package insert appears to be consistent with the listing of inactive ingredients found in the statement of components and composition appearing on page 6090 (Volume A1.14).

11. BIOAVAILABILITY/BIOEQUIVALENCE: Bio pending

Date of Review: 2/3/04 Date of Submission: Jan 28, 2004

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cc:
ANDA: 76-477
DUP/DIVISION FILE
HFD-613/APayne/JGrace (no cc)
v:\firmsnz\ranbaxy\ltrs&rev\76477ap1.Lab

2/9/04
7/16/04

LABELING APPROVAL SUMMARY

REVIEW OF PROFESSIONAL LABELING
DIVISION OF LABELING AND PROGRAM SUPPORT
LABELING REVIEW BRANCH

ANDA Number: 76477 Dates of Submission: June 2, 2011, July 25, 2011

Applicant's Name: Ranbaxy Laboratories Limited

Established Name: Atorvastatin Calcium Tablets 10 mg , 20 mg, 40 mg, 80 mg

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REMS required? NO

MedGuides and/or PPIs (505-1(e))	☐ Yes	☒ No
Communication plan (505-1(e))	☐ Yes	☒ No
Elements to assure safe use (ETASU) (505-1(f)(3))	☐ Yes	☒ No
Implementation system if certain ETASU (505-1(f)(4))	☐ Yes	☒ No
Timetable for assessment (505-1(d))	☐ Yes	☒ No

ANDA REMS acceptable?
☐ Yes ☐ No ☒ n/a

APPROVAL SUMMARY (List the package size, strength(s), and date of submission for approval):

Do you have 12 Final Printed Labels and Labeling? Yes

Container Labels (all strengths: 90s and 500s): final printed labels acceptable in 7/25/2011 e-submission

Professional Package Insert Labeling: final printed labeling acceptable in 7/25/2011 e-submission

Patient Information Sheet: final printed labeling acceptable in 7/25/2011 e-submission

SPL: DLDE acceptable in 7/25/2011 e-submission

Revisions needed before full approval: No

Was this approval based upon a petition? No

What is the RLD on the 356(h) form: Lipitor

NDA Number: 20-702

NDA Drug Name: Lipitor

NDA Firm: Pfizer Inc.

Date of Approval of NDA Insert and supplement #: 20-702/S-056; approved 6/17/09.

Has this been verified by the MIS system for the NDA? Yes

Was this approval based upon an OGD labeling guidance? No

NOTE TO CHEMIST:

Chemistry issue: Ranbaxy's new API source is from (b) (4) and is now the trihydrate crystalline form. Ranbaxy also submitted another API source (Ranbaxy's crystalline form). Read #12 (History) for more information.

FOR THE RECORD:

1. MODEL LABELING This review was based on the labeling of the RLD, Lipitor, 20-702/S-056; approved 6/17/09: The PI is now in PLR format.

   7/25/2011 labeling amendment (AF): submitted because I was unable to open the AF dated 6/2/2011

   6/2/2011 AF: gratutitious amendment submitted for several changes:

   1. Gratuitous Amendment submitted on December 04, 2009. Through this amendment, Ranbaxy proposed multiple changes including:
      - Changes in the qualitative and quantitative composition of the drug product
      - Proposed Ohm Laboratories Inc.'s Terminal Road facility as the manufacturing site of the drug product
      - Proposed the use of Atorvastatin Calcium Crystalline API from (b) (4) in the drug product

      This gratuitous amendment also included revised labeling to reflect the changes proposed as mentioned above.
   2. Gratuitous Amendment submitted on November 12, 2010. Through this amendment, an additional source of the API – Ranbaxy Laboratories Limited was proposed. Ranbaxy's DMF for Atorvastatin Calcium, USP (DMF 24139) includes two manufacturing processes for the API – Process I and Process II, and both Process I and Process II were proposed in this gratuitous amendment.

2. PATENTS/EXCLUSIVITIES: [Patent amendment dated 6/15/10]

Patent No	Patent Expiration	Use Code	Description	How Filed	Labeling Impact
5273995	Dec 28, 2010 ped jun 28, 2011	u-162	METHOD OF USE TO INHIBIT CHOLESTEROL SYNTHESIS IN A HUMAN SUFFERING FROM HYPERCHOLESTEROLEMIA	PIV	Same As
5686104	Nov 11, 2014 ped May 11, 2015	U-213	METHOD OF INHIBITING CHOLESTEROL BIOSYNTHESIS AND TREATING HYPERCHOLESTEROLEMIA AND METHOD FOR TREATING HYPERLIPIDEMIA	PIV	Same As
5969156	Jul 8, 2016 ped Jan 8, 2017	—		PIV	Same As

6126971	Jan 19, 2013 ped July 19, 2013	—		PIV	Same As
RE 40667	Jun 28, 2011*PED	U-162	Method of use to inhibit choletestrol synthesis in a human suffering from hypercholesterolemia	PIV	Same As

Ranbaxy has "Settlement" with Pfizer to sell generic atorvastatin effective from November 30, 2011. From 6/3/2011 patent amendment:

With reference to the U.S. Patent numbers 5,273,995, RE 40,667, 5,686,104; 5,969,156 and 6,126,971 Ranbaxy has maintained a Paragraph IV certification against each of these Patents. Ranbaxy informed the Agency in a letter dated April 17, 2003 that it was sued by Pfizer on U.S. Patent numbers 4,681,893 and 5,273,995 at the U.S. District Court for the District of Delaware on February 21, 2003, in response to Ranbaxy's P-IV certifications against these patents filed in connection with this ANDA (03-cv-0209). The case was appealed to the Court of Appeals for the Federal Circuit in December 2006 (06-1179). Pfizer and Ranbaxy settled their litigation on June 17, 2008 (the "Settlement"). As part of the Settlement, and amendments thereto, Pfizer has granted Ranbaxy and its Affiliates nonexclusive, non-transferable, non-sublicenseable, royalty-free and fully paid-up licenses, under the "Lipitor Patents" (as defined in Attachment 2) to make, have made, use, offer to sell, sell and import Atorvastatin Generic Tablets solely in the United States. "Lipitor Patents" includes, among others, U.S. Patent numbers 5,273,995, RE 40,667, 5,686,104; 5,969,156; and 6,126,971 effective from November 30, 2011 or earlier under certain circumstances, to make, have made, use, offer to sell, sell and/or import Ranbaxy's generic Atovastatin Calcium tablet product pursuant to and under such Pfizer patents (certain key definitions and clauses in the Settlement that are relevant to the licenses and Ranbaxy's ANDA product have been provided in the attached file). Provided in **Attachment 2** are excerpts from the settlement agreement.

3. INACTIVE INGREDIENTS

   The description of the inactive ingredients in the insert labeling appears accurate according to the composition statement. [Chemist Review #6.] Atorvastatin Calcium Tablets contain atorvastatin and the following inactive ingredients: calcium carbonate; candelilla wax, FCC; croscarmellose sodium; hydroxypropyl cellulose; hypromellose; lactose monohydrate; magnesium stearate; microcrystalline cellulose; polyethylene glycol; polysorbate 80; simethicone emulsion; talc, and titanium dioxide. This is Ranbaxy's new formulation submitted in the chemistry amendment dated 12/4/2009.

4. MANUFACTURING FACILITY OF FINISHED DOSAGE FORM

   The original manufacturer was:

   Ranbaxy Laboratories Limited
   Paonta Sahib
   District Sirmour
   Himachal Pradesh – 173 025
   India

   The current manufacturer per chemistry amendment dated 12/4/2009:

   The test product batches have been manufactured in commercial packs at the following site:

   Ohm Laboratories, Inc.
   14 Terminal Road
   New Brunswick, NJ 08901

5. FINISHED DOSAGE FORM: The tablet debossing has been accurately described in the HOW SUPPLIED section as required by 21 CFR 206, et al. (Imprinting of Solid Oral Dosage Form Products for Human Use; Final Rule,effective 9/13/95). [Chemist review #6]

NDA: LIPITOR® (atorvastatin calcium) is supplied as white, elliptical, film-coated tablets of atorvastatin calcium containing 10, 20, 40 and 80 mg atorvastatin.
10 mg tablets: coded "PD 155" on one side and "10" on the other.
Bottles of 90 and 5000 and 10 x 10 unit dose blisters
20 mg tablets: coded "PD 156" on one side and "20" on the other. Bottles of 90 and 5000 and 10 x 10 unit dose blisters.
40 mg tablets: coded "PD 157" on one side and "40" on the other. Bottles of 90 and 500
80 mg tablets: coded "PD 158" on one side and "80" on the other. Bottles of 90 and 500

ANDA:
10 mg tablets: white to off-white, elliptica (b) (4) tablets debossed with "RX12" on one side and plain on the other side.

20 mg tablets: white to off-white, elliptica (b) (4) tablets debossed with "RX828" on one side and plain on the other side.

40 mg tablets white to off-white, elliptica (b) (4) tablets debossed with "RX829" on one side and plain on the other side.

80 mg tablets white to off-white, elliptical (b) (4) tablets debossed with "RX830" on one side and plain on the other side.

6. CONTAINER/CLOSURE: [Chemist review #6]

10 mg: 90s	(b) (4)	500s	(b) (4)
20 mg: 90s		500s	
40 mg: 90s		500s	
80 mg: 90s		500s	

7. PACKAGING

RLD: 90s, 100s (10 X 10) Unit Dose, or 500s and 5000s
ANDA: All strengths: bottles of 90 and 500

8. STORAGE TEMPERATURE RECOMMENDATIONS COMPARISON
RLD: Store at controlled room temperature 20 to 25°C (68 to 77°F) [see USP]. Dispense in tight containers (USP)

ANDA: Store at 20 to 25°C (68 to 77°F) [see USP Controlled Room Temperature]. Dispense in tight containers.

USP – The DS is compendial
- **PACKAGING AND STORAGE:** Preserve in well-closed containers, and store at room temperature.

9. BIOAVAILABILITY/BIOEQUIVALENCE: Bio is pending as of July 27, 2011

10. PLR font size: the insert is size 6 font and the PPI is size 10 font

11. SPL: DLDE acceptable in July 25, 2011 e-submission. Ranbaxy's tablet sizes for all strengths are the exact same size as the RLD's.

12. History of this application

This is a very old application but it has extensive compliance issues associated with the original drug manufacturing site: Ranbaxy Laboratories Limited, Paonta Sahib. Review of this ANDA ceased because of the Paonta Sahib compliance issues.

In December 2009, Ranbaxy submitted a major amendment for the following changes: [from May 11, 2011 OCC Memo entered in DAARTS by L.Sears on 6/2/2011]

Drug Substance:
- Change in the form of the drug substance Atorvastatin Calcium from amorphous to crystalline
- Change in drug substance manufacturer from Ranbaxy Laboratories Ltd. to (b) (4)
- Revisions to drug substance specifications and test methods

Drug Product:
- Addition of Ohm Laboratories Inc., New Brunswick, NJ. as new drug product manufacturing site
- Addition of Ohm Laboratories Inc .. Terminal Road and Livingston Avenue, New Brunswick, NJ. as new analytical testing sites
- Qualitative and quantitative changes to the drug product formulation
- Changes to the drug product manufacturing process
- Revisions to the drug product specifications and test methods
- Change in the container closure system.

This was accompanied by new bioequivalence studies.
In November 2010. Ranbaxy submitted another major amendment for the following changes:
- Additional drug substance source: DMF 24139, Atorvastatin Calcium, USP (crystalline), Ranbaxy Laboratories Ltd., VilI. Toansa. Punjab. India
- Minor changes to the drug product manufacturing process using the new Ranbaxy drug substance.

These amendments constitute a new full review of the main elements of the ANDA, including CMC, bio and labeling. The Agency determined that OGD should review this ANDA because of the major amendments, Ranbaxy's "Settlement" with Pfizer, and Ranbaxy's 180 days exclusivity.

Because of compliance issues, I did not review the earlier labeling amendments and original submission. I reviewed the 6/2/2011 amendment because this piece really addressed the drug product formulation change and drug product manufacturing site change.

13. Lipitor (atorvastatin) is NOT on the MEDWATCH website.

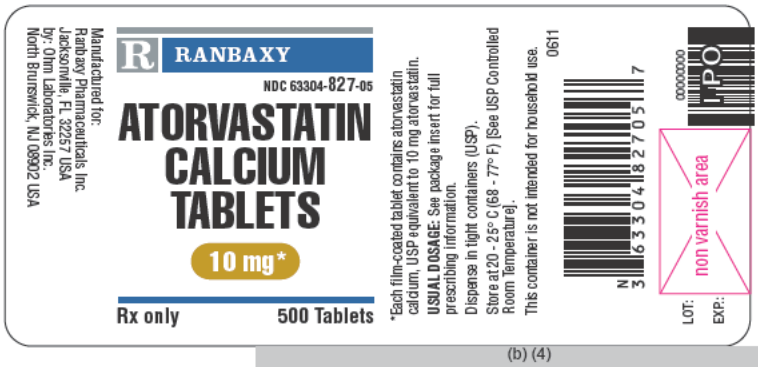
Date of Review: July 27, 2011 **Dates of Submission:** June 2, 2011, and July 25, 2011

Primary Reviewer: Thuyanh Vu **Date:**

Team Leader: John Grace **Date:**

(b) (4)

Size: 3.88" x 1.77" (98.5 x 45 mm)
Track: (b) (4)



(b) (4)

Size: 3.88" x 1.77" (98.5 x 45 mm)
Track: (b) (4)

(b) (4)

Size: 3.88" x 1.77" (98.5 x 45 mm)
Track (b) (4)

(b) (4)

Size: 5.12" x 2.36" (130 x 60 mm)
Track: (b) (4)

(b) (4)

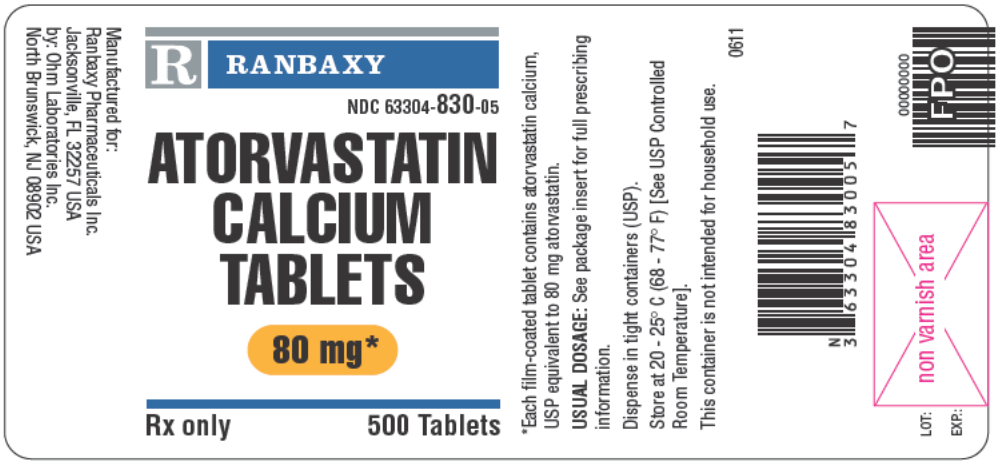
Size: 3.88" x 1.77" (98.5 x 45 mm)
Track: (b) (4)

(b) (4)

Size: 5.12" x 2.36" (130 x 60 mm)
Track: (b) (4)

(b) (4)

Size: 3.88" x 1.77" (98.5 x 45 mm)
Track: (b) (4)



(b) (4)

Size: 5.12" x 2.36" (130 x 60 mm)
Track: (b) (4)

ATORVASTATIN CALCIUM TABLETS

FPO 0000000

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use atorvastatin calcium tablets safely and effectively. See full prescribing information for atorvastatin calcium tablets.

Atorvastatin calcium tablets for oral administration

Initial U.S. Approval: 1996

INDICATIONS AND USAGE

Atorvastatin calcium tablets are an inhibitor of HMG-CoA reductase (statin) indicated as an adjunct herapy to diet to:

- Reduce he risk of MI, st oke, revascularization p ocedures, and angina in patients wi hout CHD, but wi h multiple risk factors (1.1).
- Reduce he risk of MI and st oke in patients wi h type 2 diabetes wi hout CHD, but wi h multiple risk factors (1.1).
- Reduce the risk of non-fatal MI, fatal and non-fatal st oke, revascularization p ocedures, hospitalization for CHF, and angina in patients wi h CHD (1.1).
- Reduce elevated total-C, LDL-C, apo B, and TG levels and increase HDL-C in adult patients wi h primary hyperlipidemia (hete ozygous familial and nonfamilial) and mixed dyslipidemia (1.2).
- Reduce elevated TG in patients with hypertriglyceridemia and primary dysbetalipop oteinemia (1.2).
- Reduce total-C and LDL-C in patients with homozygous familial hypercholeste olemia (HoFH) (1.2).
- Reduce elevated total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, wi h hete ozygous familial hypercholeste olemia after failing an adequate trial of diet herapy (1.2).

Limitations of Use

Atorvastatin calcium tablets have not been studied in *Fredrickson* Types I and V dyslipidemias.

DOSAGE AND ADMINISTRATION

Dose range: 10 to 80 mg once daily (2.1).

Recommended start dose: 10 or 20 mg once daily (2.1).

Patients requiring large LDL-C reduction (> 45%) may start at 40 mg once daily (2.1).

Pediatric starting dose: 10 mg once daily; maximum recommended dose: 20 mg once daily (2.2).

DOSAGE FORMS AND STRENGTHS

10, 20, 40, and 80 mg tablets (3).

CONTRAINDICATIONS

Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels (4.1).

Women who are pregnant or may become pregnant (4.3).

Nursing mothers (4.4).

Hypersensitivity to any component of his medication (4.2).

WARNINGS AND PRECAUTIONS

Skeletal muscle effects (e.g., myopathy and habdomyolysis): Risks increase when higher doses are used concomitantly wi h cyclosporine, fibrates, and st ong CYP3A4 inhibitors (e.g., clari h omycin, itraconazole, HIV p otease inhibitors). Predisposing factors include advanced age (> 65), uncont olled hypo hy oidism, and renal impairment. Rare cases of habdomyolysis wi h acute renal failure secondary to myoglobinuria have been reported. In cases of myopa hy or habdomyolysis, therapy should be temporarily withheld or discontinued (5.1).

Liver enzyme abnormalities and monitoring: Persistent elevations in hepatic transaminases can occur. Monitor liver enzymes before and during treatment (5.2).

A higher incidence of hemor hagic st oke was seen in patients without CHD but wi h st oke or TIA wi hin he previous 6 mon hs in he atorvastatin calcium 80 mg g oup vs. placebo (5.5).

ADVERSE REACTIONS

The most commonly reported adverse reactions (incidence ≥ 2%) in patients treated with atorvastatin calcium in placebo-cont olled trials regardless of causality were: nasopharyngitis, arthralgia, diar hea, pain in extremity, and urinary tract infection (6.1).

To report SUSPECTED ADVERSE REACTIONS, contact Ranbaxy Pharmaceuticals Inc. at (1-888-Ranbaxy(726-2299)) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

DRUG INTERACTIONS

Drug Interactions Associated wi h Increased Risk of Myopa hy/Rhabdomyolysis (2.6, 5.1, 7, 12.3)

Interacting Agents	Prescribing Recommendations
Cyclosporine	Do not exceed 10 mg atorvastatin daily
Clari h omycin, itraconazole, HIV p otease inhibitors (ritonavir plus saquinavir or lopinavir plus ritonavir)	Caution when exceeding doses > 20 mg atorvastatin daily. The lowest dose necessary should be used.

- Digoxin: Patients should be monitored app opriately (7.5).
- Oral Contraceptives: Values for nore hind one and e hinyl estradiol may be increased (7.6).
- Rifampin should be simultaneously co-administered with atorvastatin calcium (7.4).

USE IN SPECIFIC POPULATIONS

- Hepatic impairment: Plasma concentrations markedly increased in patients wi h ch onic alcoholic liver disease (12.3).

See 17 for PATIENT COUNSELING INFORMATION

Revised: [05/2011]

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted f om he full prescribing information are not listed

FULL PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

Therapy wi h lipid-altering agents should be only one component of multiple risk factor intervention in individuals at significantly increased risk for a he oscle otic vascular disease due to hypercholeste olemia. Drug herapy is recommended as an adjunct to diet when he response to a diet restricted in saturated fat and choleste ol and o her nonpharmacologic measures alone has been inadequate. In patients wi h CHD or multiple risk factors for CHD, atorvastatin calcium tablets can be started simultaneously wi h diet.

1.1 Prevention of Cardiovascular Disease

In adult patients wi hout clinically evident co onary heart disease, but wi h multiple risk factors for co onary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early co onary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce he risk of myocardial infarction
- Reduce he risk of st oke
- Reduce he risk for revascularization p ocedures and angina

In patients with type 2 diabetes, and wi hout clinically evident co onary heart disease, but wi h multiple risk factors for co onary heart disease such as retinopa hy, albuminuria, smoking, or hypertension, atorvastatin calcium tablets are indicated to:

- Reduce he risk of myocardial infarction
- Reduce he risk of st oke

In patients wi h clinically evident co onary heart disease, atorvastatin calcium tablets are indicated to:

- Reduce he risk of non-fatal myocardial infarction
- Reduce he risk of fatal and non-fatal st oke
- Reduce he risk for revascularization p ocedures
- Reduce he risk of hospitalization for CHF
- Reduce he risk of angina

1.2 Hyperlipidemia

Atorvastatin calcium tablets are indicated:

- As an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients wi h primary hypercholeste olemia (hete ozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb);
- As an adjunct to diet for he treatment of patients wi h elevated serum TG levels *(Fredrickson* Type IV);
- For he treatment of patients wi h primary dysbetalipop oteinemia *(Fredrickson* Type III) who do not respond adequately to diet;
- To reduce total-C and LDL-C in patients wi h homozygous familial hypercholeste olemia as an adjunct to o her lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable;
- As an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with hete ozygous familial hypercholeste olemia if after an adequate trial of diet herapy the following findings are present:

  a. LDL-C remains ≥ 190 mg/dL or

  b. LDL-C remains ≥ 160 mg/dL and:

  - here is a positive family history of premature cardiovascular disease or
  - two or more other CVD risk factors are present in the pediatric patient

1.3 Limitations of Use

Atorvastatin calcium tablets have not been studied in conditions where the major lipop otein abnormality is elevation of chylomic ons *(Fredrickson* Types I and V).

2 DOSAGE AND ADMINISTRATION

2.1 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

The recommended starting dose of atorvastatin calcium tablets is 10 or 20 mg once daily. Patients who require a large reduction in LDL-C (more than 45%) may be started at 40 mg once daily. The dosage range of atorvastatin calcium tablets is 10 to 80 mg once daily. Atorvastatin calcium tablets can be administered as a single dose at any time of he day, wi h or without food. The starting dose and maintenance doses of atorvastatin calcium tablets should be individualized according to patient characteristics such as goal of herapy and response (see current *NCEP Guidelines*). After initiation and/or upon titration of atorvastatin calcium tablets, lipid levels should be analyzed wi hin 2 to 4 weeks and dosage adjusted accordingly.

2.2 Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age)

The recommended starting dose of atorvastatin calcium tablets is 10 mg/day; the maximum recommended dose is 20 mg/day (doses greater than 20 mg have not been studied in his patient population). Doses should be individualized according to the recommended goal of herapy [see current *NCEP Pediatric Panel Guidelines*, *Clinical Pharmacology (12)*, and *Indications and Usage (1.2)*]. Adjustments should be made at intervals of 4 weeks or more.

2.3 Homozygous Familial Hypercholesterolemia

The dosage of atorvastatin calcium tablets in patients wi h homozygous FH is 10 to 80 mg daily. Atorvastatin calcium tablets should be used as an adjunct to o her lipid-lowering treatments (e.g., LDL apheresis) in hese patients or if such treatments are unavailable.

2.4 Concomitant Lipid-Lowering Therapy

Atorvastatin calcium tablets may be used wi h bile acid resins. The combination of HMG-CoA reductase inhibitors (statins) and fibrates should generally be used with caution [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

2.5 Dosage in Patients With Renal Impairment

Renal disease does not affect he plasma concentrations nor LDL-C reduction of atorvastatin calcium tablets; thus, dosage adjustment in patients wi h renal dysfunction is not necessary [see *Warnings and Precautions, Skeletal Muscle (5.1), Clinical Pharmacology, Pharmacokinetics (12.3)*].

2.6 Dosage in Patients Taking Cyclosporine, Clarithromycin, Itraconazole, or a Combination of Ritonavir plus Saquinavir or Lopinavir plus Ritonavir

In patients taking cyclosporine, herapy should be limited to atorvastatin calcium tablets 10 mg once daily. In patients taking clari h omycin, itraconazole, or in patients wi h HIV taking a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, for doses of atorvastatin calcium tablets exceeding 20 mg, app opriate clinical assessment is recommended to ensure that he lowest dose necessary of atorvastatin calcium tablets is employed [see *Warnings and Precautions, Skeletal Muscle (5.1), Drug Interactions (7)*].

3 DOSAGE FORMS AND STRENGTHS

White, elliptical, film-coated tablets containing 10, 20, 40, and 80 mg atorvastatin calcium.

4 CONTRAINDICATIONS

4.1 Active liver disease, which may include unexplained persistent elevations in hepatic transaminase levels

4.2 Hypersensitivity to any component of his medication

4.3 Pregnancy

Women who are pregnant or may become pregnant. Atorvastatin calcium may cause fetal harm when administered to a pregnant woman. Serum choleste ol and triglycerides increase during normal pregnancy, and choleste ol or choleste ol derivatives are essential for fetal development. A he oscle osis is a ch onic p ocess and discontinuation of lipid-lowering drugs during pregnancy should have little impact on he outcome of long-term herapy of primary hypercholeste olemia. There are no adequate and well-cont olled studies of atorvastatin calcium use during pregnancy; however in rare reports, congenital anomalies were observed following intrauterine exposure to statins. In rat and rabbit animal rep oduction studies, atorvastatin revealed no evidence of teratogenicity. ATORVASTATIN CALCIUM SHOULD BE ADMINISTERED TO WOMEN OF CHILDBEARING AGE ONLY WHEN SUCH PATIENTS ARE HIGHLY UNLIKELY TO CONCEIVE AND HAVE BEEN INFORMED OF THE POTENTIAL HAZARDS. If he patient becomes pregnant while taking his drug, atorvastatin calcium should be discontinued immediately and the patient apprised of he potentia hazard to he fetus [see *Use in Specific Populations (8.1)*].

4.4 Nursing mo hers

It is not known whether atorvastatin is excreted into human milk; however a small amount of another drug in his class does pass into breast milk. Because statins have he potential for serious adverse reactions in nursing infants, women who require atorvastatin calcium treatment should not breastfeed their infants [see *Use in Specific Populations (8.3)*].

5 WARNINGS AND PRECAUTIONS

5.1 Skeletal Muscle

Rare cases of rhabdomyolysis with acute renal failure secondary to myoglobinuria have been reported with atorvastatin calcium and with other drugs in this class. A history of renal impairment may be a risk factor for the development of habdomyolysis. Such patients merit closer monitoring for skeletal muscle effects.

Atorvastatin, like o her statins, occasionally causes myopa hy, defined as muscle aches or muscle weakness in conjunction wi h increases in creatine phosphokinase (CPK) values > 10 times ULN. The concomitant use of higher doses of atorvastatin wi h certain drugs such as cyclosporine and st ong CYP3A4 inhibitors (e.g., clarith omycin, itraconazole, and HIV p otease inhibitors) increases he risk of myopa hy/ habdomyolysis.

Myopathy should be considered in any patient with diffuse myalgias, muscle tenderness or weakness, and/or marked elevation of CPK. Patients should be advised to report p omptly unexplained muscle pain, tende ness, or weakness, particularly if accompanied by malaise or fever. Atorvastatin calcium therapy should be discontinued if markedly elevated CPK levels occur or myopa hy is diagnosed or suspected.

The risk of myopa hy during treatment wi h drugs in this class is increased wi h concurrent administration of cyclosporine, fibric acid derivatives, ery h omycin, clari h omycin, combination of ritonavir plus saquinavir or lopinavir plus ritonavir, niacin, or azole antifungals. Physicians considering combined herapy wi h atorvastatin calcium and fibric acid derivatives, ery h omycin, clari h omycin, a combination of ritonavir plus saquinavir or lopinavir plus ritonavir, immunosuppressive drugs, azole antifungals, or lipid-modifying doses of niacin should carefully weigh the potential benefits and risks and should carefully monitor patients for any signs or symptoms of muscle pain, tende ness, or weakness, particularly during he initial months of therapy and during any periods of upward dosage titration of either drug. Lower starting and maintenance doses of atorvastatin should be considered when taken concomitantly wi h he aforementioned drugs (see *Drug Interactions (7)*). Periodic creatine phosphokinase (CPK) determinations may be considered in such situations, but here is no assurance hat such monitoring will prevent the occurrence of severe myopa hy.

Prescribing recommendations for interacting agents are summarized in Table 1 [see also *Dosage and Administration (2.6), Drug Interactions (7), Clinical Pharmacology (12.3)*].

Table 1. Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

Interacting Agents	Prescribing Recommendations
Cyclosporine	Do not exceed 10 mg atorvastatin daily
Clari h omycin, itraconazole, HIV p otease inhibitors (ritonavir plus saquinavir or lopinavir plus ritonavir)	Caution when exceeding doses > 20 mg atorvastatin daily. The lowest dose necessary should be used.

Atorvastatin calcium therapy should be temporarily withheld or discontinued in any patient with an acute, serious condition suggestive of a myopathy or having a risk factor predisposing to the development of renal failure secondary to rhabdomyolysis (e.g., severe acute infection, hypotension, major surgery, trauma, severe metabolic, endocrine and electrolyte disorders, and uncontrolled seizures).

5.2 Liver Dysfunction

Statins, like some o her lipid-lowering therapies, have been associated wi h biochemical abnormalities of liver function. **Persistent elevations (> 3 times the upper limit of normal [ULN] occurring on 2 or more occasions) in serum transaminases occurred in 0.7% of patients who received atorvastatin calcium in clinical trials. The incidence of these abnormalities was 0.2%, 0.2%, 0.6%, and 2.3% for 10, 20, 40, and 80 mg, respectively.**

One patient in clinical trials developed jaundice. Increases in liver function tests (LFT) in other patients were not associated w th jaundice or o her clinical signs or symptoms. Upon dose reduction, drug interruption, or discontinuation, transaminase levels retu ned to or near pretreatment levels wi hout sequelae. Eighteen of 30 patients wi h persistent LFT elevations continued treatment with a reduced dose of atorvastatin calcium.

It is recommended that liver function tests be performed prior to and at 12 weeks following both the initiation of herapy and any elevation of dose, and periodically (e.g., semiannually) thereafter. Liver enzyme changes generally occur in he first 3 mon hs of treatment wi h atorvastatin calcium. Patients who develop increased transaminase levels should be monitored until he abnormalities resolve. Should an increase in ALT or AST of > 3 times ULN persist, reduction of dose or wi hdrawal of atorvastatin calcium is recommended.

Atorvastatin calcium should be used with caution in patients who consume substantial quantities of alcohol and/or have a history of liver disease. Active liver disease or unexplained persistent transaminase elevations are contraindications to he use of atorvastatin calcium [see *Contraindications (4.1)*].

5.3 Endocrine Function

Statins interfere wi h choleste ol syn hesis and theoretically might blunt adrenal and/or gonadal ste oid p oduction. Clinical studies have shown that atorvastatin calcium does not reduce basal plasma cortisol concentration or impair adrenal reserve. The effects of statins on male fertility have not been studied in adequate numbers of patients. The effects, if any, on the pituitary-gonadal axis in premenopausal women are unknown. Caution should be exercised if a statin is administered concomitantly with drugs hat may decrease the levels or activity of endogenous ste oid hormones, such as ketoconazole, spi onolactone, and cimetidine.

5.4 CNS Toxicity

Brain hemor hage was seen in a female dog treated for 3 mon hs at 120 mg/kg/day. Brain hemor hage and optic nerve vacuolation were seen in ano her female dog that was sacrificed in moribund condition after 11 weeks of escalating doses up to 280 mg/kg/day. The 120 mg/kg dose resulted in a systemic exposure app oximately 16 times he human plasma area-under-he-curve (AUC, 0 to 24 hours) based on he maximum human dose of 80 mg/day. A single tonic convulsion was seen in each of 2 male dogs (one treated at 10 mg/kg/day and one at 120 mg/kg/day) in a 2-year study. No CNS lesions have been observed in mice after ch onic treatment for up to 2 years at doses up to 400 mg/kg/day or in rats at doses up to 100 mg/kg/day. These doses were 6 to 11 times (mouse) and 8 to 16 times (rat) he human AUC (0 to 24) based on he maximum recommended human dose of 80 mg/day.

CNS vascular lesions, characterized by perivascular hemor hages, edema, and mononuclear cell infiltration of perivascular spaces, have been observed in dogs treated with o her members of his class. A chemically similar drug in this class p oduced optic nerve degeneration (Wallerian degeneration of retinogeniculate fibers) in clinically normal dogs in a dose-dependent fashion at a dose hat p oduced plasma drug levels about 30 times higher han he mean drug level in humans taking the highest recommended dose.

5.5 Use in Patients with Recent Stroke or TIA

In a post-hoc analysis of the St oke Prevention by Aggressive Reduction in Choleste ol Levels (SPARCL) study where atorvastatin calcium 80 mg vs. placebo was administered in 4,731 subjects wi hout CHD who had a st oke or TIA within the preceding 6 mon hs, a higher incidence of hemor hagic st oke was seen in he atorvastatin calcium 80 mg g oup compared to placebo (55, 2.3% atorvastatin vs. 33, 1.4% placebo; HR: 1.68, 95% CI: 1.09, 2.59; p = 0.0168). The incidence of fatal hemor hagic st oke was similar ac oss treatment g oups (17 vs. 18 for the atorvastatin and placebo g oups, respectively). The incidence of nonfatal hemor hagic st oke was significantly higher in he atorvastatin g oup (38, 1.6%) as compared to he placebo g oup (16, 0.7%). Some baseline characteristics, including hemor hagic and lacunar st oke on study entry, were associated with a higher incidence of hemor hagic st oke in he atorvastatin g oup [see *Adverse Reactions (6.1)*].

6 ADVERSE REACTIONS

The following serious adverse reactions are discussed in greater detail in o her sections of he label:

Rhabdomyolysis and myopa hy [see *Warnings and Precautions (5.1)*]

Liver enzyme abnormalities [see *Warnings and Precautions (5.2)*]

6.1 Clinical Trial Adverse Experiences

Because clinical trials are conducted under widely varying conditions, he adverse reaction rates observed in the clinical studies of a drug cannot be directly compared to rates in he clinical trials of ano her drug and may not reflect he rates observed in clinical practice.

In he atorvastatin calcium placebo-cont olled clinical trial database of 16,066 patients (8755 atorvastatin calcium vs. 7311 placebo; age range 10 to 93 years, 39% women, 91% Caucasians, 3% Blacks, 2% Asians, 4% o her) wi h a median treatment duration of 53 weeks, 9.7% of patients on atorvastatin calcium and 9.5% of he patients on placebo discontinued due to adverse reactions regardless of causality. The five most common adverse reactions in patients treated wi h atorvastatin calcium that led to treatment discontinuation and occurred at a rate greater han placebo were: myalgia (0.7%), diar hea (0.5%), nausea (0.4%), alanine aminotransferase increase (0.4%), and hepatic enzyme increase (0.4%).

The most commonly reported adverse reactions (incidence ≥ 2% and greater han placebo) regardless of causality, in patients treated wi h atorvastatin calcium in placebo cont olled trials (n = 8755) were: nasopharyngitis (8.3%), ar hralgia (6.9%), diar hea (6.8%), pain in extremity (6%), and urinary tract infection (5.7%).

Table 2 summarizes he frequency of clinical adverse reactions, regardless of causality, reported in ≥ 2% and at a rate greater han placebo in patients treated wi h atorvastatin calcium (n = 8755), f om seventeen placebo-cont olled trials.

Table 2. Clinical adverse reactions occurring in ≥ 2% in patents treated with any dose of atorvastatin calcium and at an incidence greater than placebo regardless of causality (% of patients).

Adverse Reaction*	Any dose N = 8755	10 mg N = 3908	20 mg N = 188	40 mg N = 604	80 mg N = 4055	Placebo N = 7311
Nasopharyngitis	8 3	12 9	5 3	7	4 2	8 2
Arthralgia	6 9	8 9	11.7	10 6	4 3	6 5
Diar hea	6 8	7 3	6.4	14 1	5 2	6 3
Pain in extremity	6	8 5	3 7	9 3	3 1	5 9
Urinary tract infection	5 7	6 9	6.4	8	4 1	5 6
Dyspepsia	4 7	5 9	3 2	6	3 3	4 3
Nausea	4	3 7	3 7	7 1	3 8	3 5
Musculoskeletal pain	3 8	5 2	3 2	5 1	2 3	3 6
Muscle Spasms	3 6	4 6	4 8	5 1	2.4	3
Myalgia	3 5	3 6	5 9	8.4	2 7	3 1
Insomnia	3	2 8	1 1	5 3	2 8	2 9
Pharyngolaryngeal pain	2 3	3 9	1 6	2 8	0 7	2 1

Adverse Reaction ≥ 2% in any dose greater han placebo

O her adverse reactions reported in placebo-cont olled studies include:

Body as a whole: malaise, pyrexia; *Digestive system:* abdominal discomfort, eructation, flatulence, hepatitis, cholestasis; *Musculoskeletal system*: musculoskeletal pain, muscle fatigue, neck pain, joint swelling; *Metabolic and nutritional system*: transaminases increase, liver function test abnormal, blood alkaline phosphatase increase, creatine phosphokinase increase, hyperglycemia; *Nervous system*: nightmare; *Respiratory system:* epistaxis; *Skin and appendages*: urticaria; *Special senses*: vision blurred, tinnitus; *Urogenital system:* white blood cells urine positive.

Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT)

In ASCOT [see *Clinical Studies (14.1)*] involving 10,305 participants (age range 40 to 80 years, 19% women; 94.6% Caucasians, 2.6% Africans, 1.5% South Asians, 1.3% mixed/o her) treated wi h atorvastatin calcium 10 mg daily (n = 5,168) or placebo (n = 5,137), the safety and tolerability p ofile of he g oup treated wi h atorvastatin calcium was comparable to that of he g oup treated wi h placebo during a median of 3.3 years of follow-up.

Collaborative Atorvastatin Diabetes Study (CARDS)

In CARDS [see *Clinical Studies (14.1)*] involving 2,838 subjects (age range 39 to 77 years, 32% women; 94.3% Caucasians, 2.4% Sou h Asians, 2.3% Afro-Caribbean, 1% other) wi h type 2 diabetes treated wi h atorvastatin calcium 10 mg daily (n = 1,428) or placebo (n = 1,410), here was no difference in the overall frequency of adverse reactions or serious adverse reactions between he treatment g oups during a median follow-up of 3.9 years. No cases of habdomyolysis were reported.

Treating to New Targets Study (TNT)

In TNT [see *Clinical Studies (14.1)*] involving 10,001 subjects (age range 29 to 78 years, 19% women; 94.1% Caucasians, 2.9% Blacks, 1% Asians, 2% o her) wi h clinically evident CHD treated wi h atorvastatin calcium 10 mg daily (n = 5006) or atorvastatin calcium 80 mg daily (n = 4995), there were more serious adverse reactions and discontinuations due to adverse reactions in he high-dose atorvastatin g oup (92, 1.8%; 497, 9.9%, respectively) as compared to he low-dose g oup (69, 1.4%; 404, 8.1%, respectively) during a median follow-up of 4.9 years. Persistent transaminase elevations (≥ 3 x ULN twice within 4 to 10 days) occurred in 62 (1.3%) individuals wi h atorvastatin 80 mg and in nine (0.2%) individuals wi h atorvastatin 10 mg. Elevations of CK (≥ 10 x ULN) were low overall, but were higher in the high-dose atorvastatin treatment g oup (13, 0.3%) compared to he low-dose atorvastatin g oup (6, 0.1%).

Incremental Decrease in Endpoints through Aggressive Lipid Lowering Study (IDEAL)

In IDEAL [see *Clinical Studies (14.1)*] involving 8,888 subjects (age range 26 to 80 years, 19% women; 99.3% Caucasians, 0.4% Asians, 0.3% Blacks, 0.04% o her) treated wi h atorvastatin calcium 80 mg/day (n = 4439) or simvastatin 20 to 40 mg daily (n = 4449), here was no difference in he overall frequency of adverse reactions or serious adverse reactions between he treatment g oups during a median follow-up of 4.8 years.

Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL)

In SPARCL involving 4731 subjects (age range 21 to 92 years, 40% women; 93.3% Caucasians, 3% Blacks, 0.6% Asians, 3.1% other) wi hout clinically evident CHD but wi h a st oke or transient ischemic attack (TIA) wi hin he previous 6 mon hs treated wi h atorvastatin calcium 80 mg (n = 2365) or placebo (n = 2366) for a median follow-up of 4.9 years, here was a higher incidence of persistent hepatic transaminase elevations (≥ 3 x ULN twice wi hin 4 to 10 days) in he atorvastatin g oup (0.9%) compared to placebo (0.1%). Elevations of CK (> 10 x ULN) were rare, but were higher in he atorvastatin g oup (0.1%) compared to placebo (0%). Diabetes was reported as an adverse reaction in 144 subjects (6.1%) in he atorvastatin g oup and 89 subjects (3.8%) in he placebo group [see *Warnings and Precautions (5.5)*].

In a post-hoc analysis, atorvastatin calcium 80 mg reduced he incidence of ischemic st oke (218/2365, 9.2% vs. 274/2366, 11.6%) and increased he incidence of hemor hagic st oke (55/2365, 2.3% vs. 33/2366, 1.4%) compared to placebo. The incidence of fatal hemor hagic st oke was similar between g oups (17 atorvastatin calcium vs. 18 placebo). The incidence of non-fatal hemor hagic st okes was significantly greater in he atorvastatin g oup (38 non-fatal hemor hagic st okes) as compared to he placebo g oup (16 non-fatal hemor hagic st okes). Subjects who entered he study wi h a hemor hagic st oke appeared to be at increased risk for hemor hagic st oke [7 (16%) atorvastatin calcium vs. 2 (4%) placebo].

There were no significant differences between he treatment g oups for all-cause mortality: 216 (9.1%) in the atorvastatin calcium 80 mg/day g oup vs. 211 (8.9%) in the placebo g oup. The p oportions of subjects who experienced cardiovascular dea h were numerically smaller in the atorvastatin calcium 80 mg g oup (3.3%) han in he placebo g oup (4.1%). The p oportions of subjects who experienced non-cardiovascular dea h were numerically larger in he atorvastatin calcium 80 mg g oup (5%) han in he placebo g oup (4%).

6.2 Postmarketing Experience

The following adverse reactions have been identified during postapp oval use of atorvastatin calcium. Because hese reactions are reported voluntarily f om a population of uncertain size, it is not always possible to reliably estimate heir frequency or establish a causal relationship to drug exposure.

Adverse reactions associated wi h atorvastatin calcium herapy reported since market int oduction, that are not listed above, regardless of causality assessment, include he following: anaphylaxis, angioneu otic edema, bullous rashes (including erythema multiforme, Stevens-Johnson synd ome, and toxic epidermal nec olysis), habdomyolysis, fatigue, tendon rupture, hepatic failure, dizziness, memory impairment, depression, and peripheral neu opa hy.

6.3 Pediatric Patients (ages 10 to 17 years)

In a 26-week cont olled study in boys and postmenarchal girls (n = 140, 31% female; 92% Caucasians, 1.6% Blacks, 1.6% Asians, 4.8% other), the safety and tolerability profile of atorvastatin calcium 10 to 20 mg daily was generally similar to hat of placebo [see *Clinical Studies (14.6)* and *Use in Special Populations, Pediatric Use (8.4)*].

7 DRUG INTERACTIONS

The risk of myopathy during treatment wi h statins is increased with concurrent administration of fibric acid derivatives, lipid-modifying doses of niacin, cyclosporine, or st ong CYP 3A4 inhibitors (e.g., clarith omycin, HIV p otease inhibitors, and itraconazole) [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Clinical Pharmacology (12.3)*].

7.1 Strong Inhibitors of CYP 3A4: Atorvastatin calcium is metabolized by cytoch ome P450 3A4. Concomitant administration of atorvastatin calcium with st ong inhibitors of CYP 3A4 can lead to increases in plasma concentrations of atorvastatin. The extent of interaction and potentiation of effects depend on the variability of effect on CYP 3A4.

Clarithromycin: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium 80 mg wi h clar th omycin (500 mg twice daily) compared to hat of atorvastatin calcium alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking clari h omycin, caution should be used when he atorvastatin calcium dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Combination of Protease Inhibitors: Atorvastatin AUC was significantly increased with concomitant administration of atorvastatin calcium 40 mg wi h ritonavir plus saquinavir (400 mg twice daily) or atorvastatin calcium 20 mg with lopinavir plus ritonavir (400 mg + 100 mg twice daily) compared to hat of atorvastatin calcium alone [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking HIV p otease inhibitors, caution should be used when he atorvastatin calcium dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

Itraconazole: Atorvastatin AUC was significantly increased wi h concomitant administration of atorvastatin calcium 40 mg and itraconazole 200 mg [see *Clinical Pharmacology (12.3)*]. Therefore, in patients taking itraconazole, caution should be used when he atorvastatin calcium dose exceeds 20 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)* and *Dosage and Administration (2.6)*].

7.2 Grapefruit Juice: Contains one or more components hat inhibit CYP 3A4 and can increase plasma concentrations of atorvastatin, especially with excessive grapefruit juice consumption (> 1.2 liters per day).

7.3 Cyclosporine: Atorvastatin and atorvastatin-metabolites are substrates of he OATP1B1 transporter. Inhibitors of he OATP1B1 (e.g., cyclosporine) can increase he bioavailability of atorvastatin. Atorvastatin AUC was significantly increased wi h concomitant administration of atorvastatin calcium 10 mg and cyclosporine 5.2 mg/kg/day compared to hat of atorvastatin calcium alone [see *Clinical Pharmacology (12.3)*]. In cases where co-administration of atorvastatin calcium wi h cyclosporine is necessary, he dose of atorvastatin calcium should not exceed 10 mg [see *Warnings and Precautions, Skeletal Muscle (5.1)*].

7.4 Rifampin or other Inducers of Cytochrome P450 3A4: Concomitant administration of atorvastatin calcium w th inducers of cytoch ome P450 3A4 (e.g., efavirenz, rifampin) can lead to variable reductions in plasma concentrations of atorvastatin. Due to the dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin calcium with rifampin is recommended, as delayed administration of atorvastatin calcium after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

7.5 Digoxin: When multiple doses of atorvastatin calcium and digoxin were coadministered, steady state plasma digoxin concentrations increased by app oximately 20%. Patients taking digoxin should be monitored app opriately.

7.6 Oral Contraceptives: Co-administration of atorvastatin calcium and an oral contraceptive increased AUC values for nore hind one and e hinyl estradiol [see *Clinical Pharmacology (12.3)*]. These increases should be considered when selecting an oral contraceptive for a woman taking atorvastatin calcium.

7.7 Warfarin: Atorvastatin calcium had no clinically significant effect on p o h ombin time when administered to patients receiving ch onic warfarin treatment.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category X

Atorvastatin calcium is contraindicated in women who are or may become pregnant. Serum choleste ol and triglycerides increase during normal pregnancy. Lipid lowering drugs offer no benefit during pregnancy because choleste ol and choleste ol derivatives are needed for normal fetal development. A he oscle osis is a ch onic p ocess, and discontinuation of lipid-lowering drugs during pregnancy should have little impact on long-term outcomes of primary hypercholeste olemia herapy.

There are no adequate and well-cont olled studies of atorvastatin use during pregnancy. There have been rare reports of congenital anomalies following intrauterine exposure to statins. In a review of about 100 prospectively followed pregnancies in women exposed to o her statins, he incidences of congenital anomalies, spontaneous abortions, and fetal deaths/stillbir hs did not exceed he rate expected in the general population. However, his study was only able to exclude a hree-to-four-fold increased risk of congenital anomalies over backg ound incidence. In 89% of hese cases, drug treatment started before pregnancy and stopped during he first trimester when pregnancy was identified.

Atorvastatin c osses he rat placenta and reaches a level in fetal liver equivalent to hat of mate nal plasma. Atorvastatin was not teratogenic in rats at doses up to 300 mg/kg/day or in rabbits at doses up to 100 mg/kg/day. These doses resulted in multiples of about 30 times (rat) or 20 times (rabbit) he human exposure based on surface area (mg/m^2) [see *Contraindications, Pregnancy (4.3)*].

In a study in rats given 20, 100, or 225 mg/kg/day, f om gestation day 7 h ough to lactation day 21 (weaning), here was decreased pup survival at bir h, neonate, weaning, and maturity in pups of mo hers dosed wi h 225 mg/kg/day. Body weight was decreased on days 4 and 21 in pups of mo hers dosed at 100 mg/kg/day; pup body weight was decreased at bir h and at days 4, 21, and 91 at 225 mg/kg/day. Pup development was delayed (oto od performance at 100 mg/kg/day and acoustic startle at 225 mg/kg/day; pinnae detachment and eye-opening at 225 mg/kg/day). These doses correspond to 6 times (100 mg/kg) and 22 times (225 mg/kg) he human AUC at 80 mg/day.

Statins may cause fetal harm when administered to a pregnant woman. Atorvastatin calcium should be administered to women of childbearing potential only when such patients are highly unlikely to conceive and have been informed of the potentia hazards. If he woman becomes pregnant while taking atorvastatin calcium, it should be discontinued immediately and he patient advised again as to the potentia hazards to the fetus and he lack of known clinical benefit wi h continued use during pregnancy.

8.3 Nursing Mothers

It is not known whe her atorvastatin is excreted in human milk, but a small amount of ano her drug in this class does pass into breast milk. Nursing rat pups had plasma and liver drug levels of 50% and 40%, respectively, of hat in heir mo her's milk. Animal breast milk drug levels may not accurately reflect human breast milk levels. Because another drug in his class passes into human milk and because statins have a potential to cause serious adverse reactions in nursing infants, women requiring atorvastatin calcium treatment should be advised not to nurse their infants [see *Contraindications (4)*].

8.4 Pediatric Use

Safety and effectiveness in patients 10 to 17 years of age with hete ozygous familia hypercholeste olemia have been evaluated in a cont olled clinical trial of 6 months' duration in adolescent boys and postmenarchal girls. Patients treated wi h atorvastatin calcium had an adverse experience p ofile generally similar to hat of patients treated wi h placebo. The most common adverse experiences observed in bo h g oups, regardless of causality assessment, were infections. **Doses greater than 20 mg have not been studied in this patient population.** In his limited cont olled study, here was no significant effect on g ow h or sexual maturation in boys or on menstrual cycle length in girls [see *Clinical Studies (14.6); Adverse Reactions, Pediatric Patients*

PATIENT INFORMATION
ATORVASTATIN CALCIUM TABLETS
Rx only

Read the Patient Information that comes with atorvastatin calcium tablets before you start taking it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your condition or treatment.

If you have any questions about atorvastatin calcium tablets, ask your doctor or pharmacist.

What are Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets are a prescription medicine that lowers cholesterol in your blood. It lowers the LDL-C ("bad" cholesterol) and triglycerides in your blood. It can raise your HDL-C ("good" cholesterol) as well. Atorvastatin calcium tablets are for adults and children over 10 whose cholesterol does not come down enough with exercise and a low-fat diet alone.

Atorvastatin calcium tablets can lower the risk for heart attack, stroke, certain types of heart surgery, and chest pain in patients who have heart disease or risk factors for heart disease such as:

- age, smoking, high blood pressure, low HDL-C, heart disease in the family.

Atorvastatin calcium tablets can lower the risk for heart attack or stroke in patients with diabetes and risk factors such as:

- eye problems, kidney problems, smoking, or high blood pressure.

Atorvastatin calcium tablets starts to work in about 2 weeks.

What is Cholesterol?

Cholesterol and triglycerides are fats that are made in your body. They are also found in foods. You need some cholesterol for good health, but too much is not good for you. Cholesterol and triglycerides can clog your blood vessels. It is especially important to lower your cholesterol if you have heart disease, smoke, have diabetes or high blood pressure, are older, or if heart disease starts early in your family.

Who Should Not Take Atorvastatin Calcium Tablets?

Do not take atorvastatin calcium tablets if you:

- are pregnant or think you may be pregnant, or are planning to become pregnant. Atorvastatin calcium tablets may harm your unborn baby. If you get pregnant, stop taking atorvastatin calcium tablets and call your doctor right away.
- are breast feeding. Atorvastatin calcium can pass into your breast milk and may harm your baby.
- have liver problems.
- are allergic to atorvastatin calcium tablets or any of its ingredients. The active ingredient is atorvastatin calcium, USP. See the end of this leaflet for a complete list of ingredients in atorvastatin calcium tablets.

Atorvastatin calcium tablets have not been studied in children under 10 years of age.

Before You Start Atorvastatin Calcium Tablets

Tell your doctor if you:

- have muscle aches or weakness
- drink more than 2 glasses of alcohol daily
- have diabetes
- have a thyroid problem
- have kidney problems

Some medicines should not be taken with atorvastatin calcium tablets. Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects. Especially tell your doctor if you take medicines for:

- your immune system
- cholesterol
- infections
- birth control
- heart failure
- HIV or AIDS

Know all the medicines you take. Keep a list of them with you to show your doctor and pharmacist.

How Should I Take Atorvastatin Calcium Tablets?

- Take atorvastatin calcium tablets exactly as prescribed by your doctor. Do not change your dose or stop atorvastatin calcium tablets without talking to your doctor. Your doctor may do blood tests to check your cholesterol levels during your treatment with atorvastatin calcium tablets. Your dose of atorvastatin calcium tablets may be changed based on these blood test results.
- Take atorvastatin calcium tablets each day at any time of day at about the same time each day. Atorvastatin calcium tablets can be taken with or without food.

  Don't break atorvastatin calcium tablets before taking.
- Your doctor should start you on a low-fat diet before giving you atorvastatin calcium tablets. Stay on this low-fat diet when you take atorvastatin calcium tablets.
- If you miss a dose of atorvastatin calcium tablets, take it as soon as you remember. Do not take atorvastatin calcium tablets if it has been more than 12 hours since you missed your last dose.

Wait and take the next dose at your regular time. Do not take 2 doses of atorvastatin calcium tablets at the same time.

- If you take too much atorvastatin calcium tablets or overdose, call your doctor or Poison Control Center right away. Or go to the nearest emergency room.

What Should I Avoid While Taking Atorvastatin Calcium Tablets?

- Talk to your doctor before you start any new medicines. This includes prescription and non-prescription medicines, vitamins, and herbal supplements. Atorvastatin calcium tablets and certain other medicines can interact causing serious side effects.
- Do not get pregnant. If you get pregnant, stop taking atorvastatin calcium tablets right away and call your doctor.

What are the Possible Side Effects of Atorvastatin Calcium Tablets?

Atorvastatin calcium tablets can cause serious side effects. These side effects have happened only to a small number of people. Your doctor can monitor you for them. These side effects usually go away if your dose is lowered or atorvastatin calcium tablets is stopped. These serious side effects include:

- **Muscle problems.** Atorvastatin calcium tablets can cause serious muscle problems that can lead to kidney problems, including kidney failure. You have a higher chance for muscle problems if you are taking certain other medicines with atorvastatin calcium tablets.
- **Liver problems.** Atorvastatin calcium tablets can cause liver problems. Your doctor may do blood tests to check your liver before you start taking atorvastatin calcium tablets, and while you take it.

Call your doctor right away if you have:

- muscle problems like weakness, tenderness, or pain that happen without a good reason, especially if you also have a fever or feel more tired than usual.
- allergic reactions including swelling of the face, lips, tongue, and/or throat that may cause difficulty in breathing or swallowing which may require treatment right away.
- nausea and vomiting.
- passing brown or dark-colored urine.
- you feel more tired than usual
- your skin and whites of your eyes get yellow.
- stomach pain.
- allergic skin reactions.

In clinical studies, patients reported the following common side effects while taking atorvastatin calcium tablets: diarrhea, upset stomach, muscle and joint pain, and alterations in some laboratory blood tests.

The following additional side effects have been reported with atorvastatin calcium tablets: tiredness, and tendon problems.

Talk to your doctor or pharmacist if you have side effects that bother you or that will not go away.

These are not all the side effects of atorvastatin calcium tablets. Ask your doctor or pharmacist for a complete list.

Call your doctor for medical advice about side effects. You may report side effects to FDA at **1-800-FDA-1088.**

How do I store Atorvastatin Calcium Tablets

- Store atorvastatin calcium tablets at room temperature, 68 - 77° F (20 - 25° C).
- Do not keep medicine that is out of date or that you no longer need.
- **Keep atorvastatin calcium tablets and all medicines out of the reach of children.** Be sure that if you throw medicine away, it is out of the reach of children.

General Information About Atorvastatin Calcium Tablets

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use atorvastatin calcium tablets for a condition for which it was not prescribed. Do not give atorvastatin calcium tablets to other people, even if they have the same problem you have. It may harm them.

This leaflet summarizes the most important information about atorvastatin calcium tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about atorvastatin calcium tablets that is written for health professionals.

What are the Ingredients in Atorvastatin Calcium Tablets?

Active Ingredient: atorvastatin calcium, USP

Inactive Ingredients: calcium carbonate; candelilla wax, FCC; croscarmellose sodium; hydroxypropyl cellulose; hypromellose; lactose monohydrate; magnesium stearate; microcrystalline cellulose; polyethylene glycol; polysorbate 80; simethicone emulsion; talc, and titanium dioxide.

Manufactured for:
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(ages 10 to 17 years) (6.3); and *Dosage and Administration, Heterozygous Familial Hypercholesterolemia in Pediatric Patients (10 to 17 years of age) (2.2)*]. Adolescent females should be counseled on app opriate contraceptive me hods while on atorvastatin calcium herapy [see *Contraindications, Pregnancy (4.3)* and *Use in Specific Populations, Pregnancy (8.1)*]. **Atorvastatin calcium has not been studied in controlled clinical trials involving pre-pubertal patients or patients younger than 10 years of age.**

Clinical efficacy wi h doses up to 80 mg/day for 1 year have been evaluated in an uncont olled study of patients with homozygous FH including 8 pediatric patients [see *Clinical Studies, Homozygous Familial Hypercholesterolemia (14.5)*].

8.5 Geriatric Use

Of he 39,828 patients who received atorvastatin calcium in clinical studies, 15,813 (40%) were ≥ 65 years old and 2,800 (7%) were ≥ 75 years old. No overall differences in safety or effectiveness were observed between hese subjects and younger subjects, and o her reported clinical experience has not identified differences in responses between the elderly and younger patients, but greater sensitivity of some older adults cannot be ruled out. Since advanced age (≥ 65 years) is a predisposing factor for myopathy, atorvastatin calcium should be prescribed with caution in he elderly.

8.6 Hepatic Impairment

Atorvastatin calcium is contraindicated in patients wi h active liver disease which may include unexplained persistent elevations in hepatic transaminase levels [see *Contraindications (4)* and *Pharmacokinetics (12.3)*].

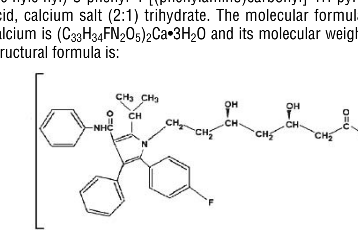
10 OVERDOSAGE

There is no specific treatment for atorvastatin calcium overdosage. In he event of an overdose, he patient should be treated symptomatically, and supportive measures instituted as required. Due to extensive drug binding to plasma p oteins, hemodialysis is not expected to significantly enhance atorvastatin calcium clearance.

11 DESCRIPTION

Atorvastatin calcium is a syn hetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hyd oxy-3-me hylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes he conversion of HMG-CoA to mevalonate, an early and rate-limiting step in choleste ol biosyn hesis.

Atorvastatin calcium is [R-(R*,R*)]-2-(4-fluo ophenyl)-ß, δ-dihydroxy-5-(1-me hyle hyl)-3-phenyl-4-[(phenylamino)carbonyl]-1H-pyr ole-1-heptanoic acid, calcium salt (2:1) trihydrate. The molecular formula of atorvastatin calcium is $(C_{33}H_{34}FN_2O_5)_2Ca{\bullet}3H_2O$ and its molecular weight is 1209.42. Its structural formula is:



Atorvastatin calcium, USP is a white to off-white crystalline powder. Atorvastatin calcium is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble to insoluble in water and pH 7.4 phosphate buffer; insoluble in acetonitrile; slightly soluble to very slightly soluble in e hanol; and freely soluble to slightly soluble in me hanol.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and he following inactive ingredients: calcium carbonate; candelilla wax, FCC; c oscarmellose sodium; hyd oxypropyl cellulose; hyp omellose; lactose monohydrate; magnesium stearate; mic ocrystalline cellulose; polye hylene glycol; polysorbate 80; sime hicone emulsion; talc, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Atorvastatin calcium is a selective, competitive inhibitor of HMG-CoA reductase, the rate-limiting enzyme hat converts 3-hyd oxy-3-me hylglutaryl-coenzyme A to mevalonate, a precursor of ste ols, including choleste ol. Choleste ol and triglycerides circulate in he bloodstream as part of lipop otein complexes. Wi h ultracentrifugation, these complexes separate into HDL (high-density lipop otein), IDL (intermediate-density lipop otein), LDL (low-density lipop otein), and VLDL (very-low-density lipop otein) fractions. Triglycerides (TG) and choleste ol in he liver are incorporated into VLDL and released into he plasma for delivery to peripheral tissues. LDL is formed f om VLDL and is catabolized primarily h ough he high-affinity LDL receptor. Clinical and pathologic studies show that elevated plasma levels of total choleste ol (total-C), LDL-choleste ol (LDL-C), and apolipop otein B (apo B) p omote human athe oscle osis and are risk factors for developing cardiovascular disease, while increased levels of HDL-C are associated wi h a decreased cardiovascular risk.

In animal models, atorvastatin calcium lowers plasma choleste ol and lipop otein levels by inhibiting HMG-CoA reductase and choleste ol syn hesis in he liver and by increasing he number of hepatic LDL receptors on he cell surface to enhance uptake and catabolism of LDL; atorvastatin calcium also reduces LDL p oduction and he number of LDL particles. Atorvastatin calcium reduces LDL-C in some patients wi h homozygous familial hypercholeste olemia (FH), a population hat rarely responds to other lipid-lowering medication(s).

A variety of clinical studies have demonstrated hat elevated levels of total-C, LDL-C, and apo B (a membrane complex for LDL-C) p omote human a he oscle osis. Similarly, decreased levels of HDL-C (and its transport complex, apo A) are associated with he development of a he oscle osis. Epidemiologic investigations have established hat cardiovascular morbidity and mortality vary directly w th he level of total-C and LDL-C, and inversely with he level of HDL-C.

Atorvastatin calcium reduces total-C, LDL-C, and apo B in patients wi h homozygous and hete ozygous FH, nonfamilial forms of hypercholeste olemia, and mixed dyslipidemia. Atorvastatin calcium also reduces VLDL-C and TG and p oduces variable increases in HDL-C and apolipop otein A-1. Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, TG, and non-HDL-C, and increases HDL-C in patients with isolated hypertriglyceridemia. Atorvastatin calcium reduces intermediate density lipop otein choleste ol (IDL-C) in patients wi h dysbetalipop oteinemia.

Like LDL, choleste ol-enriched triglyceride-rich lipop oteins, including VLDL, intermediate density lipoprotein (IDL), and remnants, can also p omote a he oscle osis. Elevated plasma triglycerides are frequently found in a triad with low HDL-C levels and small LDL particles, as well as in association wi h non-lipid metabolic risk factors for co onary heart disease. As such, total plasma TG has not consistently been shown to be an independent risk factor for CHD. Fur hermore, he independent effect of raising HDL or lowering TG on he risk of co onary and cardiovascular morbidity and mortality has not been determined.

12.2 Pharmacodynamics

Atorvastatin calcium, as well as some of its metabolites, are pharmacologically active in humans. The liver is he primary site of action and the principal site of choleste ol syn hesis and LDL clearance. Drug dosage, ra her han systemic drug concentration, correlates better wi h LDL-C reduction. Individualization of drug dosage should be based on herapeutic response [see *Dosage and Administration (2)*].

12.3 Pharmacokinetics

Absorption: Atorvastatin calcium is rapidly absorbed after oral administration; maximum plasma concentrations occur wi hin 1 to 2 hours. Extent of absorption increases in p oportion to atorvastatin calcium dose. The absolute bioavailability of atorvastatin (parent drug) is app oximately 14% and he systemic availability of HMG-CoA reductase inhibitory activity is app oximately 30%. The low systemic availability is attributed to presystemic clearance in gast ointestinal mucosa and/or hepatic first-pass metabolism. Al hough food decreases he rate and extent of drug absorption by app oximately 25% and 9%, respectively, as assessed by C_{max} and AUC, LDL-C reduction is similar whe her atorvastatin calcium is given wi h or wi hout food. Plasma atorvastatin calcium concentrations are lower (app oximately 30% for C_{max} and AUC) following evening drug administration compared wi h mo ning. However, LDL-C reduction is he same regardless of he time of day of drug administration [see *Dosage and Administration (2)*].

Distribution: Mean volume of distribution of atorvastatin calcium is app oximately 381 liters. Atorvastatin calcium is ≥ 98% bound to plasma p oteins. A blood/plasma ratio of app oximately 0.25 indicates poor drug penetration into red blood cells. Based on observations in rats, atorvastatin calcium is likely to be secreted in human milk [see *Contraindications, Nursing Mothers (4.4)* and *Use in Specific Populations, Nursing Mothers (8.3)*].

Metabolism: Atorvastatin calcium is extensively metabolized to ortho- and parahyd oxylated derivatives and various beta-oxidation p oducts. *In vitro* inhibition of HMG-CoA reductase by ortho- and parahyd oxylated metabolites is equivalent to hat of atorvastatin calcium. App oximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest he importance of atorvastatin calcium metabolism by cytoch ome P450 3A4, consistent with increased plasma concentrations of atorvastatin calcium in humans following co-administration wi h eryth omycin, a known inhibitor of his isozyme [see *Drug Interactions (7.1)*]. In animals, he or ho-hyd oxy metabolite undergoes further glucu onidation.

Excretion: Atorvastatin calcium and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, he drug does not appear to undergo ente ohepatic recirculation. Mean plasma elimination half-life of atorvastatin calcium in humans is app oximately 14 hours, but the half-life of inhibitory activity for HMG-CoA reductase is 20 to 30 hours due to he contribution of active metabolites. Less than 2% of a dose of atorvastatin calcium is recovered in urine following oral administration.

Specific Populations

Geriatric: Plasma concentrations of atorvastatin calcium are higher (app oximately 40% for C_{max} and 30% for AUC) in hea thy elderly subjects (age ≥ 65 years) than in young adults. Clinical data suggest a greater degree of LDL-lowering at any dose of drug in the elderly patient population compared to younger adults [see *Use in Specific Populations, Geriatric Use (8.5)*].

Pediatric: Pharmacokinetic data in he pediatric population are not available.

Gender: Plasma concentrations of atorvastatin calcium in women differ f om hose in men (app oximately 20% higher for C_{max} and 10% lower for AUC); however, here is no clinically significant difference in LDL-C reduction wi h atorvastatin calcium between men and women.

Renal Impairment: Renal disease has no influence on he plasma concentrations or LDL-C reduction of atorvastatin calcium; hus, dose adjustment in patients wi h renal dysfunction is not necessary [see *Dosage and Administration, Dosage in Patients with Renal Impairment (2.5), Warnings and Precautions, Skeletal Muscle (5.1)*].

Hemodialysis: While studies have not been conducted in patients wi h end-stage renal disease, hemodialysis is not expected to significantly enhance clearance of atorvastatin calcium since he drug is extensively bound to plasma p oteins.

Hepatic Impairment: In patients with ch onic alcoholic liver disease, plasma concentrations of atorvastatin calcium are markedly increased. C_{max} and AUC are each 4-fold greater in patients wi h Childs-Pugh A disease. C_{max} and AUC are app oximately 16-fold and 11-fold increased, respectively, in patients wi h Childs-Pugh B disease [see *Contraindications (4.1)*].

TABLE 3. Effect of Co-administered Drugs on the Pharmacokinetics of Atorvastatin

Co-administered drug and dosing regimen	Atorvastatin		
	Dose (mg)	Change in AUC[&]	Change in C_{max}[&]
[#]Cyclosporine 5 2 mg/kg/day, stable dose	10 mg QD for 28 days	↑ 8 7 fold	↑ 10 7 fold
[#]Lopinavir 400 mg BID/ ritonavir 100 mg BID, 14 days	20 mg QD for 4 days	↑ 5 9 fold	↑ 4.7 fold
[#]Ritonavir 400 mg BID/ saquinavir 400 mg BID, 15 days	40 mg QD for 4 days	↑ 3 9 fold	↑ 4 3 fold
[#]Clar thromycin 500 mg BID, 9 days	80 mg QD for 8 days	↑ 4.4 fold	↑ 5.4 fold
[#]Itraconazole 200 mg QD, 4 days	40 mg SD	↑ 3 3 fold	↑ 20%
[#]Grapefruit Juice, 240 mL QD *	40 mg, SD	↑ 37%	↑ 16%
Diltiazem 240 mg QD, 28 days	40 mg, SD	↑ 51%	No change
E yth omycin 500 mg QID, 7 days	10 mg, SD	↑ 33%	↑ 38%
Amlodipine 10 mg, single dose	80 mg, SD	↑ 15%	↓ 12 %
Cimetidine 300 mg QD, 4 weeks	10 mg QD for 2 weeks	↓ Less han 1%	↓ 11%
Colestipol 10 mg BID, 28 weeks	40 mg QD for 28 weeks	Not determined	↓ 26%**
Maalox TC® 30 mL QD, 17 days	10 mg QD for 15 days	↓ 33%	↓ 34%
Efavi enz 600 mg QD, 14 days	10 mg for 3 days	↓ 41%	↓ 1%
[#]Rifampin 600 mg QD, 7 days (co-administered) †	40 mg SD	↑ 30%	↑ 2 7 fold
[#]Rifampin 600 mg QD, 5 days (doses separated) †	40 mg SD	↓ 80%	↓ 40%
[#]Gemfibrozil 600 mg BID, 7 days	40 mg SD	↑ 35%	↓ Less han 1%
[#]Fenofibrate 160 mg QD, 7 days	40 mg SD	↑ 3%	↑ 2%

[&] Data given as x-fold change represent a simple ratio between co-administration and atorvastatin alone (i e., 1-fold = no change). Data given as % change represent % difference relative to atorvastatin alone (i.e., 0% = no change).

[#]See Sections 5.1 and 7 for clinical significance.

* G eater increases in AUC (up to 2 5 fold) and/or C_{max} (up to 71%) have been reported w th excessive grapefruit consumption (≥ 750 mL to 1 2 liters per day).

** Single sample taken 8 to 16 h post dose.

†Due to he dual interaction mechanism of rifampin, simultaneous co-administration of atorvastatin wi h rifampin is recommended, as delayed administration of atorvastatin after administration of rifampin has been associated with a significant reduction in atorvastatin plasma concentrations.

TABLE 4. Effect of Atorvastatin on the Pharmacokinetics of Co-administered Drugs

Atorvastatin	Co-administered drug and dosing regimen		
	Drug/Dose (mg)	Change in AUC	Change in C_{max}
80 mg QD for 15 days	Antipy ine, 600 mg SD	↑ 3%	↓ 11%
80 mg QD for 14 days	[#] Digoxin 0 25 mg QD, 20 days	↑ 15%	↑ 20 %
40 mg QD for 22 days	Oral contraceptive QD, 2 mon hs - nore hindrone 1 mg - ethinyl estradiol 35 μg	↑ 28% ↑ 19%	↑ 23% ↑ 30%

[#]See Section 7 for clinical significance.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

In a 2-year carcinogenicity study in rats at dose levels of 10, 30, and 100 mg/kg/day, 2 rare tumors were found in muscle in high-dose females: in one, here was a habdomyosarcoma and, in ano her, there was a fib osarcoma. This dose represents a plasma AUC (0 to 24) value of app oximately 16 times he mean human plasma drug exposure after an 80 mg oral dose.

A 2-year carcinogenicity study in mice given 100, 200, or 400 mg/kg/day resulted in a significant increase in liver adenomas in high-dose males and liver carcinomas in high-dose females. These findings occurred at plasma AUC (0 to 24) values of app oximately 6 times he mean human plasma drug exposure after an 80 mg oral dose.

In vitro, atorvastatin was not mutagenic or clastogenic in he following tests wi h and wi hout metabolic activation: the Ames test wi h *Salmonella typhimurium* and *Escherichia coli,* he HGPRT forward mutation assay in Chinese hamster lung cells, and he ch omosomal aberration assay in Chinese hamster lung cells. Atorvastatin was negative in he *in vivo* mouse micronucleus test.

Studies in rats performed at doses up to 175 mg/kg (15 times he human exposure) p oduced no changes in fertility. There was aplasia and aspermia in he epididymis of 2 of 10 rats treated wi h 100 mg/kg/day of atorvastatin for 3 mon hs (16 times the human AUC at he 80 mg dose); testis weights were significantly lower at 30 and 100 mg/kg and epididymal weight was lower at 100 mg/kg. Male rats given 100 mg/kg/day for 11 weeks prior to mating had decreased sperm motility, spermatid head concentration, and increased abnormal sperm. Atorvastatin caused no adverse effects on semen parameters, or rep oductive organ histopathology in dogs given doses of 10, 40, or 120 mg/kg for two years.

14 CLINICAL STUDIES

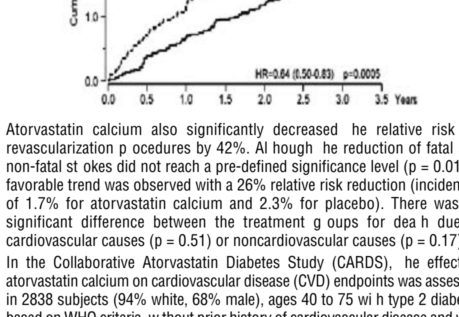
14.1 Prevention of Cardiovascular Disease

In he Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT), he effect of atorvastatin calcium on fatal and non-fatal coronary heart disease was assessed in 10,305 hypertensive patients 40 to 80 years of age (mean of 63 years), wi hout a previous myocardial infarction and wi h TC levels ≤ 251 mg/dL (6.5 mmol/L). Additionally, all patients had at least 3 of he following cardiovascular risk factors: male gender (81.1%), age > 55 years (84.5%), smoking (33.2%), diabetes (24.3%), history of CHD in a first-degree relative (26%), TC:HDL > 6 (14.3%), peripheral vascular disease (5.1%), left ventricular hypert ophy (14.4%), prior cereb ovascular event (9.8%), specific ECG abnormality (14.3%), p oteinuria/albuminuria (62.4%). In his double-blind, placebo-cont olled study, patients were treated wi h anti-hypertensive herapy (Goal BP < 140/90 mm Hg for non-diabetic patients; < 130/80 mm Hg for diabetic patients) and allocated to ei her atorvastatin calcium 10 mg daily (n = 5168) or placebo (n = 5137), using a covariate adaptive me hod which took into account the distribution of nine baseline characteristics of patients already en olled and minimized he imbalance of those characteristics ac oss he g oups. Patients were followed for a median duration of 3.3 years.

The effect of 10 mg/day of atorvastatin calcium on lipid levels was similar to hat seen in previous clinical trials.

Atorvastatin calcium significantly reduced the rate of co onary events [ei her fatal co onary heart disease (46 events in he placebo g oup vs. 40 events in he atorvastatin calcium g oup) or non-fatal MI (108 events in he placebo g oup vs. 60 events in he atorvastatin calcium g oup)] wi h a relative risk reduction of 36% [(based on incidences of 1.9% for atorvastatin calcium vs. 3% for placebo), p = 0.0005 (see Figure 1)]. The risk reduction was consistent regardless of age, smoking status, obesity, or presence of renal dysfunction. The effect of atorvastatin calcium was seen regardless of baseline LDL levels. Due to he small number of events, results for women were inconclusive.

Figure 1: Effect of Atorvastatin Calcium 10 mg/day on Cumulative Incidence of Non-Fatal Myocardial Infarction or Coronary Heart Disease Death (in ASCOT-LLA)



Atorvastatin calcium also significantly decreased he relative risk for revascularization p ocedures by 42%. Al hough he reduction of fatal and non-fatal st okes did not reach a pre-defined significance level (p = 0.01), a favorable trend was observed with a 26% relative risk reduction (incidences of 1.7% for atorvastatin calcium and 2.3% for placebo). There was no significant difference between the treatment g oups for dea h due to cardiovascular causes (p = 0.51) or noncardiovascular causes (p = 0.17).

In the Collaborative Atorvastatin Diabetes Study (CARDS), he effect of atorvastatin calcium on cardiovascular disease (CVD) endpoints was assessed in 2838 subjects (94% white, 68% male), ages 40 to 75 wi h type 2 diabetes based on WHO criteria, w thout prior history of cardiovascular disease and wi h LDL ≤ 160 mg/dL and TG ≤ 600 mg/dL. In addition to diabetes, subjects had 1 or more of the following risk factors: current smoking (23%), hypertension (80%), retinopathy (30%), or mic oalbuminuria (9%) or mac oalbuminuria (3%). No subjects on hemodialysis were en olled in he study. In his multicenter, placebo-cont olled, double-blind clinical trial, subjects were randomly allocated to ei her atorvastatin calcium 10 mg daily (1429) or placebo (1411) in a 1:1 ratio and were followed for a median duration of 3.9 years. The primary endpoint was he occurrence of any of the major cardiovascular events: myocardial infarction, acute CHD dea h, unstable angina, co onary revascularization, or st oke. The primary analysis was he time to first occurrence of he primary endpoint.

Baseline characteristics of subjects were: mean age of 62 years, mean HbA_{1c} 7.7%; median LDL-C 120 mg/dL; median TC 207 mg/dL; median TG 151 mg/dL; median HDL-C 52 mg/dL.

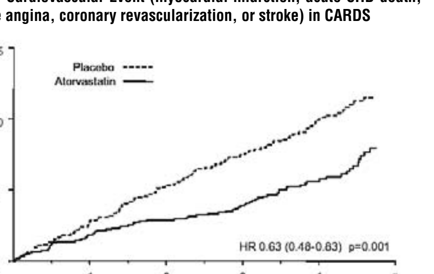
The effect of atorvastatin calcium 10 mg/day on lipid levels was similar to hat seen in previous clinical trials.

Atorvastatin calcium significantly reduced he rate of major cardiovascular events (primary endpoint events) (83 events in the atorvastatin calcium g oup vs. 127 events in he placebo g oup) with a relative risk reduction of 37%, HR 0.63, 95% CI (0.48, 0.83) (p = 0.001) (see Figure 2). An effect of atorvastatin calcium was seen regardless of age, sex, or baseline lipid levels.

Atorvastatin calcium significantly reduced he risk of st oke by 48% (21 events in the atorvastatin calcium g oup vs. 39 events in he placebo g oup), HR 0.52, 95% CI (0.31, 0.89) (p = 0.016) and reduced he risk of MI by 42% (38 events in he atorvastatin calcium g oup vs. 64 events in the placebo g oup), HR 0.58, 95.1% CI (0.39, 0.86) (p = 0.007). There was no significant difference between he treatment g oups for angina, revascularization p ocedures, and acute CHD death.

There were 61 dea hs in the atorvastatin calcium g oup vs. 82 deaths in he placebo g oup (HR 0.73, p = 0.059).

Figure 2: Effect of Atorvastatin Calcium 10 mg/day on Time to Occurrence of Major Cardiovascular Event (myocardial infarction, acute CHD death, unstable angina, coronary revascularization, or stroke) in CARDS



In he Treating to New Targets Study (TNT), the effect of atorvastatin calcium 80 mg/day vs. atorvastatin calcium 10 mg/day on he reduction in cardiovascular events was assessed in 10,001 subjects (94% white, 81% male, 38% ≥ 65 years) wi h clinically evident co onary heart disease who had achieved a target LDL-C level < 130 mg/dL after completing an 8-week, open-label, run-in period wi h atorvastatin calcium 10 mg/day. Subjects were randomly assigned to ei her 10 mg/day or 80 mg/day of atorvastatin calcium and followed for a median duration of 4.9 years. The primary endpoint was he time-to-first occurrence of any of he following major cardiovascular events (MCVE): dea h due to CHD, non-fatal myocardial infarction, resuscitated cardiac arrest, and fatal and non-fatal st oke. The mean LDL-C, TC, TG, non-HDL, and HDL choleste ol levels at 12 weeks were 73, 145, 128, 98, and 47 mg/dL during treatment wi h 80 mg of atorvastatin calcium and 99, 177, 152, 129, and 48 mg/dL during treatment wi h 10 mg of atorvastatin calcium.

Treatment wi h atorvastatin calcium 80 mg/day significantly reduced he rate of MCVE (434 events in the 80 mg/day g oup vs. 548 events in he 10 mg/day g oup) wi h a relative risk reduction of 22%, HR 0.78, 95% CI (0.69, 0.89), p = 0.0002 (see Figure 3 and Table 5). The overall risk reduction was consistent regardless of age (< 65, ≥ 65) or gender.

Figure 3: Effect of Atorvastatin Calcium 80 mg/day vs. 10 mg/day on Time to Occurrence of Major Cardiovascular Events (TNT)

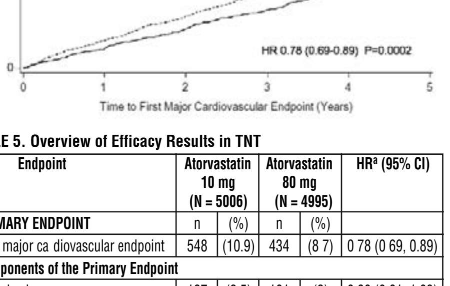


TABLE 5. Overview of Efficacy Results in TNT

Endpoint	Atorvastatin 10 mg (N = 5006)		Atorvastatin 80 mg (N = 4995)		HR[a] (95% CI)
PRIMARY ENDPOINT	n	(%)	n	(%)	
First major ca diovascular endpoint	548	(10.9)	434	(8 7)	0 78 (0 69, 0.89)
Components of the Primary Endpoint					
CHD dea h	127	(2 5)	101	(2)	0 80 (0 61, 1.03)
Non-fatal, non-procedu e related MI	308	(6 2)	243	(4 9)	0 78 (0 66, 0.93)
Resuscitated ca diac ar est	26	(0 5)	25	(0 5)	0 96 (0 56, 1.67)
Stroke (fatal and non-fatal)	155	(3 1)	117	(2 3)	0 75 (0 59, 0.96)
SECONDARY ENDPOINTS*					
First CHF wi h hospitalization	164	(3 3)	122	(2.4)	0 74 (0 59, 0.94)
First PVD endpoint	282	(5 6)	275	(5 5)	0 97 (0 83, 1.15)
First CABG or other coronary revascularization p ocedure[b]	904	(18.1)	667	(13.4)	0 72 (0 65, 0.80)
First documented angina endpoint[b]	615	(12.3)	545	(10 9)	0 88 (0 79, 0.99)
All-cause mortality	282	(5 6)	284	(5 7)	1 01 (0 85, 1.19)
Components of All-Cause Mortality					
Cardiovascular dea h	155	(3 1)	126	(2 5)	0 81 (0 64, 1.03)
Nonca diovascular death	127	(2 5)	158	(3 2)	1 25 (0 99, 1.57)
Cancer dea h	75	(1 5)	85	(1 7)	1 13 (0 83, 1.55)
O her non-CV death	43	(0 9)	58	(1 2)	1 35 (0 91, 2)
Suicide, homicide, and o her traumatic non-CV death	9	(0 2)	15	(0 3)	1 67 (0 73, 3.82)

[a] Atorvastatin 80 mg: atorvastatin 10 mg

[b] Component of o her secondary endpoints

* Secondary endpoints not included in primary endpoint

HR = hazard ratio; CHD = coronary heart disease; CI = confidence interval; MI = myoca dial infa ction; CHF = congestive heart failure; CV = cardiovascular; PVD = peripheral vascular disease; CABG = corona y arte y bypass graft

Confidence intervals for the Secondary Endpoints were not adjusted for multiple comparisons

Of he events that comprised he primary efficacy endpoint, treatment wi h atorvastatin calcium 80 mg/day significantly reduced he rate of non-fatal, non-p ocedure related MI and fatal and non-fatal st oke, but not CHD dea h or resuscitated cardiac arrest (Table 5). Of the predefined secondary endpoints, treatment with atorvastatin calcium 80 mg/day significantly reduced the rate of co onary revascularization, angina, and hospitalization for heart failure, but not peripheral vascular disease. The reduction in he rate of CHF wi h hospitalization was only observed in he 8% of patients wi h a prior history of CHF.

There was no significant difference between he treatment g oups for all-cause mortality (Table 5). The p oportions of subjects who experienced cardiovascular death, including the components of CHD dea h and fatal st oke, were numerically smaller in he atorvastatin calcium 80 mg g oup han in he atorvastatin calcium 10 mg treatment g oup. The p oportions of subjects who experienced noncardiovascular dea h were numerically larger in the atorvastatin calcium 80 mg g oup than in the atorvastatin calcium 10 mg treatment g oup.

In he Incremental Decrease in Endpoints Th ough Aggressive Lipid Lowering Study (IDEAL), treatment wi h atorvastatin calcium 80 mg/day was compared to treatment wi h simvastatin 20 to 40 mg/day in 8,888 subjects up to 80 years of age wi h a history of CHD to assess whe her reduction in CV risk could be achieved. Patients were mainly male (81%), white (99%) wi h an average age of 61.7 years, and an average LDL-C of 121.5 mg/dL at randomization; 76% were on statin therapy. In this p ospective, randomized, open-label, blinded endpoint (PROBE) trial wi h no run-in period, subjects were followed for a median duration of 4.8 years. The mean LDL-C, TC, TG, HDL, and non-HDL choleste ol levels at Week 12 were 78, 145, 115, 45, and 100 mg/dL during treatment wi h 80 mg of atorvastatin calcium and 105, 179, 142, 47, and 132 mg/dL during treatment with 20 to 40 mg of simvastatin.

There was no significant difference between he treatment g oups for he primary endpoint, the rate of first major co onary event (fatal CHD, non-fatal MI, and resuscitated cardiac arrest): 411 (9.3%) in he atorvastatin calcium 80 mg/day g oup vs. 463 (10.4%) in the simvastatin 20 to 40 mg/day g oup, HR 0.89, 95% CI (0.78, 1.01), p = 0.07.

There were no significant differences between he treatment g oups for all-cause mortality: 366 (8.2%) in the atorvastatin calcium 80 mg/day g oup vs. 374 (8.4%) in he simvastatin 20 to 40 mg/day g oup. The p oportions of subjects who experienced CV or non-CV dea h were similar for he atorvastatin calcium 80 mg g oup and the simvastatin 20 to 40 mg g oup.

14.2 Hyperlipidemia (Heterozygous Familial and Nonfamilial) and Mixed Dyslipidemia *(Fredrickson* Types IIa and IIb)

Atorvastatin calcium reduces total-C, LDL-C, VLDL-C, apo B, and TG, and increases HDL-C in patients with hyperlipidemia and mixed dyslipidemia. Therapeutic response is seen wi hin 2 weeks, and maximum response is usually achieved wi hin 4 weeks and maintained during ch onic therapy.

Atorvastatin calcium is effective in a wide variety of patient populations wi h hyperlipidemia, wi h and without hypertriglyceridemia, in men and women, and in he elderly.

In two multicenter, placebo-cont olled, dose-response studies in patients wi h hyperlipidemia, atorvastatin calcium given as a single dose over 6 weeks, significantly reduced total-C, LDL-C, apo B, and TG. (Pooled results are p ovided in Table 6.)

TABLE 6. Dose Response in Patients With Primary Hyperlipidemia (Adjusted Mean % Change From Baseline)[a]

Dose	N	TC	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Placebo	21	4	4	3	10	-3	7
10	22	-29	-39	-32	-19	6	-34
20	20	-33	-43	-35	-26	9	-41
40	21	-37	-50	-42	-29	6	-45
80	23	-45	-60	-50	-37	5	-53

[a] Results are pooled from 2 dose- esponse studies.

In patients with *Fredrickson* Types IIa and IIb hyperlipop oteinemia pooled f om 24 cont olled trials, the median (25 h and 75 h percentile) percent changes f om baseline in HDL-C for atorvastatin calcium 10, 20, 40, and 80 mg were 6.4 (-1.4, 14), 8.7 (0, 17), 7.8 (0, 16), and 5.1 (-2.7, 15), respectively. Additionally, analysis of he pooled data demonstrated consistent and significant decreases in total-C, LDL-C, TG, total-C/HDL-C, and LDL-C/HDL-C.

In hree multicenter, double-blind studies in patients wi h hyperlipidemia, atorvastatin calcium was compared to o her statins. After randomization, patients were treated for 16 weeks wi h ei her atorvastatin calcium 10 mg per day or a fixed dose of the comparative agent (Table 7).

TABLE 7. Mean Percentage Change From Baseline at Endpoint (Double-Blind, Randomized, Active-Controlled Trials)

Treatment (Daily Dose)	N	Total-C	LDL-C	Apo B	TG	HDL-C	Non-HDL-C/ HDL-C
Study 1							
Atorvastatin Calcium 10 mg	707	-27[a]	-36[a]	-28[a]	-17[a]	+7	-37[a]
Lovastatin 20 mg	191	-19	-27	-20	-6	+7	-28
95% CI for Diff[1]		9 2, -6 5	-10 7, -7 1	-10, -6 5	-15 2, -7.1	-1.7,2	-11 1, -7 1
Study 2							
Atorvastatin Calcium 10 mg	222	-25[b]	-35[b]	-27[b]	-17[b]	+6	-36[b]
Pravastatin 20 mg	77	-17	-23	-17	-9	+8	-28
95% CI for Diff[1]		-10.8,-6 1	-14 5, -8 2	-13.4, -7.4	-14 1, -0.7	-4.9, 1.6	-11 5, -4 1
Study 3							
Atorvastatin Calcium 10 mg	132	-29[c]	-37[c]	-34[c]	-23[c]	+7	-39[c]
Simvastatin 10 mg	45	-24	-30	-30	-15	+7	-33
95% CI for Diff[1]		-8 7, -2 7	-10 1, -2 6	-8, -1.1	-15 1, -0.7	-4.3, 3.9	-9.6, -1 9

[1] A negative value for the 95% CI for he difference between treatments favors atorvastatin calcium for all except HDL-C, for which a positive value favors atorvastatin calcium. If he range does not include 0, his indicates a statistically significant difference.

[a] Significantly different from lovastatin, ANCOVA, p ≤ 0.05
[b] Significantly different from pravastatin, ANCOVA, p ≤ 0.05
[c] Significantly different from simvastatin, ANCOVA, p ≤ 0 05

The impact on clinical outcomes of he differences in lipid-altering effects between treatments shown in Table 7 is not known. Table 7 does not contain data comparing the effects of atorvastatin calcium 10 mg and higher doses of lovastatin, pravastatin, and simvastatin. The drugs compared in he studies summarized in he table are not necessarily interchangeable.

14.3 Hypertriglyceridemia *(Fredrickson* Type IV)

The response to atorvastatin calcium in 64 patients wi h isolated hypertriglyceridemia treated ac oss several clinical trials is shown in he table below (Table 8). For he atorvastatin calcium-treated patients, median (min, max) baseline TG level was 565 (267 to 1502).

TABLE 8. Combined Patients With Isolated Elevated TG: Median (min, max) Percentage Change From Baseline

	Placebo (N = 12)	Atorvastatin Calcium 10 mg (N = 37)	Atorvastatin Calcium 20 mg (N = 13)	Atorvastatin Calcium 80 mg (N = 14)
Triglycerides	-12.4 (-36.6, 82.7)	-41 (-76 2, 49.4)	-38.7 (-62 7, 29 5)	-51 8 (-82.8, 41 3)
Total-C	-2 3 (-15.5, 24.4)	-28.2 (-44 9, -6 8)	-34 9 (-49 6, -15 2)	-44.4 (-63 5, -3.8)
LDL-C	3 6 (-31.3, 31 6)	-26 5 (-57 7, 9 8)	-30.4 (-53.9, 0.3)	-40.5 (-60 6,-13 8)
HDL-C	3 8 (-18.6, 13.4)	13.8 (-9.7, 61 5)	11(-3.2, 25 2)	7 5 (-10 8, 37 2)
VLDL-C	-1 (-31.9, 53 2)	-48 8 (-85 8, 57 3)	-44 6 (-62 2, -10.8)	-62 (-88.2, 37 6)
non HDL-C	-2 8 (-17 6, 30)	-33 (-52 1, -13 3)	-42 7 (-53 7, -17.4)	-51 5 (-72 9, -4.3)

14.4 Dysbetalipoproteinemia *(Fredrickson* Type III)

The results of an open-label c ossover study of 16 patients (genotypes: 14 apo E2/E2 and 2 apo E3/E2) wi h dysbetalipop oteinemia *(Fredrickson* Type III) are shown in he table below (Table 9).

TABLE 9. Open-Label Crossover Study of 16 Patients With Dysbetalipoproteinemia (*Fredrickson* Type III)

	Median (min, max) at Baseline (mg/dL)	Median % Change (min, max)	
		Atorvastatin Calcium 10 mg	Atorvastatin Calcium 80 mg
Total-C	442 (225, 1320)	-37 (-85, 17)	-58 (-90, -31)
Triglycerides	678 (273, 5990)	-39 (-92, -8)	-53 (-95, -30)
IDL-C + VLDL-C	215 (111, 613)	-32 (-76, 9)	-63 (-90, -8)
non HDL-C	411 (218, 1272)	-43 (-87, -19)	-64 (-92, -36)

14.5 Homozygous Familial Hypercholesterolemia

In a study without a concurrent cont ol g oup, 29 patients ages 6 to 37 years with homozygous FH received maximum daily doses of 20 to 80 mg of atorvastatin calcium. The mean LDL-C reduction in his study was 18%. Twenty-five patients with a reduction in LDL-C had a mean response of 20% (range of 7% to 53%, median of 24%); the remaining 4 patients had 7% to 24% increases in LDL-C. Five of he 29 patients had absent LDL-receptor function. Of hese, 2 patients also had a portacaval shunt and had no significant reduction in LDL-C. The remaining 3 receptor-negative patients had a mean LDL-C reduction of 22%.

14.6 Heterozygous Familial Hypercholesterolemia in Pediatric Patients

In a double-blind, placebo-cont olled study followed by an open-label phase, 187 boys and postmenarchal girls 10 to 17 years of age (mean age 14.1 years) with hete ozygous familial hypercholesterolemia (FH) or severe hypercholeste olemia, were randomized to atorvastatin calcium (n = 140) or placebo (n = 47) for 26 weeks and then all received atorvastatin calcium for 26 weeks. Inclusion in he study required 1) a baseline LDL-C level ≥ 190 mg/dL or 2) a baseline LDL-C level ≥ 160 mg/dL and positive family history of FH or documented premature cardiovascular disease in a first or second-degree relative. The mean baseline LDL-C value was 218.6 mg/dL (range: 138.5 to 385 mg/dL) in he atorvastatin calcium group compared to 230 mg/dL (range: 160 to 324.5 mg/dL) in he placebo g oup. The dosage of atorvastatin calcium (once daily) was 10 mg for the first 4 weeks and uptitrated to 20 mg if he LDL-C level was > 130 mg/dL. The number of atorvastatin calcium-treated patients who required uptitration to 20 mg after Week 4 during he double-blind phase was 80 (57.1%).

Atorvastatin calcium significantly decreased plasma levels of total-C, LDL-C, triglycerides, and apolipop otein B during the 26-week double-blind phase (see Table 10).

TABLE 10. Lipid-altering Effects of Atorvastatin Calcium in Adolescent Boys and Girls with Heterozygous Familial Hypercholesterolemia or Severe Hypercholesterolemia (Mean Percentage Change From Baseline at Endpoint in Intention-to-Treat Population)

DOSAGE	N	Total-C	LDL-C	HDL-C	TG	Apolipop otein B
Placebo	47	-1 5	-0.4	-1.9	1	0 7
Atorvastatin Calcium	140	-31.4	-39 6	2 8	-12	-34

The mean achieved LDL-C value was 130.7 mg/dL (range: 70 to 242 mg/dL) in he atorvastatin calcium g oup compared to 228.5 mg/dL (range: 152 to 385 mg/dL) in he placebo g oup during he 26-week double-blind phase.

The safety and efficacy of doses above 20 mg have not been studied in cont olled trials in children. The long-term efficacy of atorvastatin calcium herapy in childhood to reduce morbidity and mortality in adul hood has not been established.

15 REFERENCES

[1]National Choleste ol Education P ogram (NCEP): Highlights of he Report of he Expert Panel on Blood Choleste ol Levels in Children and Adolescents, *Pediatrics.* 89(3):495-501. 1992.

16 HOW SUPPLIED/STORAGE AND HANDLING

Atorvastatin calcium tablets 10 mg are white, elliptical, film-coated tablets, debossed with '**RX 12**' on one side and plain on he o her side. They are supplied as follows:

NDC 63304-827-90 Bottles of 90
NDC 63304-827-05 Bottles of 500

Atorvastatin calcium tablets 20 mg are white, elliptical, film-coated tablets, debossed wi h '**RX 828**' on one side and plain on he other side. They are supplied as follows:

NDC 63304-828-90 Bottles of 90
NDC 63304-828-05 Bottles of 500

Atorvastatin calcium tablets 40 mg are white, elliptical, film-coated tablets, debossed wi h '**RX 829**' on one side and plain on he other side. They are supplied as follows:

NDC 63304-829-90 Bottles of 90
NDC 63304-829-05 Bottles of 500

Atorvastatin calcium tablets 80 mg are white, elliptical, film-coated tablets, debossed wi h '**RX 830**' on one side and plain on he other side. They are supplied as follows:

NDC 63304-830-90 Bottles of 90
NDC 63304-830-05 Bottles of 500

Storage

Store at 20 - 25° C (68 - 77° F) [See USP Cont olled Room Temperature].

Dispense in tight containers (USP).

17 PATIENT COUNSELING INFORMATION

Patients taking atorvastatin calcium tablets should be advised hat choleste ol is a ch onic condition and hey should adhere to their medication along wi h heir National Choleste ol Education P ogram (NCEP)-recommended diet, a regular exercise p ogram as app opriate, and periodic testing of a fasting lipid panel to determine goal attainment.

Patients should be advised about substances they should not take concomitantly with atorvastatin *[see Warnings and Precautions (5.1)]*. Patients should also be advised to inform other healthcare professionals prescribing a new medication that they are taking atorvastatin calcium tablets.

17.1 Muscle Pain

All patients starting herapy wi h atorvastatin calcium tablets should be advised of the risk of myopathy and told to report p omptly any unexplained muscle pain, tende ness, or weakness. The risk of this occurring is increased when taking certain types of medication or consuming larger quantities (> 1 liter) of grapefruit juice. They should discuss all medication, bo h prescription and over he counter, wi h heir heal hcare p ofessional.

17.2 Liver Enzymes

It is recommended that liver function tests be performed prior to and at 12 weeks following bo h he initiation of herapy and any elevation of dose, and periodically (e.g., semiannually) thereafter.

17.3 Pregnancy

Women of childbearing age should be advised to use an effective method of bir h cont ol to prevent pregnancy while using atorvastatin calcium tablets. Discuss future pregnancy plans wi h your patients, and discuss when to stop atorvastatin calcium tablets if hey are trying to conceive. Patients should be advised hat if they become pregnant, they should stop taking atorvastatin calcium tablets and call heir heal hcare p ofessional.

17.4 Breastfeeding

Women who are breastfeeding should be advised to not use atorvastatin calcium tablets. Patients who have a lipid disorder and are breastfeeding, should be advised to discuss he options wi h heir heal hcare p ofessional.

Manufactured for:
Ranbaxy Pharmaceuticals Inc.
Jacksonville, FL 32257 USA
by: Ohm Laboratories Inc.
North Brunswick, NJ 08902 USA

June 2011

0000000

Size: 13.25" x 19.25"
Font: 6 Pt.
Track: (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

THUYANH VU
07/27/2011

JOHN F GRACE
07/29/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076477Orig1s000

CHEMISTRY REVIEWS

ANDA 076477

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, 80 mg

Ranbaxy Laboratories Limited

Haitao Li, Ph.D.
Chemistry Division I

Table of Contents

Chemistry Review Data Sheet

1. ANDA 076477

2. REVIEW #6

3. REVIEW DATE: 5/13/11

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous Documents	Document Date
FIRM:	
Original	August 19, 2002
Amendment (new correspondence)	October 9, 2002
Amendment (new correspondence)	October 10, 2002
Amendment (new correspondence)	October 17, 2002
Amendment (new correspondence)	December 9, 2002
Patent Amendment	January 8, 2003
Patent Amendment	February 10, 2003
Patent Amendment	February, 18, 2003
Patent Amendment	February, 28, 2003
Bio Telephone Amendment	March 4, 2003
Patent Amendment	March 6, 2003
Patent Amendment	March 7, 2003
Patent Amendment	March 11, 2003
Patent Amendment	March 19, 2003
Amendment to CMC NA Letter	April 11, 2003
Patent Amendment	April 17, 2003
Bio Amendment	May 29, 2003
Revision to Patent Certification	June 11, 2003
Amendment	August 14, 2003
Revision to Patent Certification	August 19, 2003
Revision to Patent Certification	August 20, 2003
Revision to Patent Certification	August 21, 2003
Revision to Patent Certification	August 22, 2003
Revision to Patent Certification	August 23, 2003

Revision to Patent Certification	August 25, 2003
Revision to Patent Certification	August 26, 2003
Revision to Patent Certification	August 27, 2003
Revision to Patent Certification	August 28, 2003
Revision to Patent Certification	September 2, 2003
Revision to Patent Certification	September 3, 2003
Revision to Patent Certification	September 4, 2003
Revision to Patent Certification	September 5, 2003
Revision to Patent Certification	September 8, 2003
Revision to Patent Certification	September 9, 2003
Revision to Patent Certification	September 10, 2003
Revision to Patent Certification	September 11, 2003
Revision to Patent Certification	September 15, 2003
Revision to Patent Certification	September 17, 2003
Revision to Patent Certification	October 22, 2003
Amendment (Labeling)	January 28, 2004
Amendment (Labeling)	March 2, 2004
Amendment (CMC)	March 16, 2004
Amendment (CMC)	August 16, 2004

FDA:	October 11, 2002
FDA acknowledgement letter	April 30, 2003
Bio Comment Letter	February 5, 2003
CMC NA Letter	May 21, 2003
CMC NA Letter	November 6, 2003
CMC NA Letter	November 18, 2003
Bio Deficiency Letter	

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	December 4, 2009
Amendment (CMC)	November 12, 2010

Firm has submitted several Amendments between 3/9/2006 and 2/14/2008 for the drug product made from amorphous drug substance. Recently, firm changed their amorphous API to crystalline form and changed the drug product formulation to improve the drug product quality and to be in-line with the innovator's product. Therefore, per the Division direction, the amendments submitted prior to 2/14/ 2008 were not considered in this review.

7. NAME & ADDRESS OF APPLICANT:

Name: Ranbaxy Laboratories Limited

Address:	Sector 18, Udyog Vihar Industrial Area Gurgaon – 122 001, India
Telephone:	91-124-5011838
Representative:	Ranbaxy Pharmaceuticals, Inc. US Agent for Ranbaxy Laboratories Limited
Address:	600 College Road East Princeton, NJ 08540
Representative:	Scott D. Tomsky
Telephone/Fax:	(609) 720-5609 / (609) 514-9797

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Ranbaxy Laboratories Limited proposed ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg is the approved, referenced listed drug, Lipitor Tablets (Atorvastatin Calcium Tablets) of NDA #20-702, held by Pfizer.

b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, 22nd Edition (2002), lists the following patents: US 4,681,893; US 5,273,995; US 5,686,104; US 5,969,156, US 6,126,971 and US 6,605,729 in connection with the above identified drug product.

c. With reference to US Patent Nos. 5,686,104; 5,969,156, US 6,126,971 and US 6,605,729 the applicant certifies that in the opinion and to the best of its knowledge, no valid or enforceable claim of said patents will be infringed by the manufacture, use or sale of Ranbaxy's Atorvastatin Calcium Tablets for which this abbreviated new drug application is submitted. Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

d. With respect to US Patent Nos. 4,681,893 and 5,273,995 the applicant certifies that in the opinion and to the best of its knowledge, the last expiring of said patents will expire on June 28, 2011. Ranbaxy Laboratories Limited requests approval of this ANDA effective after June 28, 2011.

e. The un-expired exclusivity listed for this product is set to expire on April 22, 2005, October 18, 2005 and April 18, 2006.

10. PHARMACOL. CATEGORY: Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg, 80 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

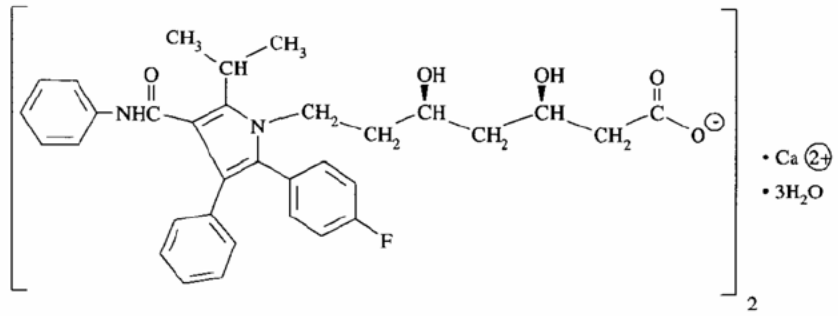
Atorvastatin Calcium

(b) (4)

CAS 134523-03-8
CAS 134523-00-5 (atorvastatin)

	(b) (4)	calcium salt trihydrate	(b) (4)
Molecular Formula		$(C_{33}H_{34}FN_2O_5)_2Ca\ 3H_2O$	
Molecular Weight		1209.42	

(b) (4)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	API	1	Inadequate	4/15/2011	Reviewed by H. Li, Ph.D.
24139	II	Ranbaxy	API	1	Inadequate		Reviewed by B. Lim, Ph.D.
See Section 26	III	See Section 26	Container/ Closure	4			

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC	RECOMMENDATION	DATE	

Chemistry Review Data Sheet

RELATED REVIEWS			REVIEWER
Microbiology	N/A		
EES	Pending		
Methods Validation	N/A		
Labeling	Pending		
Bioequivalence	Deficient		
EA	N/A		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below: Minor Amendment

The Chemistry Review for ANDA 76-477

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Not approvable (Minor)

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release tablets. It is indicated for lipid regulation.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate; candelilla wax, FCC; croscarmellose sodium; hydroxypropyl cellulose; lactose monohydrate; magnesium stearate; microcrystalline cellulose; (b) (4) (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80; simethicone emulsion.

The manufacturing process (b) (4) .

Drug Substance:
Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

(b) (4) Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly

soluble in ethanol, and freely soluble in methanol. [redacted]

The DS exhibit many polymorphic forms. The DP manufacturer for this ANDA use crystalline form of the API.

The MDD is 80 mg. Based on ICH Q3A, for DS: IT: [redacted] %, QT [redacted] %. Based on ICH Q3B, for DP: IT: [redacted] %, QT: [redacted] %.

The DS becomes an official USP compendial item on October 1, 2010.

B. Description of How the Drug Product is Intended to be Used

The DP is intended for long term use.

Atorvastatin calcium tablets 10 mg are white, elliptical, film-coated tablets, debossed with 'RX 12' on one side and plain on the other side. They are supplied as follows:

NDC 63304-827-90	Bottles of 90
NDC 63304-827-05	Bottles of 500

Atorvastatin calcium tablets 20 mg are white, elliptical, film-coated tablets, debossed with 'RX 828' on one side and plain on the other side. They are supplied as follows:

NDC 63304-828-90	Bottles of 90
NDC 63304-828-05	Bottles of 500G33

Atorvastatin calcium tablets 40 mg are white, elliptical, film-coated tablets, debossed with 'RX 829' on one side and plain on the other side. They are supplied as follows:

NDC 63304-829-90	Bottles of 90
NDC 63304-829-05	Bottles of 500

Atorvastatin calcium tablets 80 mg are white, elliptical, film-coated tablets, debossed with 'RX 830' on one side and plain on the other side. They are supplied as follows:

NDC 63304-830-90	Bottles of 90
NDC 63304-830-05	Bottles of 500

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

The application is not approved due to CMC related minor deficiencies.

III. Administrative

File path:
V:\Chemistry Division III\Team 34\Final Version For DFS Folder\ANDA76477R6.doc

Endorsements:

HFD-630/H. Li, Ph.D, CR/6/3/2011

HFD-630/L.Nagavelli, Ph.D, TL/ 6/5/2011

HFD-617/L.A. Sears, PM/

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAITAO LI
06/14/2011

LEIGH A SEARS
06/14/2011

MOHAMMED K AHMED
06/14/2011

ANDA 076477

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, 80 mg

Ranbaxy Laboratories Limited

Haitao Li, Ph.D.
Chemistry Division III

Table of Contents

Chemistry Review Data Sheet

1. ANDA 076477

2. REVIEW #7

3. REVIEW DATE: August 26, 2011; October 7, 2011

4. REVIEWER: Haitao Li, Ph.D.

5. PREVIOUS DOCUMENTS:

Previous documents not considered in the review	Document Date	
FIRM:		
Original	August 19, 2002*	* Technical data from Original submission as well as the subsequent Amendments submitted including 12/4/2008 is NOT including in this review as the material was referred to Paonta Sahib manufacturing facility.
Amendment (new correspondence)	October 9, 2002	
Amendment (new correspondence)	October 10, 2002	
Amendment (new correspondence)	October 17, 2002	
Amendment (new correspondence)	December 9, 2002	
Patent Amendment	January 8, 2003	
Patent Amendment	February 10, 2003	
Patent Amendment	February, 18, 2003	
Patent Amendment	February, 28, 2003	
Bio Telephone Amendment	March 4, 2003	
Patent Amendment	March 6, 2003	
Patent Amendment	March 7, 2003	
Patent Amendment	March 11, 2003	
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Amendment	August 14, 2003	
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Revision to Patent Certification	September 10, 2003
Revision to Patent Certification	September 11, 2003
Revision to Patent Certification	September 15, 2003
Revision to Patent Certification	September 17, 2003
Revision to Patent Certification	October 22, 2003
Amendment (Labeling)	January 28, 2004
Amendment (Labeling)	March 2, 2004
Amendment (CMC)	March 16, 2004
Amendment (CMC)	August 16, 2004

Previous documents considered in the review

Amendment (CMC)	December 4, 2009
Amendment (CMC)	November 12, 2010

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	Document Date
Amendment (CMC)	June 7, 2011
Amendment (CMC)	July 27, 2011
Amendment (CMC)	September 1, 2011
Amendment (CMC)	September 19, 2011
Amendment (CMC)	October 5, 2011

Note: Amendments dated 12/4/2009 on wards are based on the drug product manufactured at Ohm Laboratories, Inc, NJ and the approval recommendation is based on this data

7. NAME & ADDRESS OF APPLICANT:

Name: Ranbaxy Laboratories Limited

Address: Sector 18, Udyog Vihar Industrial Area
Gurgaon – 122 001, India

Telephone:	91-124-5011838
Representative:	Ranbaxy Pharmaceuticals, Inc. US Agent for Ranbaxy Laboratories Limited
Address:	600 College Road East Princeton, NJ 08540
Representative:	Scott D. Tomsky
Telephone/Fax:	(609) 720-5609 / (609) 514-9797

8. DRUG PRODUCT NAME/CODE/TYPE:

a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Atorvastatin Calcium Tablets

9. LEGAL BASIS FOR SUBMISSION:

a. The basis for Ranbaxy Laboratories Limited proposed ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg is the approved, referenced listed drug, Lipitor Tablets (Atorvastatin Calcium Tablets) of NDA #20-702, held by Pfizer.

b. According to the information published in the Electronic Orange Book, Approved Drug Products with Therapeutic Equivalence Evaluations, 22nd Edition (2002), lists the following patents: US 4,681,893; US 5,273,995; US 5,686,104; US 5,969,156, US 6,126,971 and US 6,605,729 in connection with the above identified drug product.

c. With reference to US Patent Nos. 5,686,104; 5,969,156, US 6,126,971 and US 6,605,729 the applicant certifies that in the opinion and to the best of its knowledge, no valid or enforceable claim of said patents will be infringed by the manufacture, use or sale of Ranbaxy's Atorvastatin Calcium Tablets for which this abbreviated new drug application is submitted. Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

d. With respect to US Patent Nos. 4,681,893 and 5,273,995 the applicant certifies that in the opinion and to the best of its knowledge, the last expiring of said patents will expire on June 28, 2011. Ranbaxy Laboratories Limited requests approval of this ANDA effective after June 28, 2011.

e. The un-expired exclusivity listed for this product is set to expire on April 22, 2005, October 18, 2005 and April 18, 2006.

Chemistry Review Data Sheet

10. PHARMACOL. CATEGORY: Lipid Modifier. HMG-CoA reductase inhibitor/ Antihyperlipoproteinemic agent.

11. DOSAGE FORM: Tablets

12. STRENGTH/POTENCY: 10 mg, 20 mg, 40 mg, 80 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: _X__Rx ___OTC

15a. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

_____SPOTS product – Form Completed

__X___Not a SPOTS product

15b. NANOTECHNOLOGY PRODUCT TRACKING:

_____NANO product – Form Completed (See Appendix A.4)

__X___Not a NANO product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

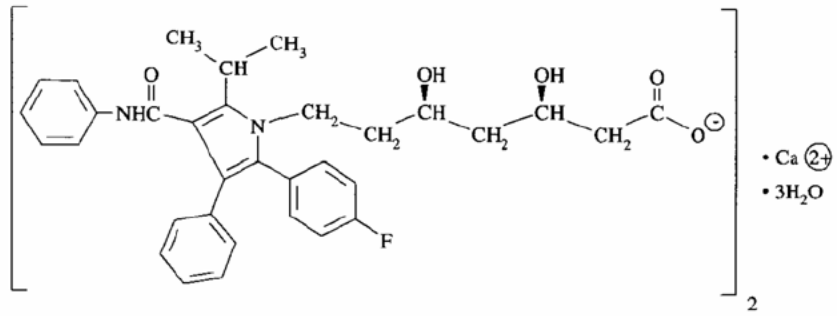
Atorvastatin Calcium

(b) (4)

CAS 134523-03-8
CAS 134523-00-5 (atorvastatin)

	(b) (4)	calcium salt trihydrate	(b) (4)
Molecular Formula		$(C_{33}H_{34}FN_2O_5)_2Ca\ 3H_2O$	
Molecular Weight		1209.42	

(b) (4)



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE[1]	STATUS[2]	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	II	(b) (4)	API	1	Adequate IR	9/28/2011	Reviewed by H. Li, Ph.D.
24139	II	Ranbaxy	API	1	Adequate	10/14/2011	Reviewed by B. Lim, Ph.D.
See Section 26	III	See Section 26	Container/ Closure	4	N/A		

[1] Action codes for DMF Table:
1 – DMF Reviewed.
Other codes indicate why the DMF was not reviewed, as follows:
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available
7 – Other (explain under "Comments")

[2] Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
N/A		

18. STATUS:

CONSULTS/ CMC	RECOMMENDATION	DATE	

RELATED REVIEWS			REVIEWER
Microbiology	N/A		
EES	Acceptable	10/25/2011	D. SMITH
Methods Validation	N/A		
Labeling	Approvable	7/29/2011	VU, THUYANH
Bioequivalence Dissolution	Adequate Adequate	10/25/2011	Chun, Nam
EA	Acceptable		
Radiopharmaceutical	N/A		

19. ORDER OF REVIEW

The application submission(s) covered by this review was taken in the date order of receipt. ____ Yes __X__ No If no, explain reason(s) below:

The application is expedited by Office. Attached below is Bob West's e-mail dated 6/6/2011.

From: West, Robert L
Sent: Monday, June 06, 2011 8:21 AM
To: Sayeed, Vilayat A
Cc: Read, David T
Subject: RE: Ranbaxy AIP Memo and Letter

Yes, it's official with the signing by Dr. Woodcock of our memorandum and the letter to Ranbaxy telling them we're reviewing their ANDA.

Bob

From: Sayeed, Vilayat A
Sent: Monday, June 06, 2011 7:55 AM
To: West, Robert L
Subject: RE: Ranbaxy AIP Memo and Letter

Bob

Is this ANDA expedited

Vilayat

The Chemistry Review for ANDA 076477

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

Approvable

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Product:

The proposed DP, Atorvastatin Calcium tablets, is a non-sterile, oral, immediate release tablets. It is indicated for lipid regulation.

Atorvastatin calcium tablets for oral administration contain 10, 20, 40, or 80 mg atorvastatin and the following inactive ingredients: calcium carbonate; candelilla wax, FCC; croscarmellose sodium; hydroxypropyl cellulose; lactose monohydrate; magnesium stearate; microcrystalline cellulose; (b) (4) (hypromellose, polyethylene glycol, talc, titanium dioxide); polysorbate 80; simethicone emulsion.

The manufacturing process (b) (4) .

Drug Substance:
Atorvastatin calcium is a synthetic lipid-lowering agent. Atorvastatin is an inhibitor of 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase. This enzyme catalyzes the conversion of HMG-CoA to mevalonate, an early and rate-limiting step in cholesterol biosynthesis.

(b) (4) Atorvastatin calcium is a white to off-white crystalline powder that is insoluble in aqueous solutions of pH 4 and below. Atorvastatin calcium is very slightly soluble in distilled water, pH 7.4 phosphate buffer, and acetonitrile, slightly

soluble in ethanol, and freely soluble in methanol. (b) (4)

The DS exhibit many polymorphic forms. The DP manufacturer for this ANDA use crystalline form of the API.

The MDD is 80 mg. Based on ICH Q3A, for DS: IT: (b) (4) %, QT (b) (4) %. Based on ICH Q3B, for DP: IT: (b) (4) %, QT: (b) (4) %.

The DS is an official USP compendial item.

B. Description of How the Drug Product is Intended to be Used

The DP is intended for long term use.

Atorvastatin calcium tablets 10 mg are white, elliptical, film-coated tablets, debossed with 'RX 12' on one side and plain on the other side. They are supplied as follows:
NDC 63304-827-90 Bottles of 90
NDC 63304-827-05 Bottles of 500

Atorvastatin calcium tablets 20 mg are white, elliptical, film-coated tablets, debossed with 'RX 828' on one side and plain on the other side. They are supplied as follows:
NDC 63304-828-90 Bottles of 90
NDC 63304-828-05 Bottles of 500

Atorvastatin calcium tablets 40 mg are white, elliptical, film-coated tablets, debossed with 'RX 829' on one side and plain on the other side. They are supplied as follows:
NDC 63304-829-90 Bottles of 90
NDC 63304-829-05 Bottles of 500

Atorvastatin calcium tablets 80 mg are white, elliptical, film-coated tablets, debossed with 'RX 830' on one side and plain on the other side. They are supplied as follows:
NDC 63304-830-90 Bottles of 90
NDC 63304-830-05 Bottles of 500

Store at 20° to 25°C (68° to 77°F) [See USP Controlled Room Temperature].

C. Basis for Approvability or Not-Approval Recommendation

The CMC review is currently acceptable per the review team recommendations. ANDA approvability is pending Division review, other disciplines and/or EES. This CMC review may require an addendum based on recommendations made by other review disciplines.

III. Administrative

File path:
V:\Chemistry Division III\Team 34\Final Version For DFS Folder\ANDA76477R7_11042011.doc

Endorsements:
HFD-630/H. Li, Ph.D, CR/11/04/2011
HFD-630/L.Nagavelli, Ph.D, TL/11/04/2011
HFD-617/L.A. Sears, PM/11/04/2011

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAITAO LI
11/04/2011

LAXMA R NAGAVELLI
11/04/2011

LEIGH A SEARS
11/04/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076477Orig1s000

BIOEQUIVALENCE REVIEWS

5 - Tell from about spec.

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 76-477	SPONSOR: Ranbaxy Laboratories, Limited, India Abha Pant, U.S. Agent, Princeton, NJ
DRUG AND DOSAGE FORM:	Atorvastatin Calcium Tablets
STRENGTH(S):	10, 20, 40, and 80 mg
TYPES OF STUDIES:	Fasted and fed on 80 mg strength
CLINICAL STUDY SITE:	Clinical Pharmacology Unit, Ranbaxy Research Laboratories, Majeedia Hospital, Jamia Hamdard (Hamdard University) Hamdard Nagar, NeDelhi 110 062, India
ANALYTICAL SITE:	Clinical Pharmacology & Pharmacokinetics Ranbaxy Research Laboratories Plot No. 20, Sector 18, Udyog Vihar Industrial Area Gurgaon 122001, Haryana, India

STUDY SUMMARY : The studies demonstrate that the test product, Ranbaxy's Atorvastatin Calcium Tablet, 80 mg, is bioequivalent to the reference product, Pfizer's Lipitor® Tablet, 80 mg under fasting and non-fasting conditions.

DISSOLUTION : The dissolution data for the test products (10 mg, 20 mg, 40 mg, and 80 mg) is acceptable. Waivers for the 10 mg, 20 mg and 40 mg strengths are granted.

DSI INSPECTION STATUS

Inspection needed: No	Inspection status:	Inspection results:
First Generic: Yes New facility: No For cause _____ Other _____	Inspection requested: (date) Inspection completed: (date)	

PRIMARY REVIEWER: James E. Chaney BRANCH: I

INITIAL: JEC DATE: 4/16/2003

TEAM LEADER: Yih-Chain Huang BRANCH: I

INITIAL: YCH DATE: 4/17/2003

DIRECTOR, DIVISION OF BIOEQUIVALENCE: DALE P. CONNER, Pharm.D.

INITIAL : DPC DATE : 4/30/03

BIOEQUIVALENCY COMMENTS

ANDA: 76-477 APPLICANT: Ranbaxy Laboratories, Limited, India

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10, 20, 40, and 80 mg

The Division of Bioequivalence has completed its review of your submission(s)acknowledged on the cover sheet and has no further questions at this time.

We acknowledge that the following dissolution testing has been incorporated into your stability and quality control programs:

> The dissolution testing should be conducted in 900 ml of 0.05M phosphate buffer, pH 6.8 using USP apparatus 2 (paddle) at 75 rpm.

We recommend the following dissolution specification:

> NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes.

In the future please select your concentrations of Q.C. samples to fit within the concentration range of the study samples. Also, concentrations of standards in the calibration curves should be chosen on the basis of the concentration range expected in the study. Please refer to the Guidance for Industry Bioanalytical Method Validation issued in May 2001.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these regulatory reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

2.1

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	76-477
Drug Product Name	Atorvastatin Calcium Tablets
Strength	10, 20, 40, and 80 mg
Applicant Name	Ranbaxy Laboratories, Limited, India
Address	Sector-18, UdyogVihar, Gurgaon India 122001 Abha Pant, U.S. Agent, Princeton, NJ
Submission Date(s)	August 19, 2002 (original)
Amendment Date(s)	May 29, 2003 (current)
Reviewer	James E. Chaney
File Location	V:\FIRMSNZ\RANBAXY\LTRS&REV\76477A0503.doc

Review of an Amendment Requesting Change of Dissolution Testing Specifications

EXECUTIVE SUMMARY

This is a review of an amendment. On August 19, 2002 the firm submitted two acceptable *in vivo* bioequivalence studies (single-dose fasting, and non-fasting) on the 80 mg strength and acceptable dissolution testing data on the 10, 20, 40 and 80 mg strengths. The waiver requests were found acceptable for the 10, 20, and 40 mg strengths based on (b) (4) composition and comparative dissolution testing on the lower strengths. The recommended dissolution specification was that NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes. In the current amendment the firm states that it feels the specification proposed by the agency is too stringent and requests that the dissolution specification of "NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes" be changed to "NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in (b) (4) minutes". The Division of Bioequivalence has found that the firm is not justified in its request to change the specifications.

ORIGINAL AUGUST 19, 2002 ANDA SUBMISSION

On August 19, 2002 the firm submitted two acceptable *in vivo* bioequivalence studies (single-dose fasting, and non-fasting) on the 80 mg strength and comparative dissolution testing data on the 10, 20, 40 and 80 mg strengths. The firm's dissolution testing was conducted in 900 ml of 0.05M phosphate buffer, pH 6.8 using USP apparatus 2 (paddle) at 75 rpm and the recommended dissolution specification was that NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes.

CURRENT SUBMISSION

1. The firm maintains that the specification proposed by the agency was too stringent and has requested that the dissolution specification of "NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes" be changed to "NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in (b) (4) minutes".

2. The firm states that compliance with the limit of "NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes" may be difficult for the following reasons:

- The product is film-coated and hence the dissolution testing at 15 minutes would very much depend on the disintegration/dissolution of the film component of the individual tablets.
- Slight batch-to-batch variability may lead to noncompliance using the stringent limit of the FDA recommended specification.
- Limited current availability of dissolution data

3. Also, the firm refers to the mean dissolution data presented in its 4/11/03 response to Question #5 of the 2/5/03 deficiency letter in which the reviewing Chemistry Division of OGD asked the firm to justify its proposed wide hardness ranges by submitting dissolution data for tablets compressed at the high and low ends of the hardness ranges. The mean dissolution data submitted in the 4/11/03 submission with the ranges of percent dissolved (no individual data) submission is shown in Table 1.

Table 1

Strength	Existing Limits (Kp)	Hardness Range Studied (Kp)	Mean % Atorvastatin Dissolved (Range of % Atorvastatin Dissolved)			
			15 min	30 min	45 min	60 min
10 mg	(b) (4)	(b) (4)				
20 mg	(b) (4)					
40 mg	(b) (4)					
80 mg	(b) (4)					

Reviewer's Note: Ranbaxy does not state in this amendment how many tablets were used for the hardness testing (probably six). The firm has merely presented the data without any explanation of how it would support its request for the specification change.

COMMENTS

1. The RLD is film-coated and it met the recommended specifications. Film coating should not be a factor for consideration and offers no support for the requested change of specifications.

2. Data (mean values and ranges without individual tablet data or number of tablets tested) presented regarding dissolution *vs.* hardness provide insufficient support for changing the dissolution specifications.

   All the degrees of hardness tested on all strengths gave average percent dissolved values of (b) (4) or more at 15 minutes. However, the ranges are quite variable and the 40 mg and 80 mg tablets had one or more tablets which were less than (b) (4) dissolved in 15 minutes.

3. The originally submitted dissolution testing data on the test and reference bio-lots at the 15 minutes time point is shown in Table 2.

Table 2. *In-Vitro* Dissolution Testing Results at 15 Minutes from the Original Submission

Strength	Test Atorvastatin Calcium Tablets			Reference Lipitor® Tablets		
(mg)	Mean	%CV	Range	Mean	%CV	Range
10	97	1	(b) (4)	100	2	(b) (4)
20	96	3		98	3	
40	95	3		98	1	
80	96	3		97	2	

All strengths of the test and reference products had mean percent dissolved values of (b) (4) % or greater at 15 minutes.

4. On 5/21/03 (subsequent to the current bio-amendment) in view of the fact DBE had recommended the dissolution specification of (b) (4) dissolved in 15 minutes the OGD Chemistry Division requested dissolution study data at the 15 minutes time point all strengths of the biolots in all container/closure configurations that had been stored under accelerated stability testing conditions. On 8/14/03 the firm responded to the OGD Chemistry Division with the information shown in Table 3. The firm carried out the dissolution profiling studies at 15, 30, 45 and 60 minutes on the 3 months accelerated condition samples of all the packs of all four strengths. Additionally, dissolution profiling was conducted on the current stability samples (12 months CRT) of all the package configurations of all four strengths.

Table 3.

Strength	Batch No.	Pack	Condition*	% Atorvastatin Dissolved			
				15 min	30 min	45 min	60 min
10 mg	1201336	(b) (4)	3 M Accl	98.6	98.3	99.8	99.9
			12 M CRT	91.9	99.9	99.6	100.5
			3 M Accl	96.7	96.6	97.8	97.9
			12 M CRT	97.7	101.8	100.4	101.3
20 mg	1201334		3 M Accl	97.7	98.4	98.8	100.2
			12 M CRT	94.2	96.5	96.7	97.2
			3 M Accl	93.9	96.1	95.4	96.7
			12 M CRT	96.1	99.2	98.6	99.0
40 mg	1201328		3 M Accl	93.1	96.6	96.5	97.2
			12 M CRT	94.9	97.5	98.1	98.7
			3 M Accl	93.2	96.4	95.8	96.6
			12 M CRT	95.5	98.5	99.2	99.7
80 mg	1200558		3 M Accl	93.2	96.5	97.3	97.1
			12 M CRT	85.2	97.7	98.5	99.0
		500's	3 M Accl	92.0	95.2	94.4	97.8
			12 M CRT	88.3	96.9	97.9	98.8

* "3 M Accl" is abbreviation for 3 months stability testing under accelerated and "12 M CRT" is abbreviation for 12 months stability testing at room temperature.

The above stability testing data suggest that the firm would not have a problem meeting the FDA recommended specification of NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium dissolved in 15 minutes.

RECOMMENDATIONS

1. The dissolution data presented on the tablets at the extreme upper and lower limits of tablet hardness do not support the proposed change of specification from NLT (b) (4) (Q) in 15 minutes to NLT (b) (4) (Q) in (b) (4) minutes.

2. The dissolution testing should be incorporated into the firm's manufacturing and controls programs. The dissolution testing should be conducted in 900 ml of 0.05M phosphate buffer, pH 6.8 using USP apparatus 2 (paddle) at 75 rpm. The test product should meet the following specification:

   NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes.

The firm should be informed of the above recommendations.

James E. Chaney

James E. Chaney, Ph.D.
Division of Bioequivalence
Review Branch I

RD INITIALED YCHuang
FT INITIALED YCHuang Date 11/18/2003

Concur: Barbara M. Davit Date 11/18/03

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence

JEC/111803

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ANDA No.	76-477
Drug Product Name	Atorvastatin Calcium Tablets
Strength	10, 20, 40, and 80 mg
Applicant Name	Ranbaxy Laboratories, Limited, India

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-477 APPLICANT: Ranbaxy Laboratories, Limited, India
Abha Pant, U.S. Agent, Princeton, NJ

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10, 20, 40, and 80 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Your request to increase the time at which NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved from 15 minutes to (b) (4) minutes is denied.

Please continue to use the following dissolution testing in your stability and quality control programs:

The dissolution testing should be conducted in 900 ml of 0.05M phosphate buffer, pH 6.8 using USP apparatus 2 (paddle) at 75 rpm.

We recommend the following dissolution specification:

NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes.

Sincerely yours,

Barbara M. Davit

for Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

BIOEQUIVALENCY DEFICIENCIES

ANDA: 76-477 APPLICANT: Ranbaxy Laboratories, Limited, India
Abha Pant, U.S. Agent, Princeton, NJ

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10, 20, 40, and 80 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Your request to increase the time at which NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved from 15 minutes to (b) (4) minutes is denied.

Please continue to use the following dissolution testing in your stability and quality control programs:

The dissolution testing should be conducted in 900 ml of 0.05M phosphate buffer, pH 6.8 using USP apparatus 2 (paddle) at 75 rpm.

We recommend the following dissolution specification:

NLT (b) (4) (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes.

Sincerely yours,

for Barbara M. Davit

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

CC: ANDA 76-477
ANDA DUPLICATE
DIVISION FILE
FIELD COPY
DRUG FILE

HFD-652/ J. Chaney J. Chaney 11/18/2003
HFD-652/ Y. Huang YH 11/18/2003
HFD-650/ A. Sigler for
HFD-650/ D. Conner BWD 11/18/03

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BIOEQUIVALENCY - ACCEPTABLE Submission date: May 29, 2003
(Bioequivalence testing submitted 8/19/02) was found acceptable but dissolution specification proposed in current 5/29/03 amendment is unacceptable.)

STUDY AMENDMENT (STA) 01C Strengths: 10, 20, 40, and 80 mg
(Request to change dissolution specification is denied) Outcome: UN

Outcome Decisions: UN - Unacceptable

NOTE:
AC - Acceptable
NC - No Action
UN - Unacceptable
IC - Incomplete

Outcome Decision: Unacceptable

WINBIO COMMENTS:

The currently reviewed May 29, 2003 amendment proposing the new release specification of NLT (b)(4) (Q) of the labeled amount of atorvastatin calcium is dissolved in (b)(4) minutes is unacceptable.

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	076477					
Drug Product Name	Atorvastatin Calcium Tablets					
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg					
Applicant Name	Ranbaxy Laboratories Ltd., India					
Address	Plot # GP-5, Sector 18, HSIDC, Old Delhi, Gurgaon Road, Gurgaon, 122015, Hariyana, India					
Applicant's Point of Contact	Usha Sankaran, US Agent, 600 College Road East, Ranbaxy Inc., Princeton, NJ 08540					
Contact's Telephone Number	609-720-5304					
Contact's Fax Number	609-514-9797					
Original Submission Date(s)	August 19, 2002					
Submission Date(s) of Amendment(s) Under Review	**December 9, 2009**					
Reviewer	S. P. Shrivastava, Ph.D.					
Study Number (s)	**R09-1032**	**R09-1033**	**BE-248-ATOR-2009**	**BE-249-ATOR-2009**	**365-ATORV-09**	**3023-ATORV-08**
Study Type (s)	Fasting	Fed	Fasting	Fed	Fasting	Fed
Strength (s)	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg
Clinical Site	**Cetero Research**		**Clinical Services Fortis Clinical Research Ltd.**		**Ranbaxy Labs. Ltd.**	
Clinical Site Address	4801 Amber Valley Pkwy. Fargo, ND 58104		Ltd., Sunflag Hospital & Research Centre Sector-16A, Faridabad 121 002, Haryana, India		Majeedia Hospital, Hamdard Nagar New Delhi India	
Analytical Site	(b) (4)				**Ranbaxy Labs. Ltd**	
Analytical Site Address					Plot No. GP-5, Sector 18, HSIDC, Gurgaon, Haryana, India	
Dissolution Testing Site	Ranbaxy Laboratory Ltd.					
DSI Inspection Status	No DSI inspection is pending or necessary					
Overall Review Result	**INADEQUATE**					
Waiver Request Result	**INADEQUATE :** 10, 20 and 40 mg					
DSI Report Result	**Clinical: ADEQUATE.** **Analytical: ADEQUATE**					

Bioequivalence Study Tracking/Supporting Document #	**Study/Test Type**	**Strength**	**Review Result**
Supporting Document # 1	**Dissolution**	80 mg	**INADEQUATE**
	Dissolution	40 mg	**INADEQUATE**
	Dissolution	20 mg	**INADEQUATE**
	Dissolution	10 mg	**INADEQUATE**

Supporting Document # 1	**Fasting (Pivotal)**	80 mg	**ADEQUATE**
	Fed (Pivotal)	80 mg	**ADEQUATE**
	Fasting (BE-248-ATOR-2009)	80 mg	**INADEQUATE**
	Fed (BE-249-ATOR-2009)	80 mg	**INADEQUATE**
	Fasting (365-ATORV-09)	80 mg	**INADEQUATE**
	Fed (3023-ATORV-08)	80 mg	**INADEQUATE**
	Permeability Study	**N/A**	**N/A**
	Solubility Study	**N/A**	**N/A**

1. EXECUTIVE SUMMARY

This application references Atorvastatin Calcium Tablets, 10, 20, 40 and 80 mg [Lipitor®, Pfizer, NDA 020702, Approved 10, 20 mg, 40 mg-12/17/1996; 80 mg-4/7/2000 (RLD)]. The firm has previously conducted acceptable single-dose fasting and fed studies on 80 mg tablets, and dissolution testing results on all strengths (see JEChaney, C:\Documents and Settings\shrivastavas\My Documents\076477n1209.doc, C:\Documents and Settings\shrivastavas\My Documents\076477n1209.doc, SHRIVASTAVA, SURENDRA P 09/27/2007 N/A 09/27/2007 REV-BIOEQ-01(General Review) Original-1, SHRIVASTAVA, SURENDRA P 06/19/2008 N/A 06/19/2008 REV-BIOEQ-01(General Review) Original-1). In this amendment, the firm has made CMC changes [API from amorphous (Ranbaxy Lab, Paonta Sahib's API) to crystalline form ((b) (4) s API), component and composition, manufacturing process and manufacturing site (Ohm Labs, N.J.)]. The firm did not provide specific reason for these proposed changes. It is probably due to the regulatory issues related to the original manufacturing site. To support the CMC changes the firm has submitted additional single-dose fasting and fed studies on 80 mg strength and requested waivers of BE studies for 10, 20 and 40 mg tablets. The firm has also submitted summary data for four pilot studies conducted.

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This application contains the results of fasting and fed bioequivalence (BE) studies comparing the test product, Atorvastatin Calcium Tablets, 80 mg, to the corresponding reference product, Pfizer's Lipitor® (Atorvastatin Calcium) Tablets, 80 mg. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The data analyses were based on actual sampling times. The results are summarized in the tables below.

Atorvastatin: Fasting and Fed Studies

Atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. R09-1032, N=76 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	130541.4	131063.3	1.00	94.04	105.50
AUC$^{\infty}$ (pg·hr/mL)	132122.6	132569.7	1.00	94.10	105.56
Cmax (pg/mL)	32751.40	33186.70	0.99	88.24	110.37

Atorvastatin, 1 X 80 mg Fed Bioequivalence Study No. R09-1033, N=76 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	128437.5	128865.9	1.00	94.53	105.09
AUC$^{\infty}$ (pg·hr/mL)	130112.9	130682.9	1.00	94.24	105.19
Cmax (pg/mL)	27847.28	29025.88	0.96	83.20	110.63

Ortho-hydroxy Atorvastatin: Fasting and Fed

Ortho-hydroxy Atorvastatin Fasting Bioequivalence Study No. R09-1032, N=76 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr * pg/ml)	172630.2	168593.4	1.02	96.44	108.72
AUC$^{\infty}$ (hr * pg/ml)	174365.2	170216.5	1.02	96.41	108.85
Cmax (pg /ml)	29865.76	29897.59	1.00	89.65	111.31

Ortho-hydroxy Atorvastatin Fed Bioequivalence Study No. R09-1033 N=76 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr * pg/ml)	142055.4	143318.7	0.99	95.76	102.59
AUC$^{\infty}$ (hr * pg/ml)	143728.6	145312.9	0.99	95.59	102.34
Cmax (pg/ml)	20093.50	20613.33	0.97	86.64	109.67

Para-hydroxy Atorvastatin: Fasting and Fed

Para-hydroxy Atorvastatin Fasting Bioequivalence Study No. R09-1032, N=76 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr * pg/ml)	19003.56	19153.00	0.99	91.57	107.51
AUC$^{\infty}$ (hr * pg/ml)	22702.34	22582.77	1.01	92.26	109.54
Cmax (pg/ml)	926.56	920.80	1.01	91.02	111.24

Para-hydroxy Atorvastatin Fed Bioequivalence Study No. R09-1033, N=76 Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (hr * pg/ml)	16282.37	16691.03	0.98	92.86	102.48
AUC$^{\infty}$ (hr * pg/ml)*	20166.96	21036.43	0.96	90.16	101.93
Cmax (pg/ml)	748.86	751.79	1.00	91.79	108.09

The firm's fasting and fed BE studies are **adequate**. It should be noted that Ranbaxy's Atorvastatin Calcium tablets formulated with amorphous form (Ranbaxy Lab, Paonta Sahib's API) as well as crystalline form ((b) (4) API) meet the 90% CI BE criteria, indicating minimal effect of polymorphic forms of Atorvastatin on BE.

The firm has also conducted four pilot studies prior to conducting the pivotal studies. The formulations of the pilot and pivotal study lots are identical. The outline of the studies and PK results calculated and submitted by the firm are provided in the Appendix, 4.2.3, Pilot Studies. Brief summary of study results are provided below. Three pilot studies failed in meeting the 90% CI BE criteria of 80-125% for Atorvastatin for Cmax (see the tables below). In one fasting study (3023-ATORV-08), the study failed the 90% CI criteria for all three PK parameters. Supporting data for ortho-hydroxy and para-hydroxy atorvastatin were within the 80-125% for all PK parameters.

Pilot Study No. BE-248-ATOR-2009 (Fasting)

Atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. BE-248-ATOR-2009, N=13 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	260419.4	258840.1	100.61	88.77	114.02
AUC$^{\infty}$ (pg·hr/mL)	267467.1	267743.1	99.90	88.40	112.89
Cmax (pg/mL)	64499.7	56519.2	114.12	98.09	132.77

o-Hydroxy-atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. BE-248-ATOR-2009, N=13 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	350853.5	367271.8	95.53	85.81	106.35
AUC$^{\infty}$ (pg·hr/mL)	360728.8	379194.9	95.13	85.92	105.33
Cmax (pg/mL)	44150.4	47491.5	92.96	80.31	107.61

p-Hydroxy-atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. BE-248-ATOR-2009, N=13 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	60859.8	58051.9	104.84	91.86	119.65
AUC$^{\infty}$ (pg·hr/mL)	77672.6	81200.2	95.66	79.44	115.19
Cmax (pg/mL)	2843.6	2744.7	103.60	79.10	1.35.71

Pilot Study No. BE-249-ATOR-2009 (Fed)

Atorvastatin, 1 X 80 mg Fed Bioequivalence Study No. BE-249-ATOR-2009, N=11 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	242952.3	259905.7	93.48	83.17	105.06
AUC∞ (pg·hr/mL)	248746.0	267284.7	93.06	82.65	104.79
Cmax (pg/mL)	35381.5	41654.3	84.94	67.25	107.29

o-Hydroxy-atorvastatin, 1 X 80 mg Fed Bioequivalence Study No. BE-249-ATOR-2009, N=11 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	259172.2	274254.4	94.50	85.54	104.40
AUC∞ (pg·hr/mL)	266859.8	282781.6	94.37	84.79	105.03
Cmax (pg/mL)	22242.0	23285.0	95.52	77.11	118.32

p-Hydroxy-atorvastatin, 1 X 80 mg Fed Bioequivalence Study No. BE-249-ATOR-2009, N=11 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	50029.6	54633.7	91.57	79.47	105.52
AUC∞ (pg·hr/mL)	65801.4	69412.4	94.80	76.26	117.83
Cmax (pg/mL)	2353.8	2549.8	92.31	74.86	113.84

Pilot Study No. 365 ATORV 09 (Fasting)

Atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. 365-ATORV-09, N=17 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	141611.9	147967.4	95.70	86.25	106.19
AUC∞ (pg·hr/mL)	146607.3	151162.0	96.99	87.09	108.00
Cmax (pg/mL)	40973.0	44346.5	92.39	79.15	107.85

o-Hydroxy-atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. 365-ATORV-09, N=17 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	191925.6	203921.5	94.12	---	---
AUC∞ (pg·hr/mL)	197647.5	207615.1	95.20	---	---
Cmax (pg/mL)	32834.0	35202.9	93.27	---	---

p-Hydroxy-atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. 365-ATORV-09, N=17 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	28639.2	30296.4	94.53	---	---
AUC∞ (pg·hr/mL)	44923.1	43450.9	103.39	---	---
Cmax (pg/mL)	1351.6	1449.0	93.28	---	---

Pilot Study No. 3023-ATORV-08 (Fasting)

Atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. 3023-ATORV-08, N=12 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	188361.4	161668.4	116.51	102.58	132.33
AUC∞ (pg·hr/mL)	193533.8	165196.5	117.15	103.36	132.79
Cmax (pg/mL)	50953.4	51224.7	99.47	77.73	127.30

o-Hydroxy-atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. 3023-ATORV-08, N=12 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	151743.0	132166.7	114.81	---	---
AUC∞ (pg·hr/mL)	155994.1	138140.2	112.92	---	---
Cmax (pg/mL)	22407.1	20881.4	107.31	---	---

p-Hydroxy-atorvastatin, 1 X 80 mg Fasting Bioequivalence Study No. 3023-ATORV-08, N=12 (Males) Least-Square Geometric Means, Point Estimates and 90% Confidence Intervals					
Parameter (units)	**Test**	**Reference**	**Ratio**	**90% C.I.**	
AUC0-t (pg·hr/mL)	29086.2	25540.4	113.88	---	---
AUC∞ (pg·hr/mL)	41559.2	40578.1	102.42	---	---
Cmax (pg/mL)	1395.7	1182.6	118.02	---	---

There is an FDA-recommended dissolution method (900 mL of 0.05 Phosphate buffer at pH 6.8 and Paddle at 75 rpm). In the original application, the firm preferred to use the (b) (4) Vessels instead of USP-2 Vessels, because it had added advantages (lower variability in data). The firm's response was found acceptable (see the reviews - v:\firmsnz\ranbaxy\ltrs&rev\76477n0802.doc; v:\firmsnz\ranbaxy\ltrs&rev\76477a0503.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0906.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0807.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0108.doc).

The firm has also submitted dissolution testing results comparing its new test products (10, 20, 40 and 80 mg strengths, manufactured with (b) (4) API) with the RLD. This time the firm has used the FDA-recommended method (using USP Paddles at 75 rpm, instead of the (b) (4) Vessels). The firm's dissolution testing method is non-discriminatory. Thus, >85% of the drug in the dosage form dissolves in 10 minutes. Therefore, the firm should conduct dissolution testing as follows using the Paddle speed at 50 rpm:

Medium:	0.05M Phosphate Buffer, pH 6.8 at 37 ^{0}C
Volume:	900 mL
USP Apparatus:	II (Paddle) at 50 rpm
Dosage Units:	12 each for Test and Reference

The waiver requests for *in vivo* BE study requirements for the firm's lower strengths of the test product, 10 mg, 20 mg and 40 mg, can not be granted due to deficiency in dissolution data.

A routine DSI Inspection of the clinical site, Cetero Research, Amber Valley Pkwy, Fargo, ND, was completed on 5/15/2009, with a VAI outcome for NDA 22418. The inspectors observed omissions in safety reporting, and objectionable practices in recruiting of subjects and in record-keeping practices. The reviewer verified the Case Report Forms (CRFs) for the dates of entry, changes in the records, and changes in inclusion/exclusion criteria. The entries in the CRFs were documented, signed and dated appropriately. There were no changes or major modifications in the CRFs for subjects. Adverse events observed in the fasting and fed studies were minor, and were recorded appropriately in the CRFs. It should be noted that the studies were conducted after this DSI inspection, i.e. during 10/4/2009-10/18/2009 period, which may have some effect on the improved record-keeping procedure.

A routine DSI Inspection of the Analytical site, (b) (4), was conducted during (b) (4), and the report was completed on (b) (4), with a VAI outcome for NDA (b) (4) (Clinical and analytical studies on (b) (4))[1]. The DSI cited the firm for discrepancies in long-term stability data generated by the firm. In response, the firm conducted additional long-term stability studies and the outcome was confirmed. The DSI concluded that there was no significant impact on the outcome of the study.

There is no DSI inspection of clinical or analytical sites pending or necessary for this product.

[1]DARRTS, NDA (b) (4) (b) (4) CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Type 5- New Formulation or New Manufacturer)

2. TABLE OF CONTENTS

3. SUBMISSION SUMMARY

3.1.Drug Product Information[2,3]

Test Product	Atorvastatin Calcium Tablets, EQ. 10 mg, 20 mg, 40 mg, and 80 mg Base
Reference Product	Lipitor® (atorvastatin calcium) Tablets, EQ. 10 mg, 20 mg, 40 mg, and 80 mg Base (EQ. 80 mg Base is designated as the RLD strength)
RLD Manufacturer	Pfizer, Inc.
NDA No.	020702
RLD Approval Date	07 April 2000 (EQ 80 mg Base) 17 December 1996 (EQ 10 mg, 20 mg, and 40 mg Base)
Aqueous solubility of Atorvastatin Calcium (RLD)	Water: 0.11 mg/mL 0.1 N HCl 0.01 mg/mL 0.05 M Sodium Phosphate, pH 7.4: 0.70 mg.mL
Polymorphs (RLD)	See Appendix, Chemical Polymorphs (RLD)

[2] Electronic Orange Book: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.
[3] DailyMed Labeling, http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=36811

Indication	LIPITOR® is an inhibitor of HMG-CoA reductase (statin) indicated for the followings: **Prevention of cardiovascular disease** In adult patients without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as age, smoking, hypertension, low HDL-C, or a family history of early coronary heart disease, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke • Reduce the risk for revascularization procedures and angina In patients with type 2 diabetes, and without clinically evident coronary heart disease, but with multiple risk factors for coronary heart disease such as retinopathy, albuminuria, smoking, or hypertension, LIPITOR is indicated to: • Reduce the risk of myocardial infarction • Reduce the risk of stroke In patients with clinically evident coronary heart disease, LIPITOR is indicated to: • Reduce the risk of non-fatal myocardial infarction • Reduce the risk of fatal and non-fatal stroke • Reduce the risk for revascularization procedures • Reduce the risk of hospitalization for CHF • Reduce the risk of angina

Indication	**Hypercholesterolemia** LIPITOR® is indicated: • as an adjunct to diet to reduce elevated total-C, LDL-C, apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial) and mixed dyslipidemia *(Fredrickson* Types IIa and IIb); • as an adjunct to diet for the treatment of patients with elevated serum TG levels*(Fredrickson* Type IV); • for the treatment of patients with primary dysbetalipoproteinemia *(Fredrickson* Type III) who do not respond adequately to diet; • to reduce total-C and LDL-C in patients with homozygous familial hypercholesterolemia as an adjunct to other lipid lowering treatments (eg, LDL apheresis) or if such treatments are unavailable. • as an adjunct to diet to reduce total-C, LDL-C, and apo B levels in boys and postmenarchal girls, 10 to 17 years of age, with heterozygous familial hypercholesterolemia if after an adequate trial of diet therapy the following findings are present: a. LDL-C remains ≥ 190 mg/dL or b. LDL-C remains ≥ 160 mg/dL and: There is a positive family history of premature cardiovascular disease or two, or other CVD risk factors are present in the pediatric patient

3.2.PK/PD Information[4]

Bioavailability	LIPITOR® is rapidly absorbed after oral administration; maximum plasma concentrations occur within 1 to 2 hours. Extent of absorption increases in proportion to LIPITOR® dose. The absolute bioavailability of atorvastatin (parent drug) is approximately 14% and the systemic availability of HMG-CoA reductase inhibitory activity is approximately 30%. The low systemic availability is attributed to presystemic clearance in gastrointestinal mucosa and/or hepatic first-pass metabolism. Plasma LIPITOR® concentrations are lower (approximately 30% for Cmax and AUC) following evening drug administration compared with morning. However, LDL-C reduction is the same regardless of the time of day of drug administration.
Food Effect	Although food decreases the rate and extent of drug absorption by approximately 25% and 9%, respectively, as assessed by Cmax and AUC, LDL-C reduction is similar whether LIPITOR® is given with or without food.
Tmax	1 to 2 hours.
Metabolism	LIPITOR® is extensively metabolized to ortho- and para-hydroxylated derivatives and various beta-oxidation products. *In vitro* inhibition of HMG-CoA reductase by ortho- and para-hydroxylated metabolites is equivalent to that of LIPITOR®. Approximately 70% of circulating inhibitory activity for HMG-CoA reductase is attributed to active metabolites. *In vitro* studies suggest the importance of LIPITOR® metabolism by cytochrome P450 3A4, consistent with increased plasma concentrations of LIPITOR® in humans following co-administration with erythromycin, a known inhibitor of this isozyme [see *Drug Interactions (7.1)*]. In animals, the ortho-hydroxy metabolite undergoes further glucuronidation

[4] DailyMed Labeling, http://dailymed.nlm.nih.gov/dailymed/drugInfo.cfm?id=36811

Excretion	LIPITOR® and its metabolites are eliminated primarily in bile following hepatic and/or extra-hepatic metabolism; however, the drug does not appear to undergo enterohepatic recirculation. Less than 2% of a dose of LIPITOR® is recovered in urine following oral administration.
Half-life	Mean plasma elimination half-life of LIPITOR® in humans is approximately 14 hours, but the half-life of inhibitory activity for HMGCoA reductase is 20 to 30 hours due to the contribution of active metabolites.
Drug Specific Issues (if any)	**N/A**

3.3.OGD Recommendations for Drug Product

Number of studies recommended:	2, Fasting and Fed

1.	**Type of study:**	Fasting
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	EQ. 80 mg Base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	N/A

2.	**Type of study:**	Fed
	Design:	Single-dose, two-treatment, two-period crossover in-vivo
	Strength:	EQ. 80 mg Base
	Subjects:	Normal healthy males and females, general population
	Additional Comments:	N/A

Analytes to measure (in plasma/serum/blood):	Atorvastatin, ortho- and para-hydroxylated metabolites of atorvastatin[5]
Bioequivalence based on:	90% CI of Atorvastatin
Waiver request of in-vivo testing:	EQ.10 mg, 20 mg, and 40 mg Base based on (i) acceptable bioequivalence studies on the 80 mg strength, (ii) (b) (4) across all strengths, and (iii) acceptable in vitro dissolution testing of all strengths.
Source of most recent recommendations[6]:	Draft Guidance on Atorvastatin (finalized 05/2008)

Summary of OGD or DBE History (for details, see Appendix 4.4):	There are currently no approved generic drug products[7].

[5] The ortho- and para- hydroxylated metabolites of atorvastatin are formed by ***presystemic metabolism*** and contribute meaningfully to efficacy. For the metabolites, the following data should be submitted: individual and mean concentrations, individual and mean pharmacokinetic parameters, and geometric means and ratios of means for AUC and Cmax.

[6] Individual Product Bioequivalence Recommendations: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm. Last

[7] Electronic Orange Book: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

	The DBE has reviewed the following ANDAs for Atorvastatin Calcium Tablets[6]: • ANDA 078773 (Teva) • ANDA 077575 (Sandoz) • ANDA 076477 (Ranbaxy Labs) • ANDA 090548 (Apotex) • ANDA 091624 (Kudco) • ANDA 091226 (Matrix)

3.4.Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	Yes	1
Single-dose fed	Yes	1
Steady-state	No	--
In vitro dissolution	Yes	4
Waiver requests	Yes	3
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	Yes	---
Amendments	Yes	---
Pilot Studies	Yes	4

3.5.Pre-Study Bioanalytical Method Validation – Fasting and Fed Studies

Information Requested R09-1032	Data
Bioanalytical method validation report location	Section analyt-validation
Analyte	Atorvastatin, p-hydroxy-atorvastatin and o- hydroxy-atorvastatin
Internal standard (IS)	Atorvastatin-d_5, p-hydroxy-atorvastatin-d_5 and o- hydroxy-atorvastatin-d_5
Method description	This method involves the extraction of atorvastatin, p-hydroxy-atorvastatin and o- hydroxy-atorvastatin and the internal standards from human EDTA K_2 plasma by automated liquid-liquid extraction. Samples are kept frozen at -80°C prior to analysis and 0.100 mL of plasma was used for analysis.
Limit of quantitation (pg/mL)	50.06 for atorvastatin 50.30 for p-hydroxy-atorvastatin 50.06 for o-hydroxy-atorvastatin
Average recovery of drug (%)	94.56, 93.56 and 92.67% for atorvastatin 89.17, 90.63 and 87.70% for p-hydroxy-atorvastatin 92.86, 96.43 and 94.45% for o-hydroxy-atorvastatin
Average recovery of IS (%)	75.17% for atorvastatin 86.12% for p-hydroxy-atorvastatin 81.85% for o-hydroxy-atorvastatin
Standard curve concentrations (pg/mL)	50.06 to 50060.00 pg/mL for atorvastatin 50.30 to 2515.00 pg/mL for p-hydroxy-atorvastatin 50.06 to 50060.00 pg/mL for o-hydroxy-atorvastatin
QC concentrations (pg/mL)	150.18, 15018.00 and 35042.00 for atorvastatin 150.90, 754.50, 1760.50 for p-hydroxy-atorvastatin 150.18, 15018.00 and 35042.00 for o-hydroxy-atorvastatin
QC Intraday precision range (%)	1.86 to 7.99 for atorvastatin 1.70 to 7.45 for p-hydroxy-atorvastatin 2.23 to 12.16 for o-hydroxy-atorvastatin
QC Intraday accuracy range (%)	-3.82 to 4.40 for atorvastatin -1.79 to 12.37 for p-hydroxy-atorvastatin -2.37 to 0.93 for o-hydroxy-atorvastatin
QC Interday precision range (%)	2.87 to 5.28 for atorvastatin 3.59 to 6.50 for p-hydroxy-atorvastatin 2.28 to 6.73 for o-hydroxy-atorvastatin
QC Interday accuracy range (%)	97.07 to 101.60 for atorvastatin 96.33 to 101.30 for p-hydroxy-atorvastatin 97.33 to 101.20 for o-hydroxy-atorvastatin
Bench-top stability (hrs)	9 hours and 44 minutes at 4°C
Stock stability (days)	Analytes: 355 days at -80°C for atorvastatin and o-hydroxy-atorvastatin and 356 days at -80°C for p-hydroxy-atorvastatin IS: 350 days at -80°C
Processed stability (hrs)	69 at 4°C hours and 26 hours at room temperature
Freeze-thaw stability (cycles)	4 cycles
Long-term storage stability (days)	91 days at -80°C (with QC fortified with lactone) 254 days at -80°C (with QC not fortified)
Dilution integrity	QC3 diluted 1/2: CV (%) 3.82 %Nominal (%) 101.67% for

	atorvastatin QC3 diluted 1/2: CV (%) 5.67 %Nominal (%) 103.99% for p-hydroxy-atorvastatin QC3 diluted 1/2: CV (%) 3.60 %Nominal (%) 100.01% for o-hydroxy-atorvastatin DQC diluted 1/20: CV (%) 4.03% Nominal (%) 97.36% for atorvastatin DQC diluted 1/20: CV (%) 3.49% Nominal (%) 97.66% for p-hydroxy-atorvastatin DQC diluted 1/20: CV (%) 2.39% Nominal (%) 98.55% for o-hydroxy-atorvastatin
Selectivity	No interfering peaks noted in blank plasma samples

SOPs submitted	Yes	
Bioanalytical method is acceptable	Yes	

Comments on the Pre-Study Method Validation: Acceptable.

3.6.In Vivo Studies

3.6.1. Single-dose Fasting and Fed Studies

Table 1. Summary of all in vivo Bioequivalence Studies – Fasting study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD/%CV) Atorvastatin						Study Report Location
					C_{max} (pg/mL)	T_{max}* (hr)	AUC_{0-t} (pg.h/mL)	$AUC_{0-\infty}$ (pg.h/mL)	T½ (hr)	K_{el} (hr^{-1})	
R09-1032	This study assessed the relative bioavailability of 80 mg Atorvastatin Calcium Tablets (containing atorvastatin calcium equivalent to 80 mg atorvastatin) manufactured by OHM Laboratories, Inc., USA (A subsidiary of Ranbaxy Pharmaceuticals., USA) compared to that of 80 mg LIPITOR® Tablets (containing atorvastatin calcium equivalent to 80 mg atorvastatin) distributed by Parke Davis, Division of Pfizer Inc., USA following a single oral dose (1 x 80 mg tablet) in healthy adult subjects when administered under fasting conditions.	Randomized, single-dose, two-way open-label crossover study. Study Type: Pivotal	**T:** Atorvastatin Calcium 80 mg Tablets, [Batch No. RI560901]; Expiry Date: 04/2012 1 Tablet, Oral. **R:** Lipitor® 80 mg Tablets, [Lot No. 04558V]; Expiry Date: Mar. 2011] 1 Tablet, Oral.	A total of eighty (80) healthy subjects were enrolled in the study. Seventy-six 76 (65/11) subjects completed both the periods of the study. Mean age: 32.3 years (Completed Subjects) Range: 18-75 years	**Test** 36832.41 (19732.92/ 53.57) **Ref.** 39355.78 (29836.55/ 75.81)	**Test** 0.67 (0.33 – 4.00) **Ref.** 0.83 (0.33 – 5.00)	**Test** 142053.43 (63781.13/ 44.90) **Ref.** 146669.01 (86731.92/5 9.13)	**Test** 143492.83 (63704.69/44.40) **Ref.** 149109.24 (87000.77/58.35)	**Test** 10.85 (4.51/41.56) **Ref.** 11.56 (4.04/34.93)	**Test** 0.0733 (0.0260/ 35.45) **Ref.** 0.0676 (0.0255/ 37.74)	Not applicable
					2-Hydroxy Atorvastatin (o-Hydroxy Atorvastatin)						
					Test 33005.19 (17207.40/ 52.14) **Ref.** 34805.71 (22994.37/ 66.06)	**Test** 1.13 (0.50 – 4.00) **Ref.** 1.25 (0.50 – 8.00)	**Test** 184760.51 (77096.54/ 41.73) **Ref.** 184564.40 (96169.46/ 52.11)	**Test** 186392.97 (77046.88/41.34) **Ref.** 185902.46 (97605.53/52.50)	**Test** 12.38 (4.32/34.86) **Ref.** 12.75 (5.53/43.36)	**Test** 0.0629 (0.0225/ 35.70) **Ref.** 0.0608 (0.0182/ 29.89)	
					4-Hydroxy Atorvastatin (p-Hydroxy Atorvastatin)						
					Test 1256.25 (1473.65/ 117.31) **Ref.** 1388.32 (2508.61/1 80.69)	**Test** 5.50(0.45 – 20.00) **Ref.** 5.00 (0.50 – 20.00)	**Test** 22375.81 (13811.67/61.7 3) **Ref.** 22959.79 (16547.67/ 72.07)	**Test** 26707.84 (14544.99/54.46) **Ref.** 26993.07 (17654.22/65.40)	**Test** 20.29 (6.08/29.95) **Ref.** 20.80 (6.83/32.83)	**Test** 0.0370 (0.0103/ 27.92) **Ref.** 0.0368 (0.0115/ 31.38)	

Table 2. Summary of all in vivo Bioequivalence Studies – Fed Study

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD/%CV) Atorvastatin						Study Report Location
					C_{max} (pg/mL)	T_{max}* (hr)	AUC_{0-t} (pg.h/mL)	$AUC_{0-\infty}$ (pg.h/mL)	T½ (hr)	K_{el} (hr^{-1})	
R09-1033	This study assessed the relative bioavailability of 80 mg Atorvastatin Calcium Tablets (containing atorvastatin calcium equivalent to 80 mg atorvastatin) manufactured by OHM Laboratories, Inc., USA (A subsidiary of Ranbaxy Pharmaceuticals., USA) compared to that of 80 mg LIPITOR® Tablets (containing atorvastatin calcium equivalent to 80 mg atorvastatin) distributed by Parke Davis, Division of Pfizer Inc., USA following a single oral dose (1 x 80 mg tablet) in healthy adult subjects when administered under fed conditions.	Open label, balanced, randomized two treatment, two-period, two-sequence, single-dose crossover bioequivalence study conducted under fed conditions. Study Type: Pivotal	**T:** Atorvastatin Calcium 80 mg Tablets, [Batch No. RI560901]; Expiry Date: 04/2012 1 Tablet, Oral. **R:** Lipitor® 80 mg Tablets, [Lot No. 04558V]; Expiry Date: Mar. 2011] 1 Tablet, Oral.	A total of eighty (80) healthy subjects were enrolled in the study. Seventy-six 76 (68/08) subjects completed both the periods of the study. Mean age: 31.5 years (Completed Subjects) Range: 18-66 years							Not Applicable
					Test 32951.43 (20583.59 /62.47) **Ref.** 34640.92 (23571.60 /68.05)	Test 1.25 (0.67 – 6.00) **Ref.** 1.50 (0.67 – 6.00)	**Test** 138560.34 (56625.52/ 40.87) **Ref.** 139944.23 (60772.30/ 43.43)	**Test** 140725.92 (57485.52/ 40.85) **Ref.** 140979.68 (61162.07/ 43.38)	**Test** 11.00 (3.79/ 34.45) **Ref.** 11.02 (3.52/ 31.93)	**Test** 0.0702 (0.0249/ 35.48) **Ref.** 0.0710 (0.0290/ 40.81)	
					2-Hydroxy Atorvastatin (o-Hydroxy Atorvastatin)						
					Test 22919.48 (13242.51 /57.78) **Ref.** 23411.10 (13356.42 /57.05)	Test 1.50 (0.67 – 10.00) **Ref.** 1.50 (0.67 – 6.00)	**Test** 152698.60 (65513.28/ 42.90) **Ref.** 153484.89 (64078.48/ 41.75)	**Test** 154489.16 (65711.81/ 42.53) **Ref.** 155658.15 (64501.02/ 41.44)	**Test** 12.93 (6.17/ 47.77) **Ref.** 14.16 (5.37/ 37.92)	**Test** 0.0616 (0.0198/ 32.17) **Ref.** 0.0551 (0.0185/ 33.56)	
					4-Hydroxy Atorvastatin (p-Hydroxy Atorvastatin)						
					Test 917.90 (738.33/ 80.44) **Ref.** 900.63 (603.19/ 66.97)	Test **8.05 (0.67 – 36.00)** **Ref.** 8.00 (1.00 – 36.00)	**Test 18596.20 (10240.31/ 55.07)** **Ref.** 18900.65 (10085.81/ 53.36)	**Test 22000.45 (11167.28/ 50.76)** **Ref.** 23346.13 (11033.23/ 47.26)	**Test 23.95 (7.83/ 32.68)** **Ref.** 24.85 (9.38/ 37.75)	**Test** 0.0320 (0.0100/ 31.22) **Ref.** 0.0316 (0.0108/ 34.15)	

Table 3. Statistical Summary of the Comparative Bioavailability Data- Fasting Study

Atorvastatin Dose (80 mg) Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)				
Fasting Bioequivalence Study (Study No. R09-1032)				
Parameter	**Test**	**Reference**	**Ratio (%)**	**90% CI**
AUC_{0-t}	130541.42 pg.hr/ml	131063.27 pg.hr/ml	99.60	(95.63, 103.74)
$AUC_{0-\infty}$	133165.11 pg.hr/ml	133615.74 pg.hr/ml	99.66	(95.72, 103.77)
C_{max}	32751.40 pg/ml	33186.70 pg/ml	98.69	(91.18, 106.82)
2-Hydroxy Atorvastatin (o-Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means				
Fasting Bioequivalence Study (Study No. R09-1032)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	172630.15 pg.hr/ml	168593.41 pg.hr/ml	102.39	
$AUC_{0-\infty}$	173921.96 pg.hr/ml	169783.81 pg.hr/ml	102.44	
C_{max}	29865.76 pg/ml	29897.59 pg/ml	99.89	
4-Hydroxy Atorvastatin (p-Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means				
Fasting Bioequivalence Study (Study No. R09-1032)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	19003.56 pg.hr/ml	19153.00 pg.hr/ml	99.22	
$AUC_{0-\infty}$	24554.18 pg.hr/ml	24470.43 pg.hr/ml	100.34	
C_{max}	926.56 pg/ml	920.80 pg/ml	100.63	

Table 4. Statistical Summary of the Comparative Bioavailability Data- Fed Study

Atorvastatin Dose (80 mg) Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)				
Fed Bioequivalence Study (Study No. R09-1033)				
Parameter	**Test**	**Reference**	**Ratio (%)**	**90% CI**
AUC_{0-t}	128437.49 pg.hr/ml	128865.94 pg.hr/ml	99.67	(96.00, 103.47)
$AUC_{0-\infty}$	130112.86 pg.hr/ml	130682.95 pg.hr/ml	99.56	(95.87, 103.40)
C_{max}	27847.28 pg/ml	29025.88 pg/ml	95.94	(86.75, 106.11)
2-Hydroxy Atorvastatin (o-Hydroxy Atorvastatin) **Least Square Geometric Means, Ratio of Means**				
Fed Bioequivalence Study (Study No. R09-1033)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	142055.40 pg.hr/ml	143318.73 pg.hr/ml	99.12	
$AUC_{0-\infty}$	143728.64 pg.hr/ml	145312.87 pg.hr/ml	98.91	
C_{max}	20093.50 pg/ml	20613.33 pg/ml	97.48	
4-Hydroxy Atorvastatin (p-Hydroxy Atorvastatin) **Least Square Geometric Means, Ratio of Means**				
Fed Bioequivalence Study (Study No. R09-1033)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	16282.37 pg.hr/ml	16691.03 pg.hr/ml	97.55	
$AUC_{0-\infty}$	20166.96 pg.hr/ml	21036.43 pg.hr/ml	95.87	
C_{max}	748.86 pg/ml	751.79 pg/ml	99.61	

Table 5. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Fasting:

Atorvastatin (Used Repeat Values for Subjects 48 and 49, N=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	130541.4	131063.3	1.00	94.04	105.50
LAUCI	132122.6	132569.7	1.00	94.10	105.56
LCMAX	32751.40	33186.70	0.99	88.24	110.37

Used original values for Subject #48 and 49 (n=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	130658.6	131386.9	0.99	93.87	105.35
LAUCI	131359.0	132150.3	0.99	93.86	105.27
LCMAX	32751.40	33186.70	0.99	88.24	110.37

Excluding Subject #48 and 49 (n=74)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	129576.1	129971.6	1.00	93.98	105.76
LAUCI	131158.7	131478.5	1.00	94.04	105.82
LCMAX	32562.07	32949.87	0.99	88.08	110.88

Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer (Continued)

Fed:

Atorvastatin (Used Repeat Values for Subjects 47, n=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	128437.5	128865.9	1.00	94.53	105.09
LAUCI	130112.9	130682.9	1.00	94.24	105.19
LCMAX	27847.28	29025.88	0.96	83.20	110.63

Used original values for Subject #47 (n=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	128501.9	128788.4	1.00	94.67	105.16
LAUCI	129322.5	129512.3	1.00	94.76	105.22
LCMAX	27847.28	29025.88	0.96	83.20	110.63

Atorvastatin (Excluding Subject # 47, n=75)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	127697.8	127310.6	1.00	95.28	105.59
LAUCI	129313.2	129009.6	1.00	95.04	105.71
LCMAX	27882.98	28714.35	0.97	84.31	111.84

Table 6. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Ortho-hydroxy Atorvastatin (n=76)

Fasting

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	172630.2	168593.4	1.02	96.44	108.72
LAUCI	174365.2	170216.5	1.02	96.41	108.85
LCMAX	29865.76	29897.59	1.00	89.65	111.31

Fed

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	142055.4	143318.7	0.99	95.76	102.59
LAUCI	143728.6	145312.9	0.99	95.59	102.34
LCMAX	20093.50	20613.33	0.97	86.64	109.67

Table 7. Statistical Summary of the Comparative Bioavailability Data Calculated by the Reviewer

Para-hydroxy Atorvastatin (n=76)

Fasting

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	19003.56	19153.00	0.99	91.57	107.51
LAUCI	22702.34	22582.77	1.01	92.26	109.54
LCMAX	926.56	920.80	1.01	91.02	111.24

Fed

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	16282.37	16691.03	0.98	92.86	102.48
LAUCI	20166.96	21036.43	0.96	90.16	101.93
LCMAX	748.86	751.79	1.00	91.79	108.09

3.6.2. Reanalysis of Study Samples

Table 8. Reanalysis of Study Samples: Fasting, Atorvastatin

Study No. R09-1032
A Bioequivalence Study of 80 mg Atorvastatin Calcium Tablets versus 80 mg Lipitor® Tablets under Fasting Conditions
Additional information in bioanalytical report

Atorvastatin Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable IS response	4	3	0.09	0.07	4	3	0.09	0.07
Loss of sample during processing	0	7	0	0.15	0	7	0.00	0.15
Sample concentration above upper limit of quantification	33	45	0.73	0.99	33	45	0.73	0.99
Sample reanalyzed to obtain confirming value	4	2	0.09	0.04	2	1	0.04	0.02
Rejected sample dilution	1	0	0.02	0.00	1	0	0.02	0.00
Sample repeated or reinjected by error	5	2	0.11	0.04	0	0	0.00	0.00
Sample stability exceeding validation data	0	2	0.00	0.04	0	2	0.00	0.04
Total	47	61	1.04	1.33	40	58	0.88	1.27

1 - If no repeats were performed for pharmacokinetic reasons, insert "0.0."

T: 1 tablet of test product, Atorvastatin Calcium 80 mg Tablets (containing atorvastatin calcium equivalent to 80 mg atorvastatin) manufactured by OHM Laboratories Inc., USA [A subsidiary of Ranbaxy Pharmaceuticals Inc., USA]

R: 1 tablet of reference product, 80 mg LIPITOR® Tablets (containing atorvastatin calcium equivalent to 80 mg atorvastatin) distributed by Parke Davis, Division of Pfizer Inc., USA

Table 9. Reanalysis of Study Samples: Fasting, p-Hydroxy-atorvastatin

Study No. R09-1032 A Bioequivalence Study of 80 mg Atorvastatin Calcium Tablets versus 80 mg Lipitor® Tablets under Fasting Conditions Additional information in bioanalytical report								
p-Hydroxy-Atorvastatin Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable IS response	2	1	0.04	0.02	2	1	0.04	0.02
Loss of sample during processing	26	6	0.57	0.13	26	6	0.57	0.13
Sample concentration above upper limit of quantification	20	36	0.44	0.79	20	36	0.44	0.79
Sample reanalyzed to obtain confirming value	4	3	0.09	0.07	2	1	0.04	0.02
Rejected sample dilution	4	1	0.09	0.02	4	1	0.09	0.02
Sample repeated or reinjected by error	5	3	0.00	0.07	0	0	0.00	0.00
Sample stability exceeding validation data	0	2	0.00	0.04	0	2	0.00	0.04
Total	61	52	1.35	1.15	54	47	1.19	1.04

Table 10. Reanalysis of Study Samples: Fasting, o-Hydroxy- atorvastatin

Study No. R09-1032 A Bioequivalence Study of 80 mg Atorvastatin Calcium Tablets versus 80 mg Lipitor® Tablets under Fasting Conditions Additional information in bioanalytical report								
o-Hydroxy-Atorvastatin	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
Reason why assay was repeated	**Actual number**		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Poor chromatography	1	4	0.02	0.09	1	4	0.02	0.09
Unacceptable IS response	2	1	0.04	0.02	2	1	0.04	0.02
Loss of sample during processing	0	10	0.00	0.22	0	10	0.00	0.22
Sample concentration above the upper limit of quantitation	21	19	0.46	0.42	21	19	0.46	0.42
Sample reanalyzed to obtain confirming value	4	2	0.09	0.04	2	1	0.04	0.02
Sample repeated or reinjected by error	5	2	0.11	0.04	5	2	0.11	0.04
Sample stability exceeding validation data	2	0	0.04	0.00	2	0	0.04	0.00
Total	35	38	0.76	0.83	33	37	0.71	0.81

Table 11. Reanalysis of Study Samples: Fed, Atorvastatin

Study No. R09-1033 A Bioequivalence Study of 80 mg Atorvastatin Calcium Tablets versus 80 mg Lipitor® Tablets under Fed Conditions Additional information in bioanalytical report								
Atorvastatin Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable IS response	1	4	0.03	0.10	1	4	0.03	0.10
Loss of sample during processing	3	0	0.08	0.00	3	0	0.08	0.00
Sample reanalyzed to obtain a confirming value	3	4	0.08	0.10	1	2	0.03	0.05
Sample concentration above the upper limit of quantitation	23	29	0.60	0.76	23	29	0.60	0.76
Total	30	37	0.79	0.96	28	35	0.74	0.91

Table 12. Reanalysis of Study Samples: Fed, p-Hydroxy-atorvastatin

Study No. R09-1033 A Bioequivalence Study of 80 mg Atorvastatin Calcium Tablets versus 80 mg Lipitor® Tablets under Fed Conditions Additional information in bioanalytical report								
p-Hydroxy-Atorvastatin Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Unacceptable IS response	0	2	0.00	0.05	0	2	0.00	0.05
Loss of sample during processing	4	0	0.10	0.00	4	0	0.10	0.00
Sample concentration below or above the modified calibration curve	27	14	0.71	0.37	27	14	0.71	0.37
Sample reanalyzed to obtain a confirming value	3	4	0.08	0.10	2	2	0.05	0.05
Rejected sample dilution	4	0	0.10	0.00	4	0	0.10	0.00
Total	38	20	0.99	0.52	37	18	0.96	0.47

Table 13. Reanalysis of Study Samples: Fed, o-Hydroxy-atorvastatin

Study No. R09-1033 A Bioequivalence Study of 80 mg Atorvastatin Calcium Tablets versus 80 mg Lipitor® Tablets under Fed Conditions Additional information in bioanalytical report								
o-Hydroxy-Atorvastatin Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic[1]	0	0	0.00	0.00	0	0	0.00	0.00
Poor chromatography	1	4	0.03	0.10	1	4	0.03	0.10
Unacceptable IS response	1	4	0.03	0.10	1	4	0.03	0.10
Loss of sample during processing	3	0	0.08	0.00	3	0	0.08	0.00
Sample reanalyzed to obtain a confirming value	4	4	0.10	0.10	2	2	0.05	0.05
Sample concentration above the upper limit of quantitation	8	8	0.21	0.21	8	8	0.21	0.21
Total	17	20	0.45	0.51	15	18	0.40	0.46

4.1.7 Samples Reanalyzed to Obtain Confirming Value (Code G)

Study samples may have to be reanalyzed to obtain confirming values for one of the following reasons:

- When the reassay value of a diluted sample reanalyzed for code "D" is less than 85% of the nominal concentration of the upper limit of quantitation. No confirmation is necessary if the reassayed value of the diluted sample is equal to or higher than 85% of the nominal concentration of the upper limit of quantitation.
- When a pre-dose sample presents a concentration higher than the lower limit of quantitation.

  Positive pre-dose samples may not have to be repeated for certain reasons, such as but not limited to:

  - Multiple-dose studies;
  - Concentration below 5% of the Cmax value for the subject/period for FDA submissions;
  - Endogenous analytes.

  The reason for repeating or not repeating a positive pre-dose sample must be documented on an Additional Information Form, filed with the study data and discussed in the analytical report.

  For unexpected positive pre-dose samples, it is recommended to reanalyze each sample aliquot available to simplify the root cause analysis. Moreover, if a pre-dose sample was collected during the check-in process in the clinic, this pre-dose sample should also be analyzed in duplicate to strengthen the root cause analysis.

- When the percentage of difference (% difference) between the first and the second reportable value of a sample is greater than 20%, as described in the sample reassay flow chart (refer to Addendum 02).

  The % difference between values is calculated as follows:

$$\frac{\text{(Reassay Value – Original Value)}}{\text{Average}} \times 100$$

Samples may be reassayed for additional confirmation reasons such as being part of an investigation process, and documented in the study raw data as well as in the analytical report (in general, samples coded G should be discussed in the analytical report). Reanalysis for confirmation should be performed in duplicate using both the first and second aliquots and must be approved by the bioanalytical direction.

A sample reanalyzed to confirm the value will be coded "G" and its concentration is to be included in the analytical repeat table of the analytical report. Refer to section 4.4.2 for details on the final value to be reported.

4.1.2 Unacceptable Internal Standard Response (Code B)

Any study sample analysis presenting an internal standard response beyond the acceptance criteria detailed below must be rejected, unless specified otherwise by technical reasons or by specific criteria described in the bioanalytical method SOP. Examples of acceptable technical reasons are: loss of extraction solvent or improper volume of reconstitution solution.

Criteria for study samples:

Methods using stable isotope-labelled internal standard:

- ± 70% of the mean internal standard response of accepted calibration standards and quality control samples.

  For example: for a mean of 100000, all study samples with an internal standard response between 30000 and 170000 would be acceptable.

Methods using structural analog internal standard:

- ± 50% of the mean internal standard response of accepted calibration standards and quality control samples.

  For example: for a mean of 100000, all study samples with an internal standard response between 50000 and 150000 would be acceptable.

A study sample presenting an unacceptable internal standard response will be coded "B" and its concentration will be identified as NRV in the analytical repeat table of the analytical report. The repeated value will be reported in the final concentration table of the analytical report.

Samples presenting an internal standard response below 5% of the mean internal standard response of accepted calibration standards and quality control samples are not coded B but C4. Refer to section 4.1.3 below,

Code B is not applicable to CS and QC samples and for immunoassay methods.

4.1.3 Incomplete Analysis (Code C)

An incomplete analysis is defined as a sample for which a concentration cannot be obtained due to technical reasons, such as:

- C1: Sample loss during a processing step, such as during extraction, filtration or protein precipitation.
- C2: Equipment failure, such as laboratory equipment, analytical instrumentation or computer failure.
- C3: Improper sample identification (e.g. discrepancy between the injection vial identification and the sample name on the injection sequence, sample tube label is unreadable, mislabelling by the technician, etc.).
- C4: The internal standard response is ≤ 5% of the mean internal standard responses (C4).

A sample reanalyzed for incomplete analysis will be coded "C" (C1, C2, C3, C4) and its concentration will be identified as NRV in the analytical repeat table of the analytical report. The repeated value will be reported in the final concentration table of the analytical report.

Code C4 is not applicable for immunoassay methods.

Firm's Explanation of Unexpected Values - Fasting Study:

Unexpected results were obtained for samples 48-P1-0.417h and 49-P1-0.417h. These samples were thus coded G (sample reanalyzed to obtain a confirming value) and reanalyzed in duplicate. After reviewing the results obtained for the repeat analyses, a mix-up between the two samples during the initial analysis was suspected. Results are presented below:

48-P1-0.417h	Concentration (pg/mL)			
	First analysis	Second Analysis Set 1	Second Analysis Set 2	Reported value
Atorvastatin	1748.31	20205.49	20585.51	20205.49
p-Hydroxy-Atorvastatin	<52.82	393.53	378.76	393.53
o-Hydroxy-Atorvastatin	62.29	10394.03	11339.90	10394.03

49-P1-0.417h	Concentration (pg/mL)			
	First analysis	Second Analysis Set 1	Second Analysis Set 2	Reported value
Atorvastatin	21281.84	1605.22	1622.02	1605.22
p-Hydroxy-Atorvastatin	394.46	<52.82	<52.82	<52.82
o-Hydroxy-Atorvastatin	11270.19	58.10	52.90	58.10

Unexpected results were also obtained for sample 48-P2-10h. Sample was coded G for atorvastatin and o-hydroxy-atorvastatin. Sample was coded D (concentration above the calibration range) and then G for p-hydroxy-atorvastatin. A technical error was suspected since no problems were identified in the run where the first analysis was performed. Results are presented below:

48-P2-10h	Concentration (pg/mL)			
	First analysis	Second Analysis Set 1	Second Analysis Set 2	Reported value
Atorvastatin	7841.49	3582.17	4117.09	3582.17
o-Hydroxy-Atorvastatin	12083.23	6691.63	7628.01	6691.63

48-P2-10h	Concentration (pg/mL)			
	First analysis	Repeat Analysis	Confirming Repeat Analysis	Reported value
p-Hydroxy-Atorvastatin	>2640.75	793.48	911.56	793.48

Firm's Explanation of Unexpected Values - Fed Study:

Unexpected results were obtained for sample 47-P1-1.5h. The sample was thus coded G (sampl reanalyzed to obtain a confirming value) and reanalyzed in duplicate. Meanwhile, sample 47-P2-1.5 analyzed in the same run was coded D (sample above the calibration range) for atorvastatin and als reanalyzed in one replicate. After reviewing the results obtained for the repeat analyses, a mix-up betwee the two samples during the initial analysis was suspected. Sample 47-P2-1.5h was therefore coded G fc p-hydroxy-atorvastatin and o-hydroxy-atorvastatin to obtain a confirming value. The first repeat analyse results were reported as the final concentrations. However, no confirming value could be obtained fc p-hydroxy-atorvastatin. Therefore, NRV (no reportable value) was reported. All these reanalyses wer performed according to SOP ANI 156.12. Results are presented below:

47-P1-1.5h	Concentration (pg/mL)			
	First analysis	Second Analysis Set 1	Second Analysis Set 2	Reported value
Atorvastatin	4006.02	61260.26	59439.96	61260.26
p-Hydroxy-Atorvastatin	<52.82	812.53	796.55	812.53
o-Hydroxy-Atorvastatin	1686.17	44293.13	44024.34	44293.13

47-P2-1.5h	Concentration (pg/mL)			
	First analysis	Repeat Analysis	Confirming Repeat Analysis	Reported value
Atorvastatin	>52563.00	4281.04	4269.21	4281.04

47-P2-1.5h	Concentration (pg/mL)			
	First analysis	Second Analysis Set 1	Second Analysis Set 2	Reported value
p-Hydroxy-Atorvastatin	753.16	NRV	NRV	NRV
o-Hydroxy-Atorvastatin	40952.63	1777.34	1702.00	1777.34

Samples 61-P2-2.25h and 70-P2-2.75h gave no concentrations upon first analysis while adjacer sampling times gave high concentrations. The samples were coded G to confirm the results obtained an reanalyzed using both sets of aliquots. Following review of the results, it was strongly suspected that n sample was added in either tube during sample extraction of the initial analytical run. Results ai presented below:

61-P2-2.25h	Concentration (pg/mL)			
	First analysis	Second Analysis Set 1	Second Analysis Set 2	Reported value
Atorvastatin	<52.56	10483.47	10586.19	10483.47
p-Hydroxy-Atorvastatin	<52.82	196.31	193.42	196.31
o-Hydroxy-Atorvastatin	<52.56	11047.84	11636.74	11047.84

70-P2-2.75h	Concentration (pg/mL)			
	First analysis	Second Analysis Set 1	Second Analysis Set 2	Reported value
Atorvastatin	<52.56	12372.85	11961.02	12372.85
p-Hydroxy-Atorvastatin	<52.82	273.42	266.93	273.42
o-Hydroxy-Atorvastatin	<52.56	5287.64	5451.18	5287.64

Did use of recalculated plasma concentration data change study outcome?

- There were no PK repeats. However in the fasting study, the firm suspected a sample mix-up between Sub 48-Per1-0.417h (Test) and Sub 49-Per1-0.417h (Test), repeated the analyses and used the repeat values in statistical analysis. Similarly, the firm considered unexpected concentration values for Sub 48-Per2-10h (Reference), due to unidentifiable technical error, repeated the analyses and used the repeat values in statistical analysis. However, in a laboratory setting, sample mix-up and unidentifiable technical error can not be accurately verified. Therefore, the reviewer analyzed the Atorvastatin data using original and repeat values. ANOVA analysis for Atorvastatin was also carried out after excluding Subjects 48 and 49 (n=74). Both analyses met 90% confidence interval BE criteria (see comment on page 59). The original, repeat and accepted values are given in the Appendix (see Section 4.6, 4.7, Repeat Analysis – Fasting, Repeat Analysis – Fed).

- In the fed study, there were no PK repeats. However, the firm suspected a sample mix-up between Sub 47-Per1-1.5h (Reference) and Sub 47-Per2-1.5h (Test), repeated the analyses and used the repeat values in statistical analysis. Since, in a laboratory setting, sample mix-up can not be accurately verified, the reviewer analyzed the Atorvastatin data using original and repeat values. ANOVA analysis for Atorvastatin was also carried out after excluding Subjects 47 (n=75). Both analyses met 90% confidence intervals BE criteria (see comment on page 83).

- In order to save additional valuable data for the subject, the reviewer prefers the analysis with original values (n=76).

Comments from the Reviewer: Analytical methods and methods validations are **acceptable**.

3.6.3. Pilot Studies

The firm has also conducted four pilot studies prior to conducting the pivotal studies. The formulations of the pilot and pivotal study lots are identical. The outline of the studies and PK results calculated and submitted by the firm are provided in the Appendix, 4.2.3, Pilot Studies. Brief summary of study results are provided below. Three pilot studies failed in meeting the 90% CI BE criteria of 80-125% for Atorvastatin for Cmax (see Tables 14-16 below). In one fasting study (3023-ATORV-08), the study failed the 90% CI criteria for all three PK parameters (Table 17). Supporting data for ortho-hydroxy and para-hydroxy atorvastatin were within the 80-125% for all PK parameters.

1. Study no. BE-248-ATOR-2009

A single dose three way cross-over fasting study (Study No: BE-248-ATOR-2009) for Atorvastatin calcium tablet 80 mg with test batch no B204130 against US reference (Lipitor 80 mg tablet B.No. 22537V, Pfizer USA) and Canada reference (Lipitor 80 mg tablets B.No. 0378088, Pfizer Canada)

2. Study no BE-249-ATOR-2009

A single dose two way cross over fed study (Study No BE-249-ATOR-2009) for Atorvastatin calcium tablet 80 mg with test batch No. B204130 against reference (Lipitor 80 mg tablets, Pfizer USA) with batch no 22537V.

3. Study no 365_ATORV_09

A single dose three way cross-over fasting study (Study No. 365_Atorv_09) for Atorvastatin calcium tablet 80 mg with test batch no. ANK (3926)071A against reference (Lipitor 80 mg tablet, Pfizer USA) with batch no 04558V and Belgium reference (Lipitor 80 mg tablet) with batch no 0904118B.

4. Study no 3023_ATROV_08

A single dose two way cross over fasting study (Study No 3023_ATORV_08) for Atorvastatin calcium tablet 80 mg with test batch no. ANK (3926)049 against reference (Lipitor 80 mg tablets, Pfizer USA) with batch no 22537V.

Summary of Pilot study Results: Summary results are given in the tables below:

Table 14. Statistical Summary of in vivo Bioequivalence Study – Fasting (Pilot)

Fasted Bioequivalence study (Study No. BE-248-ATOR-2009)

Parameter	Test	Reference (R1)	Reference (R2)	Ratio % (T/R1)	90 % C.I	Ratio (T/R2)	90 % C.I
AUC_{0-t} (ng.h/mL)	Atorvastatin: 260.4194, Ortho hydroxy atorvastatin: 350.8535, Para hydroxy atorvastatin: 60.8598	Atorvastatin: 258.8401, Ortho hydroxy atorvastatin: 367.2718, Para hydroxy atorvastatin: 58.0519	Atorvastatin: 257.4199, Ortho hydroxy atorvastatin: 348.6631, Para hydroxy atorvastatin: 62.3408	Atorvastatin: 100.61, Ortho hydroxy atorvastatin: 95.53, Para hydroxy atorvastatin: 104.84	Atorvastatin: 88.77 - 114.02, Ortho hydroxy atorvastatin: 85.81 - 106.35, Para hydroxy atorvastatin: 91.86 - 119.65	Atorvastatin: 101.17, Ortho hydroxy atorvastatin: 100.63, Para hydroxy atorvastatin: 97.62	Atorvastatin: 89.26 - 114.65, Ortho hydroxy atorvastatin: 90.39 - 112.02, Para hydroxy atorvastatin: 85.54 - 111.42
AUC_{inf} (ng.h/mL)	Atorvastatin: 267.4671, Ortho hydroxy atorvastatin: 360.7288, Para hydroxy atorvastatin: 77.6726	Atorvastatin: 267.7431, Ortho hydroxy atorvastatin: 379.1949, Para hydroxy atorvastatin: 81.2002	Atorvastatin: 264.1815, Ortho hydroxy atorvastatin: 358.4202, Para hydroxy atorvastatin: 83.0985	Atorvastatin: 99.90, Ortho hydroxy atorvastatin: 95.13, Para hydroxy atorvastatin: 95.66	Atorvastatin: 88.40 - 112.89, Ortho hydroxy atorvastatin: 85.92 - 105.33, Para hydroxy atorvastatin: 79.44 - 115.19	Atorvastatin: 101.24, Ortho hydroxy atorvastatin: 100.64, Para hydroxy atorvastatin: 93.47	Atorvastatin: 89.59 - 114.41, Ortho hydroxy atorvastatin: 90.90 - 111.44, Para hydroxy atorvastatin: 77.62 - 112.56

R1= US Reference (Lipitor® USA); R2=Canadian Reference

C_{max} (ng/mL)	Atorvastatin: 64.4997, Ortho hydroxy atorvastatin: 44.1504, Para hydroxy atorvastatin: 2.8436	Atorvastatin: 56.5192, Ortho hydroxy atorvastatin: 47.4915, Para hydroxy atorvastatin: 2.7447	Atorvastatin: 60.4934, Ortho hydroxy atorvastatin: 44.4694, Para hydroxy atorvastatin: 2.4195	Atorvastatin: 114.12, Ortho hydroxy atorvastatin: 92.96, Para hydroxy atorvastatin: 103.60	Atorvastatin: 98.09 - 132.77, Ortho hydroxy atorvastatin: 80.31 - 107.61, Para hydroxy atorvastatin: 79.10 - 135.71	Atorvastatin: 106.62, Ortho hydroxy atorvastatin: 99.28, Para hydroxy atorvastatin: 117.53	Atorvastatin: 91.65 - 124.05, Ortho hydroxy atorvastatin: 85.77 - 114.93, Para hydroxy atorvastatin: 89.73 - 153.95

Table 15. Statistical Summary of in vivo Bioequivalence Study – Fed (Pilot, BE-247-ATOR-2009)

Parameter	Test (T)	Reference (R)	Ratio% (T/R)	90 % C.I
AUC_{0-t} (ng.h/mL)	Atorvastatin: 242.9523, Ortho hydroxy atorvastatin: 259.1722, Para hydroxy atorvastatin: 50.0296	Atorvastatin: 259.9057, Ortho hydroxy atorvastatin: 274.2544, Para hydroxy atorvastatin: 54.6337	Atorvastatin: 93.48, Ortho hydroxy atorvastatin: 94.50, Para hydroxy atorvastatin: 91.57	Atorvastatin:83.17 - 105.06, Ortho hydroxy atorvastatin: 85.54 - 104.40, Para hydroxy atorvastatin: 79.47 - 105.52
AUC_{inf} (ng.h/mL)	Atorvastatin: 248.7460, Ortho hydroxy atorvastatin:266.8598, Para hydroxy atorvastatin: 65.8014	Atorvastatin: 267.2847, Ortho hydroxy atorvastatin: 282.7816, Para hydroxy atorvastatin: 69.4124	Atorvastatin: 93.06, Ortho hydroxy atorvastatin: 94.37, Para hydroxy atorvastatin: 94.80	Atorvastatin: 82.65 - 104.79, Ortho hydroxy atorvastatin: 84.79 - 105.03, Para hydroxy atorvastatin: 76.26 - 117.83
C_{max} (ng/mL)	Atorvastatin: 35.3815, Ortho hydroxy atorvastatin: 22.2420, Para hydroxy atorvastatin: 2.3538	Atorvastatin: 41.6543, Ortho hydroxy atorvastatin: 23.2850, Para hydroxy atorvastatin: 2.5498	Atorvastatin: 84.94, Ortho hydroxy atorvastatin: 95.52, Para hydroxy atorvastatin: 92.31	Atorvastatin: 67.25 - 107.29, Ortho hydroxy atorvastatin: 77.11 - 118.32, Para hydroxy atorvastatin: 74.86 - 113.84

Table 16. Statistical Summary of in vivo Bioequivalence Study – Fasting (Pilot)

Table 3 Statistical Summary of the Comparative Bioavailability Data

Atorvastatin Dose (80 mg) Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)							
Fasting Bioequivalence Study (Study No. 365_ATORV_09)							
Parameter	Test	Reference 1	Reference 2	Ratio T/R1(%)	Ratio T/R2(%)	90% CI T/R1	90% CI T/R2
AUC_{0-t}	141.6119 ng.h/mL	147.9674 ng.h/mL	149.7027 ng.h/mL	95.70	94.60	86.25 – 106.19	85.25 - 104.96
$AUC_{0-\infty}$	146.6073 ng.h/mL	151.1620 ng.h/mL	153.6251 ng.h/mL	96.99	95.43	87.09 – 108.00	85.70 - 106.27
C_{max}	40.9730 ng/mL	44.3465 ng/mL	43.1425 ng/mL	92.39	94.97	79.15 – 107.85	81.36 - 110.86
2-Hydroxy Atorvastatin (o- Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means							
Fasting Bioequivalence Study (Study No. 365_ATORV_09)							
Parameter	Test	Reference 1	Reference 2	Ratio T/R1(%)	Ratio T/R2(%)		
AUC0-t	191.9256 ng.h/mL	203.9215 ng.h/mL	210.2465 ng.h/mL	94.12	91.29		
AUC0-∞	197.6475 ng.h/mL	207.6151 ng.h/mL	215.5512 ng.h/mL	95.20	91.69		
C max	32.8340 ng/mL	35.2029 ng/mL	35.4423 ng/mL	93.27	92.64		
4-Hydroxy Atorvastatin (p- Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means							
Fasting Bioequivalence Study (Study No. 365_ATORV_09)							
Parameter	Test	Reference 1	Reference 2	Ratio T/R1(%)	Ratio T/R2(%)		
AUC0-t	28.6392 ng.h/mL	30.2964 ng.h/mL	30.8193 ng.h/mL	94.53	92.93		
AUC0-∞	44.9231 ng.h/mL	43.4509 ng.h/mL	44.1560 ng.h/mL	103.39	101.74		
C max	1.3516 ng/mL	1.4490 ng/mL	1.5280 ng/mL	93.28	88.45		

R1= US Reference (Lipitor® USA); R2=Belgium Reference

Table 17. Statistical Summary of in vivo Bioequivalence Study – Fasting (Pilot)

Atorvastatin Dose (80 mg) Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)				
Fasting Bioequivalence Study (Study No. 3023_ATORV_08)				
Parameter	**Test**	**Reference**	**Ratio (%)**	**90% CI**
AUC_{0-t}	188.3614 ng.h/mL	161.6684 ng.h/mL	116.51	102.58 – 132.33
$AUC_{0-\infty}$	193.5338 ng.h/mL	165.1965 ng.h/mL	117.15	103.36 – 132.79
C_{max}	50.9534 ng/mL	51.2247 ng/mL	99.47	77.73 – 127.30
2-Hydroxy Atorvastatin (o-Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means				
Fasting Bioequivalence Study (Study No. 3023_ATORV_08)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	151.7430 ng.h/mL	132.1667 ng.h/mL	114.81	
$AUC_{0-\infty}$	155.9941 ng.h/mL	138.1402 ng.h/mL	112.92	
C_{max}	22.4071 ng/mL	20.8814 ng/mL	107.31	
4-Hydroxy Atorvastatin (p-Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means				
Fasting Bioequivalence Study (Study No. 3023_ATORV_08)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	29.0862 ng.h/mL	25.5404 ng.h/mL	113.88	
$AUC_{0-\infty}$	41.5592 ng.h/mL	40.5781 ng.h/mL	102.42	
C_{max}	1.3957 ng/mL	1.1826 ng/mL	118.02	

3.7.Formulation

Location in appendix	See Appendix, Formulation Data
If a tablet, is the RLD scored?	No
If a tablet, is the test product biobatch scored	No
Is the formulation acceptable?	From its original acceptable formulation, the firm has made major changes in polymorphic form, components and composition, manufacturing process and manufacturing site. The new formulation is **ACCEPTABLE.**
If not acceptable, why?	N/A

3.8.In Vitro Dissolution

There is an FDA recommended dissolution method (900 mL of 0.05 Phosphate buffer at pH 6.8 and Paddle at 75 rpm). However, in the original application, the firm preferred to use the (b) (4) Vessels instead of USP-2 Vessels, because it had added advantages (lower variability in data). The firm had conducted acceptable dissolution testing on Atorvastatin Calcium Tablets, 10, 20 40 and 80 mg, using the FDA recommended method, and had repeated the testing using (b) (4) Vessels as requested by the DBE. The firm's response was found acceptable. Waivers of bioequivalence study for 40 mg, 20 mg and 10 mg strength Tablets were granted (see the reviews - v:\firmsnz\ranbaxy\ltrs&rev\76477n0802.doc; v:\firmsnz\ranbaxy\ltrs&rev\76477a0503.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0906.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0807.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0108.doc).

It should be noted that since the time the above dissolution method with (b) (4) vessels was accepted, the DBE has changed its recommendation regarding the use of (b) (4) vessels. Currently, (b) (4) vessels are not recommended for release and stability dissolution testing since (b) (4) vessels are not compendial vessels and have not been adequately standardized.

However, in the current amendment, the firm has used the FDA recommended method as follows:

Location of DBE Dissolution Review	See Appendix, Section 4.4, Dissolution Data
Source of Method (USP, FDA or Firm)	**FDA**
Medium	pH 6.8 phosphate buffer @ 37°C
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
Firm's specification	NLT (b) (4) (Q) in 15 minutes
DBE-recommended specification	Will be set on review of additional data
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Fast dissolving (>85% in 15 minutes)
Is method acceptable?	No.
If not then why?	The firm is requested to provide additional dissolution data.

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
Fast dissolving (>85% in 15 minutes)			

3.9.Waiver Request(s)

Strengths for which waivers are requested	10, 20 and 40 mg
Proportional to strength tested in vivo?	Yes
Is dissolution acceptable?	No. The firm will be requested to acknowledge the acceptance of recommended dissolution specification.
Waivers granted?	**DENIED**
If not then why?	Pending firm's acknowledgement of the acceptance of recommended dissolution specification.

3.10. DSI Inspection Audit of the Clinical Site, Cetero Research, Fargo, ND

A routine DSI Inspection of the clinical site, Cetero Research, Amber Valley Pkwy, Fargo, ND, was conducted during 12/15/2008-12/17/2008, and the report was completed on 5/15/2009 with a VAI outcome for NDA 022418 (Bioequivalence study of 105 mg

Fenofibric Acid Tablets vs. 145 mg Tricor® tablets under fasting conditions)[8]. The DSI concluded the clinical findings as follows:

- It is objectionable that PRACS Institute-Cetero Research failed to report subject #04's miscarriage to the IRB and failed to completely assure subject safety. As per the protocol, the IRB should be notified of all SAEs.[1] Furthermore, DSI plans to follow-up and determine if the firm has implemented corrective actions by reporting all SAEs to the IRB.
- It is objectionable that the firm changed 50 of the 54 subjects' CRFs from being study eligible to being study ineligible without clarification, more than 8 months after study completion. DSI recommends that the review division evaluate the extent of these subject deviations, and also consider the impact of enrolling these ineligible subjects.

The reviewer verified the CRFs for the dates of entry, changes in the records, and changes in inclusion/exclusion criteria. The entries in the CRFs were documented, signed and dated appropriately. There were no changes or major modifications in the CRFs for subjects. Adverse events observed in the fasting and fed studies were minor and were recorded appropriately in the CRFs. It should be noted that the studies were conducted after this DSI inspection, i.e. during 10/4/2009-10/18/2009 period, which may have some effect on the improved record-keeping procedure.

A routine DSI Inspection of the Analytical site, (b) (4) (b) (4) was conducted during (b) (4), and the report was completed on (b) (4) with a VAI outcome for NDA (b) (4) (Clinical and analytical studies on (b) (4))[9]. The DSI cited the firm for discrepancies in long-term stability data generated by the firm. The firm conducted additional long-term stability studies and the outcome was confirmed. The DSI concluded the analytical findings as follows:

3. The analytical observation cited in the Form FDA-483 should not have significant impact on the outcomes of the studies.

There is no DSI inspection of clinical or analytical sites pending or necessary for this product.

[8] DARRTS, NDA 022418, DSI Inspection of the Clinical Site for NDA 022418, 5/15/2009, http://darrts fda.gov:9602/darrts/ViewDocument?documentId=090140af80139865

[9] DARRTS, NDA (b) (4) (b) (4) CONSULT REV-DSI-05(Bioequivalence Establishment Inspection Report Review) Original-1 (Type 5- New Formulation or New Manufacturer)

3.11. Deficiency Comments

1. The dissolution testing data based on the FDA-recommended method were insufficiently discriminating with greater than 85% of the drug in the dosage form dissolved in 10 minutes. Therefore, the firm is asked to conduct additional dissolution testing with the decreased paddle speed of 50 rpm:

   Medium: 0.05M Phosphate Buffer, pH 6.8 at 37 ^{0}C
   Volume: 900 mL
   USP Apparatus: II (Paddle) at 50 rpm
   Dosage Units: 12 each for Test and Reference of all strengths
   Recommended Sampling Times: 10, 15, 20, 30, 45 minutes and until at least (b) (4) dissolved.

3.12. Recommendations

1. The Division of Bioequivalence **accepts** the fasting BE study (R09-1032) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #R1560901 comparing it to Pfizer, Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V.

2. The Division of Bioequivalence **accepts** the fed BE study (R09-1033) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #R1560901 comparing it to Pfizer, Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V.

3. The Division of Bioequivalence acknowledges the pilot fasting BE study (BE-248-ATOR-2009) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #B204130 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA), and Canada Lipitor®, 80 mg, Lot # B0378088 (Pfizer, Canada).

4. The Division of Bioequivalence acknowledges the pilot fed BE study (BE-249-ATOR-2009) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #B204130 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA).

5. The Division of Bioequivalence acknowledges the pilot fasting BE study (365-_ATORV_09) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #ANK (3926)071A comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V (Pfizer, USA), and Belgium Lipitor®, 80 mg, Lot # 0904118B (Pfizer, Belgium).

6. The Division of Bioequivalence acknowledges the pilot fasting BE study (3023-_ATORV_08) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #ANK (3926)049 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA).

7. The dissolution testing conducted by Ranbaxy Laboratories Ltd. on its Atorvastatin Calcium, 10, 20, 40 and 80 mg Tablets comparing it with Pfizer's Lipitor® Tablets, 10, 20, 40 and 80 mg Tablets, respectively, is **incomplete** due to deficiency #1 cited above.

8. The formulations for the 10, 20 and 40 mg strengths are (b) (4) to the 80 mg strength of the test product, which underwent bioequivalence testing. However, waivers of in vivo bioequivalence study requirements for 10, 20 and 40 mg strengths Tablet of the test product cannot be granted at this time due to deficiency #1 cited above.

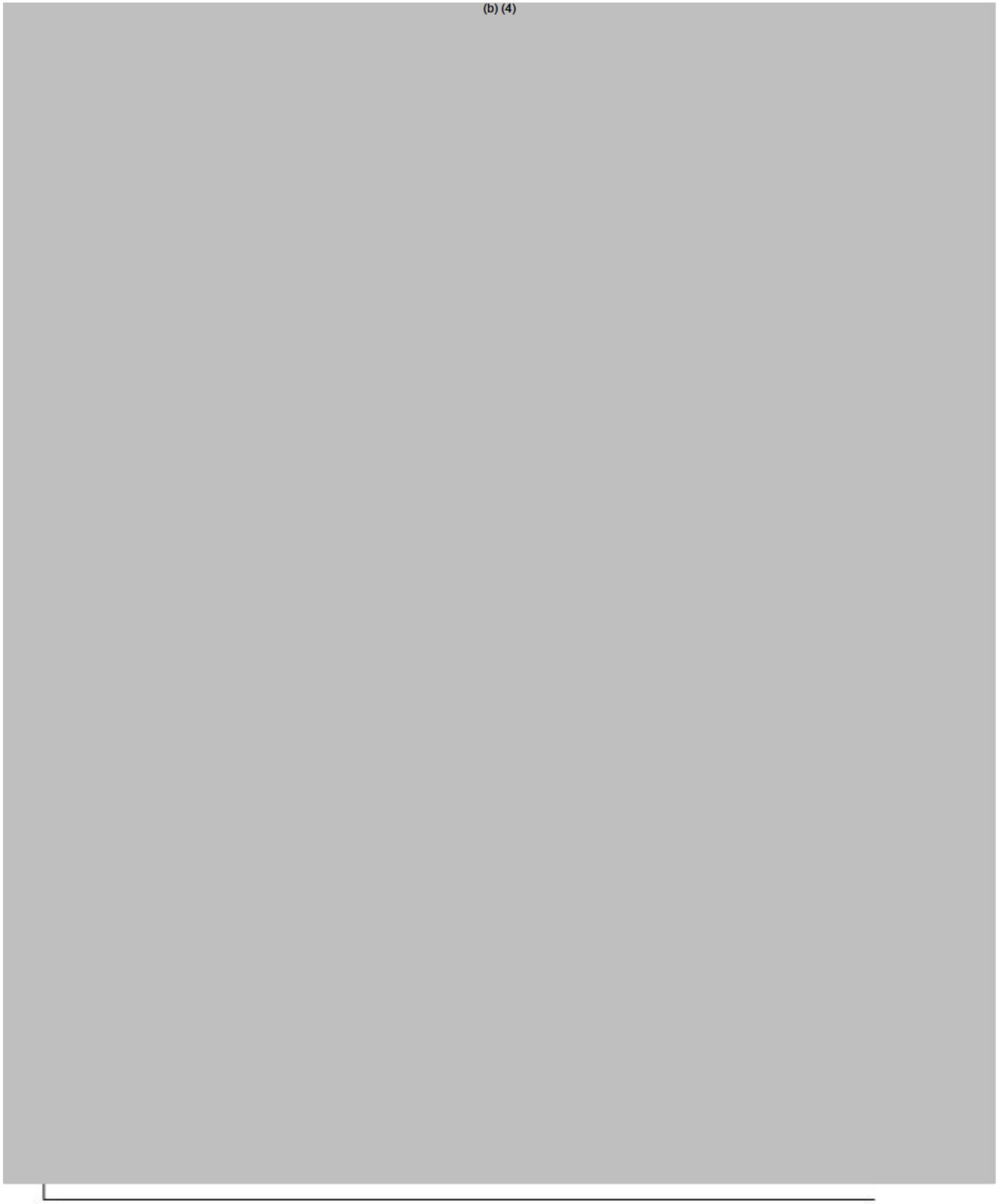
3.13. Comments for Other OGD Disciplines

Discipline	Comment
Chemistry	From its original acceptable formulation, the firm has made major changes in polymorphic form, components and composition, manufacturing process and manufacturing site. Therefore, the Chemistry should look into the CMC aspects.

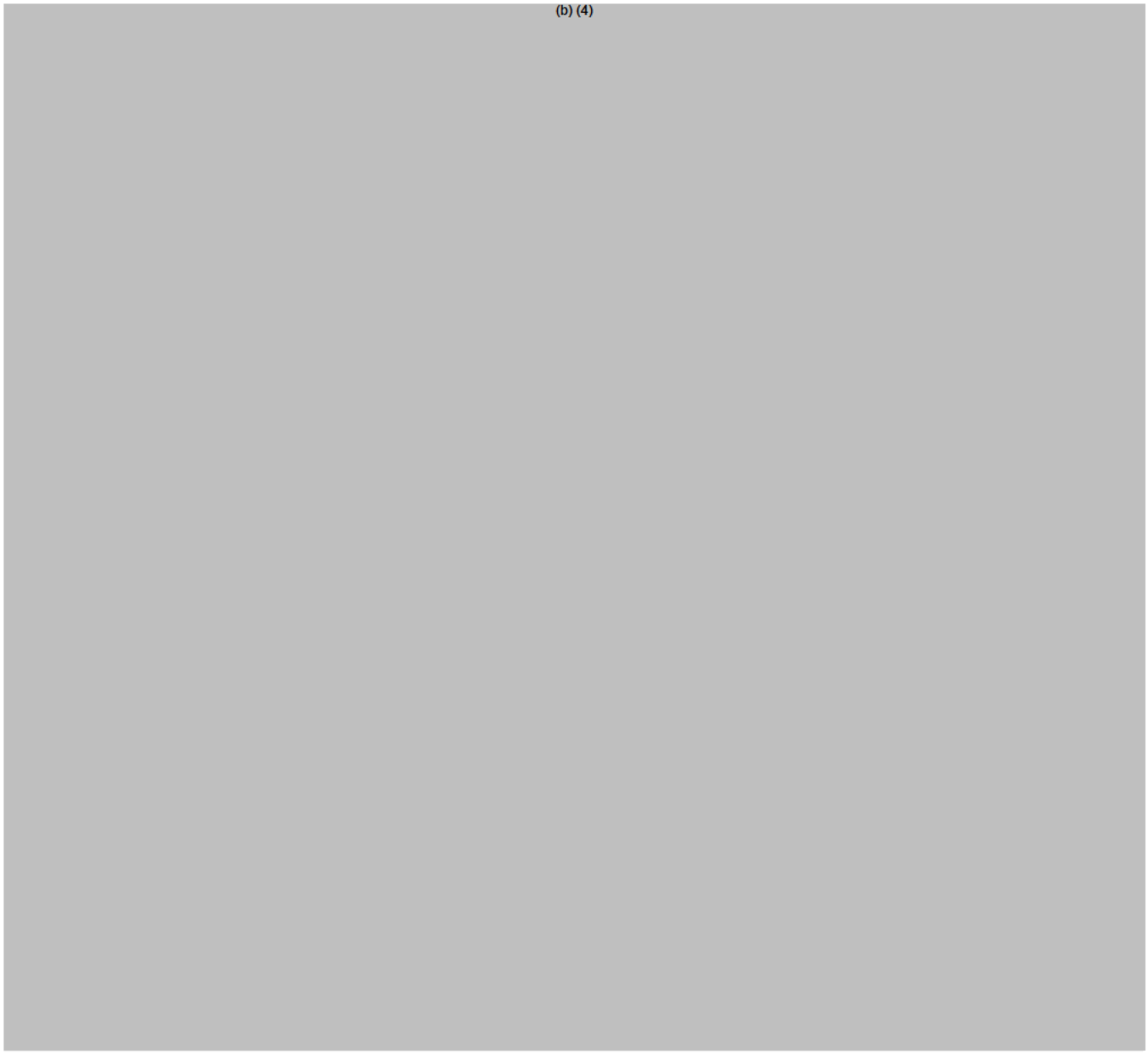
4. APPENDIX

4.1. Chemical Polymorphs (RLD)

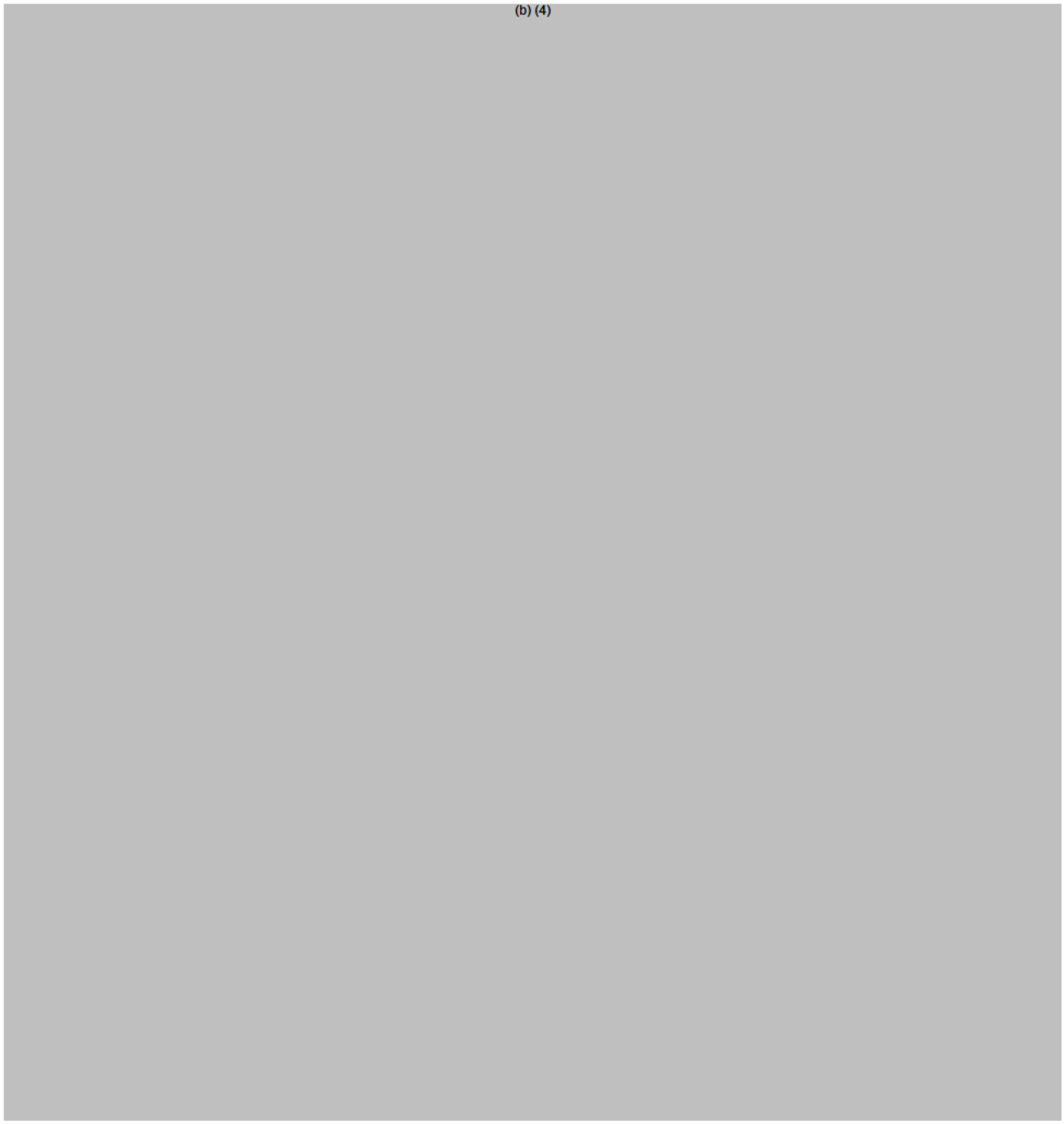
(b) (4)



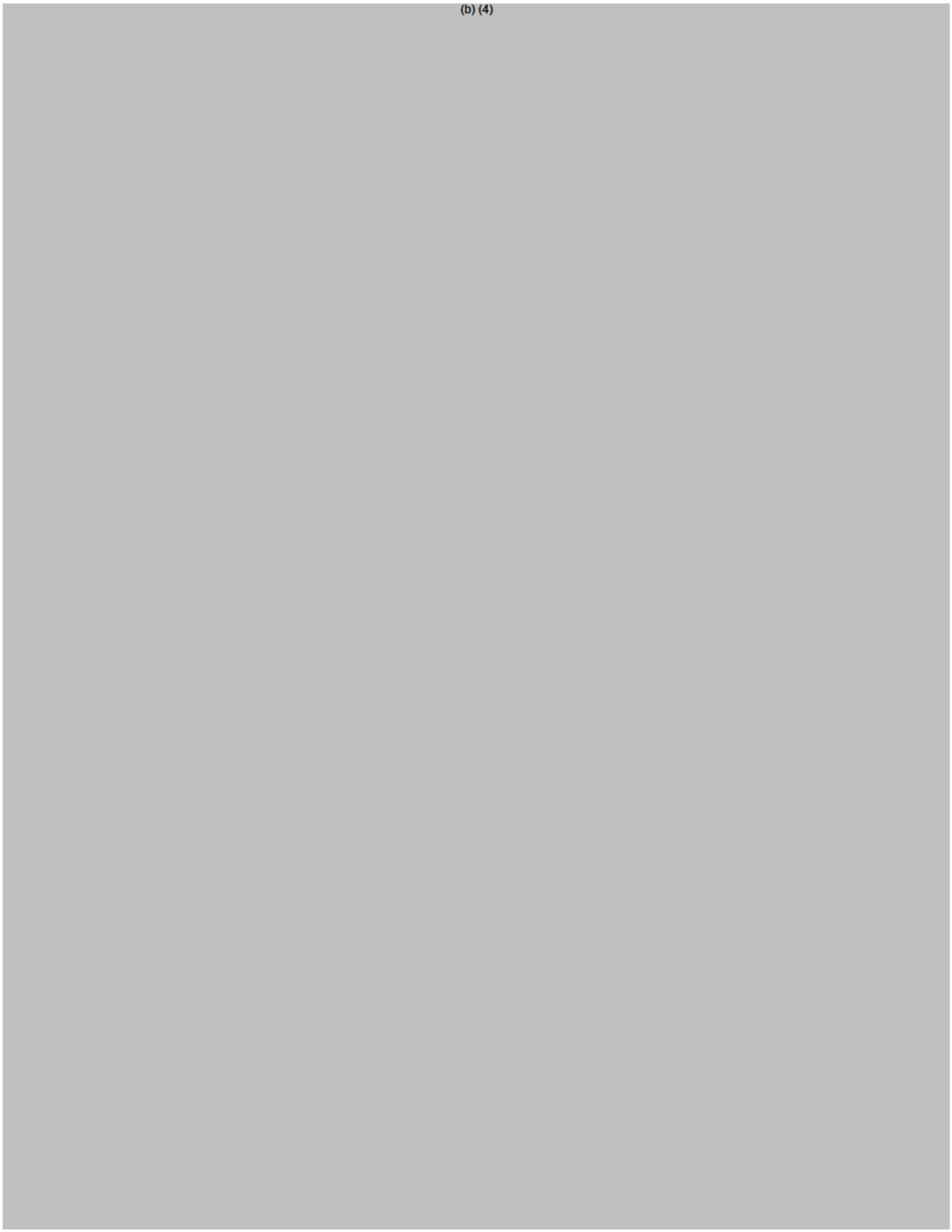
(b) (4)



(b) (4)



(b) (4)



Particle Size Distribution:

(b) (4)

4.2.Individual Study Reviews

4.2.1. Single-dose Fasting Bioequivalence Study

4.2.1.1.Study Design

Table 18 Study Information

Study Number	R09-1032
Study Title	A Bioequivalence Study of 80 mg Atorvastatin Calcium Tablets Versus 80 mg Lipitor® Tablets Under Fasting Conditions.
Clinical Site (Name, Address, Phone #)	Clinical Services Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104 Phone: (701) 239-4750 Clinical Laboratory Facility Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104 Phone: (701) 239-4750
Principal Investigator	Anthony R. Godfrey, Pharm.D. Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104 USA Phone: (701) 239-4750
Dosing Dates	PERIOD I: 04 October 2009 PERIOD II: 18 October 2009
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	2009-10-26 to 2009-11-23
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	50 days (2009-10-04 to 2009-11-23)

In this amendment, the firm has made CMC changes: Changed API from amorphous (Ranbaxy Lab, Paonta Sahib's API) to crystalline form (b) (4) API); made qualitative and quantitative changes in components and composition; made manufacturing process change; and manufacturing site change (Ohm Labs, N.J.).

Table 19. Product information

Product	Test	Reference
Treatment ID	T	R
Product Name	Atorvastatin calcium tablets 80 mg	Lipitor Tablets 80 mg
Manufactured by	OHM Laboratories INC.	Pfizer Ireland Pharmaceuticals,
Batch No.	RI560901	04558V
Manufacture Date	May 2009	-
Expiry Date	April 2012	Mar 2011
Strength	80 mg	80 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4) tablets	-
Production Batch Size	tablets	-
Potency	102.0%	97.3%
Content Uniformity (mean, %CV)	102.2%	97.7%
Dose Administered	1x80 mg	1x80 mg
Route of Administration	Oral	Oral

Table 20. Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	80 Enrolled, Subjects were dosed; 76 completed the study
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	**TR:** 1, 3, 6, 8, 11, 12, 15, 16, 19, 20, 22, 24, 26, 27, 29, 31, 34, 36, 38, 40, 41, 44, 47, 48, 49, 50, 53, 54, 57, 60, 61, 63, 65, 67, 70, 72, 74, 76, 78, 79 **RT:** 2, 4, 5, 7, 9, 10, 13, 14, 17, 18, 21, 23, 25, 28, 30, 32, 33, 35, 37, 39, 42, 43, 45, 46, 51, 52, 55, 56, 58, 59, 62, 64, 66, 68, 69, 71, 73, 75, 77, 80
Blood Sampling Times	Pre-dose and at 0.167, 0.25, 0.333, 0.417, 0.5, 0.583, 0.667, 0.833, 1, 1.25. 1.5, 1.75, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 16, 20, 24, 36, 48, 60, 72 and 96 hours post dose
Blood Volume Collected/Sample	3 mL in K2-EDTA was used.
Blood Sample Processing/Storage	After collection, blood samples were cooled; immediately centrifuged; plasma samples were separated, and stored at -80 ^{0}C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Subjects fasted overnight for at least 10 hours prior to drug administration and then for a further 4 hours following drug administration.
Length of Confinement	Subjects were confined to clinical facility from at least 36 hours prior to each drug administration until after the 24-hour blood sample collection.
Safety Monitoring	Subjects were monitored throughout the study.
Drug Specific Information	None

Comments on Study Design: The study design is **acceptable**.

4.2.1.2.Clinical Results

Table 21. Demographics Profile of Subjects Completing the Bioequivalence Study

R09-1032			
		Treatment Groups	
		Test Product N=76[1]	Reference Product N=76[1]
Age (years)	Mean ± SD	32.3 ± 15.7	32.3 ± 15.7
	Range	18 - 75	18 - 75
Age Groups	< 18	-	-
	18 – 39	56 (73.7%)	56 (73.7%)
	40 – 64	16 (21.1%)	16 (21.1%)
	65 – 75	4 (5.3%)	4 (5.3%)
	> 75	-	-
Sex	Male	65 (85.5%)	65 (85.5%)
	Female	11 (14.5%)	11 (14.5%)
Hispanic or Latino Race	N	-	-
	A	-	-
	B	-	-
	I	-	-
	W	1 (1.3%)	1 (1.3%)
Not Hispanic or Latino Race	N	1 (1.3%)	1 (1.3%)
	A	5 (6.6%)	5 (6.6%)
	B	4 (5.3%)	4 (5.3%)
	I	-	-
	W	64 (84.2%)	64 (84.2%)
	WBN	1 (1.3%)	1 (1.3%)
BMI	Mean ± SD	25.7 ± 3.1	25.7 ± 3.1
	Range	20.0 - 32.0	20.0 - 32.0
Other Factors			

Table 22. Dropout Information, Fasting Bioequivalence Study

R09-1032				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
12	Withdrew consent prior to Period II check in.	I	No	N/A
23	Withdrew consent prior to Period II dosing.	I	No	N/A
36	Dropped by Investigator due to flu symptoms prior to Period II check in.	I	No	N/A
41	Dropped by Investigator due to AE (vomiting) Period I, after study hour 0.667.	I	No	N/A

Table 23. Study Adverse Events, Fasting Bioequivalence Study

Body System/Adverse Event[1]	Reported Incidence by Treatment Groups	
	R09-1032	
	Test N=79[2]	Reference N=77[2]
	n (%)[3]	n (%)[3]
Eye disorders		
Dry eye	-	1 (1.30%)
Gastrointestinal disorders		
Nausea	1 (1.27%)	1 (1.30%)
Vomiting	1 (1.27%)	-
General disorders and administration site conditions		
Pyrexia	1 (1.27%)	1 (1.30%)
Injury, poisoning and procedural complications		
Joint sprain	-	1 (1.30%)
Investigations		
Aspartate aminotransferase increased	1 (1.27%)	-
Musculoskeletal and connective tissue disorders		
Back pain	-	1 (1.30%)
Myalgia	1 (1.27%)	-
Pain in jaw	1 (1.27%)	-
Nervous system disorders		
Dizziness	4 (5.06%)	5 (6.49%)
Headache	1 (1.27%)	1 (1.30%)
Respiratory, thoracic and mediastinal disorders		
Cough	1 (1.27%)	-
Nasal congestion	-	1 (1.30%)
Oropharyngeal pain	1 (1.27%)	2 (2.60%)
Rhinorrhoea	1 (1.27%)	-
Total	11 (13.92%)	9 (11.69%)

Table 24. Protocol Deviations, Fasting Bioequivalence Study

R09-1032		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Period I, not confined to study unit for at least 36 hours prior to dosing (Subject 50)	N/A	N/A
Period I, -12.00 no query (Subjects 02, 03, and 36)	N/A	N/A
Period I, pre-dose vital signs collected greater than 90 minutes prior to dosing (Subject 42)	N/A	N/A
Period I, 0.417 hour, no PK sample	26	N/A
Period I, 0.667 hour, no PK sample	N/A	51
Period I, 36.00 hour, no PK sample or query	N/A	18, 62, 64
Period I, 48.00 hour, no PK sample or query	01, 76	N/A
Period I, 60.00 hour, no PK sample or query	11, 40, 50, 59, 67, 72	59
Period I, 72.00 hour, no PK sample or query	33	11
Period I, 96.00 hour, no PK sample or query	11	N/A
Period I, 0.25 hour, exact time of sample collection inadvertently not documented	N/A	51
Period II, 72.00 hour , no PK sample or query	43	72
Period II, 96.00 hour , no PK sample or query	45, 73	N/A
Period II, 0.583 hour no PK sample	N/A	15
Period II, 0.667 hour no PK sample	10	N/A
Period II, 36.00 hour no PK sample or query	N/A	01
Period II, 48.00 hour no PK sample or query	73, 75	76, 78
Period II, 60.00 hour no PK sample or query	28	11, 40, 67
Completed exit procedures greater than 14 days from last PK collection	N/A	12, 36
Exit query not completed	N/A	41

Comments on Dropouts/Adverse Events/Protocol Deviations: Subject #41 vomited within an hour (Tmax 1-2 hrs), Subject #36 had flu and Subject #12 and 26 withdrew consent. Therefore, dropout is acceptable. The adverse events and protocol deviations were minor and did not compromise the outcome of the study.

4.2.1.3.Bioanalytical Results

Table 25. Assay Validation – Within the Fasting BE Study - Atorvastatin

Bioequivalence Study No. R09-1032 Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	50.06	100.12	2503.00	5006.00	10012.00	20024.00	40048.00	50060.00
Mean (pg/ml)	49.59	101.83	2582.75	5065.87	10265.38	19836.49	38989.22	47999.55
Interday Precision (%CV)	4.96	4.97	3.19	3.51	3.44	3.21	3.28	4.54
Interday Accuracy (% bias)	-0.94	1.71	3.19	1.20	2.53	-0.94	-2.64	-4.12
Linearity	0.9921 to 0.9993							
Linearity Range (pg/mL)	50.06 to 50060.00							
Sensitivity/LOQ (pg/mL)	50.06							

Bioequivalence Study No R09-1032 Atorvastatin				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	150.18	3766.50	15018.00	35042.00
Mean (pg/ml)	161.84	3894.59	15443.69	35305.98
Interday Precision (%CV)	15.08	3.86	4.14	4.47
Interday Accuracy (%)	107.76	103.40	102.83	100.75
Interday Accuracy (%) (% bias)	7.76	3.40	2.83	0.75

Table 26. Assay Validation – Within the Fasting BE Study: p-Hydroxy-atorvastatin

Bioequivalence Study No. R09-1032 p-Hydroxy-Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	50.30	100.60	125.75	251.50	503.00	1006.00	2012.00	2515.00
Mean (pg/ml)	49.90	100.93	127.73	251.35	507.87	996.71	2009.78	2492.33
Interday Precision (%CV)	6.77	5.67	5.73	4.83	4.02	3.85	2.96	4.11
Interday Accuracy (% bias)	-0.80	0.33	1.57	-0.06	0.97	-0.92	-0.11	-0.90
Linearity	0.9902 to 0.9987							
Linearity Range (pg/mL)	50.03 to 2515.00							
Sensitivity/LOQ (pg/mL)	50.03							

Bioequivalence Study No. R09-1032 p-Hydroxy-Atorvastatin				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	150.90	226.35	754.50	1760.50
Mean (pg/ml)	152.52	218.78	768.26	1787.72
Interday Precision (%CV)	13.78	5.94	4.40	4.23
Interday Accuracy (%)	101.07	96.66	101.82	101.55
Interday Accuracy (% bias)	1.07	-3.34	1.82	1.55

Table 27. Assay Validation – Within the Fasting BE Study: o-Hydroxy-atorvastatin

Bioequivalence Study No. R09-1032 o-Hydroxy-Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	50.06	100.12	2503.00	5006.00	10012.00	20024.00	40048.00	50060.00
Mean (pg/ml)	49.77	101.23	2533.23	5012.39	10126.49	19832.91	39683.05	49553.45
Interday Precision (%CV)	7.41	5.85	2.80	2.68	2.57	2.70	2.53	3.42
Interday Accuracy (% bias)	-0.58	1.11	1.21	0.13	1.14	-0.95	-0.91	-1.01
Linearity	0.9942 to 0.9996							
Linearity Range (pg/mL)	50.06 to 50060.00							
Sensitivity/LOQ (pg/mL)	50.06							

Bioequivalence Study No. R09-1032 o-Hydroxy-Atorvastatin				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	150.18	3754.50	15018.00	35042.00
Mean (pg/ml)	160.01	3768.85	15344.32	35647.55
Interday Precision (%CV)	14.92	3.96	3.93	3.93
Interday Accuracy (%)	106.55	100.38	102.17	101.73
Interday Accuracy (% bias)	6.55	0.38	2.17	1.73

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes
Were chromatograms serially or randomly selected?	Serially (1-11, 13-17)

Comments on Chromatograms: Acceptable

Table 28. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ANI 156.12	2009-07-10	Sample Reassays and Reporting of Final Concentrations

Title: Preparation, Identification, Acceptance Criteria of Stock Solutions, Calibration Standards, Quality Controls and Reference Solutions		
Effective Date: 2009-07-06	**SOP & Version #** ANI 153_13	**Page** 1 of 19

Table 29. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No PK repeats
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: The PK parameters were calculated from actual plasma concentration data using actual collection time. There were no PK repeats; however, the firm repeated samples to confirm values. The original, repeat and accepted

values are given in the Appendix (see Section 4.6, 4.7, Repeat Analysis – Fasting, Repeat Analysis – Fed). The firm's repeat analytical values because of mix-up, etc. for Subjects #48 and 49 are not acceptable (see below, Pharmacokinetic Results).

4.2.1.4.Pharmacokinetic Results

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer carried out the ANOVA analysis for 76 subjects for Atorvastatin, o-Hydroxy-atorvastatin and p-Hydroxy-atorvastatin using TWOWAY CONTINU.SAS (for firm's accepted repeat values for Sub #48 and 49) and TWOWAY CALCKE.SAS (for original values for Sub #48 and 49).

- There were no PK repeats. However, the firm suspected a sample mix-up between Sub 48-Per1-0.417h (Test) and Sub 49-Per1-0.417h (Test), repeated the analyses and used the repeat values in statistical analysis. Similarly, the firm considered unexpected concentration values for Sub 48-Per2-10h (Reference), due to unidentifiable technical error, repeated the analyses and used the repeat values in statistical analysis. However, in a laboratory setting, sample mix-up and unidentifiable technical error can not be accurately verified. Therefore, the reviewer analyzed the Atorvastatin data using original and repeat values. ANOVA analysis for Atorvastatin was also carried out after excluding Subjects 48 and 49 (n=74).

- The summary of PK data and results are presented as follows: Atorvastatin in Tables 30-40 and Fig. 1; o-Hydroxy-atorvastatin in Tables 41-45 and Fig. 2; and p-Hydroxy-atorvastatin in Tables 46-50 and Fig. 3.

- The pharmacokinetic parameters and 90% confidence intervals for Atorvastatin in plasma (n=76) calculated by the reviewer agree with firm's calculations.

- The 90% CIs for LAUCt, LAUCi and LCmax parameters for Atorvastatin with original and repeat values, and after excluding Subjects #48 and 49 (n=74), are within the 80-125%. In order to save additional valuable data on the subject, the reviewer prefers the analysis with original values (n=76).

- The supporting data, i.e., the pharmacokinetic parameters and point-estimates for the metabolite, o-Hydroxy-atorvastatin and p-Hydroxy-atorvastatin in plasma (n=76), calculated by the reviewer agree with firm's calculations.

- The point estimates (n=76) for LAUCt, LAUCi and LCmax parameters for o-Hydroxy-atorvastatin and p-Hydroxy-atorvastatin are within the 80-125%.

Summary and Conclusions, Single-Dose Fasting Bioequivalence Study: The study is **acceptable.**

Table 30. Arithmetic Mean Pharmacokinetic Parameters-Atorvastatin (n=76)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	142053.4	44.90	60424.87	352636.1	146669.0	59.13	53217.85	690363.4	0.97
AUCI	pg hr/mL	143492.8	44.40	62319.21	354059.6	149109.2	58.35	56740.32	691708.2	0.96
CMAX	pg/mL	36832.41	53.57	9890.31	119235.6	39355.78	75.81	5707.92	233740.7	0.94
TMAX	hr	0.667	.	0.33	4.00	0.833	.	0.33	5.00	0.80
KE	hr-1	0.073	35.45	0.03	0.14	0.068	37.74	0.03	0.20	1.08
THALF	hr	10.853	41.56	4.78	26.45	11.565	34.93	3.49	20.71	0.94

* Tmax values are presented as median, range

Table 31. Arithmetic Mean Pharmacokinetic Parameters-Atorvastatin (n=76) (Used original values for Subject #48 and 49)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	142163.4	44.87	60424.87	352636.1	147035.5	59.07	53217.85	691063.4	0.97
AUCI	pg hr/mL	142815.0	44.66	60868.32	353348.2	147738.8	58.80	54084.99	691795.2	0.97
CMAX	pg/mL	36832.41	53.57	9890.31	119235.6	39355.78	75.81	5707.92	233740.7	0.94
TMAX	hr	0.667	.	0.33	4.00	0.833	.	0.33	5.00	0.80
KE	hr-1	0.144	18.90	0.07	0.23	0.141	21.98	0.05	0.21	1.02
THALF	hr	5.019	22.07	3.05	9.95	5.219	28.65	3.27	13.10	0.96

Table 32. Arithmetic Mean Pharmacokinetic Parameters-Atorvastatin (n=74) (Excluded Subjects #48 and 49)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	141316.4	45.43	60424.87	352636.1	145920.8	60.10	53217.85	690363.4	0.97
AUCI	pg hr/mL	142755.9	44.91	62319.21	354059.6	148374.0	59.30	56740.32	691708.2	0.96
CMAX	pg/mL	36696.34	53.89	9890.31	119235.6	39070.07	76.80	5707.92	233740.7	0.94
TMAX	hr	0.667	.	0.33	4.00	0.783	.	0.33	5.00	0.85
KE	hr-1	0.073	35.89	0.03	0.14	0.068	37.84	0.03	0.20	1.08
THALF	hr	10.909	41.75	4.78	26.45	11.519	35.47	3.49	20.71	0.95

Table 33. Geometric Means and 90% Confidence Intervals - Firm Calculated Atorvastatin and metabolites (n=76)

Atorvastatin Dose (80 mg) Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)				
Fasting Bioequivalence Study (Study No. R09-1032)				
Parameter	**Test**	**Reference**	**Ratio (%)**	**90% CI**
AUC_{0-t}	130541.42 pg.hr/ml	131063.27 pg.hr/ml	99.60	(95.63, 103.74)
$AUC_{0-\infty}$	133165.11 pg.hr/ml	133615.74 pg.hr/ml	99.66	(95.72, 103.77)
C_{max}	32751.40 pg/ml	33186.70 pg/ml	98.69	(91.18, 106.82)
2-Hydroxy Atorvastatin (o-Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means				
Fasting Bioequivalence Study (Study No. R09-1032)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	172630.15 pg.hr/ml	168593.41 pg.hr/ml	102.39	
$AUC_{0-\infty}$	173921.96 pg.hr/ml	169783.81 pg.hr/ml	102.44	
C_{max}	29865.76 pg/ml	29897.59 pg/ml	99.89	
4-Hydroxy Atorvastatin (p-Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means				
Fasting Bioequivalence Study (Study No. R09-1032)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	19003.56 pg.hr/ml	19153.00 pg.hr/ml	99.22	
$AUC_{0-\infty}$	24554.18 pg.hr/ml	24470.43 pg.hr/ml	100.34	
C_{max}	926.56 pg/ml	920.80 pg/ml	100.63	

Table 34. Geometric Means and 90% Confidence Intervals - Reviewer Calculated Atorvastatin (n=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	**Test**	**Reference**	**(T/R)**	**Lower**	**Upper**
LAUCT	130541.4	131063.3	1.00	94.04	105.50
LAUCI	132122.6	132569.7	1.00	94.10	105.56
LCMAX	32751.40	33186.70	0.99	88.24	110.37

Table 35. Geometric Means and 90% Confidence Intervals - Reviewer Calculated Atorvastatin (Used Original values for Subject #48 and 49, n=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	**Test**	**Reference**	**(T/R)**	**Lower**	**Upper**
LAUCT	130658.6	131386.9	0.99	93.87	105.35
LAUCI	131359.0	132150.3	0.99	93.86	105.27
LCMAX	32751.40	33186.70	0.99	88.24	110.37

Table 36. Geometric Means and 90% Confidence Intervals - Reviewer Calculated Atorvastatin (Excluded Subjects #48 and 49, n=74)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	129576.1	129971.6	1.00	93.98	105.76
LAUCI	131158.7	131478.5	1.00	94.04	105.82
LCMAX	32562.07	32949.87	0.99	88.08	110.88

Table 37. Additional Study Information, Fasting Study-Atorvastatin (n=76)

Root mean square error, AUC0-t	0.150425	
Root mean square error, AUC∞	0.149355	
Root mean square error, Cmax	0.292756	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	76	76
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	76	0.99	0.96	1.0
Reference	76	0.99	0.94	1.0

Table 38. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study Atorvastatin (n=76)

	Test (n=76)		Reference (n=76)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.17	557.02	162.39	499.17	175.76	1.12
0.25	3912.35	152.85	3558.62	137.94	1.10
0.33	10976.82	103.79	10754.90	114.64	1.02
0.42	19212.53	86.49	17131.26	98.79	1.12
0.50	24312.32	82.40	21395.16	96.74	1.14
0.58	25445.27	79.48	24261.61	86.68	1.05
0.67	24927.88	68.84	24250.19	75.96	1.03
0.83	22973.84	60.73	23654.35	74.34	0.97
1.00	20744.59	61.72	22191.04	73.41	0.93
1.25	19328.41	61.37	20268.36	70.89	0.95
1.50	17779.42	57.00	20064.82	83.26	0.89
1.75	17014.06	58.54	19163.06	103.34	0.89
2.00	17925.24	61.45	20590.75	130.01	0.87
2.50	15656.59	81.67	17766.30	120.81	0.88
3.00	14067.70	78.60	15292.50	127.76	0.92
4.00	10836.51	70.52	10984.68	90.79	0.99
5.00	10617.44	51.27	10728.30	58.18	0.99
6.00	7995.52	47.04	7942.36	46.26	1.01
8.00	5287.56	49.78	5313.14	46.59	1.00
10.00	3974.02	54.68	4016.98	49.48	0.99
12.00	3671.41	54.68	3574.04	46.26	1.03
16.00	1440.57	52.24	1466.58	52.59	0.98
20.00	989.26	53.63	1035.06	64.94	0.96
24.00	631.01	61.06	657.20	63.56	0.96
36.00	375.77	62.53	396.50	70.11	0.95
48.00	143.05	102.56	146.31	71.31	0.98
60.00	102.30	163.34	90.04	103.57	1.14
72.00	30.64	198.92	29.05	183.28	1.05
96.00	4.02	418.85	4.18	446.80	0.96

Table 39. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study Atorvastatin (Used Original Concentration Values for Subjects #48 and 49, n=76)

	Test (n=76)		Reference (n=76)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.17	557.02	162.39	499.17	175.76	1.12
0.25	3912.35	152.85	3558.62	137.94	1.10
0.33	10976.82	103.79	10754.90	114.64	1.02
0.42	19228.79	86.41	17131.26	98.79	1.12
0.50	24312.32	82.40	21395.16	96.74	1.14
0.58	25445.27	79.48	24261.61	86.68	1.05
0.67	24927.88	68.84	24250.19	75.96	1.03
0.83	22973.84	60.73	23654.35	74.34	0.97
1.00	20744.59	61.72	22191.04	73.41	0.93
1.25	19328.41	61.37	20268.36	70.89	0.95
1.50	17779.42	57.00	20064.82	83.26	0.89
1.75	17014.06	58.54	19163.06	103.34	0.89
2.00	17925.24	61.45	20590.75	130.01	0.87
2.50	15656.59	81.67	17766.30	120.81	0.88
3.00	14067.70	78.60	15292.50	127.76	0.92
4.00	10836.51	70.52	10984.68	90.79	0.99
5.00	10617.44	51.27	10728.30	58.18	0.99
6.00	7995.52	47.04	7942.36	46.26	1.01
8.00	5287.56	49.78	5313.14	46.59	1.00
10.00	3974.02	54.68	4073.02	49.95	0.98
12.00	3671.41	54.68	3574.04	46.26	1.03
16.00	1440.57	52.24	1466.58	52.59	0.98
20.00	989.26	53.63	1035.06	64.94	0.96
24.00	631.01	61.06	657.20	63.56	0.96
36.00	375.77	62.53	396.50	70.11	0.95
48.00	143.05	102.56	146.31	71.31	0.98
60.00	102.30	163.34	90.04	103.57	1.14
72.00	30.64	198.92	29.05	183.28	1.05
96.00	4.02	418.85	4.18	446.80	0.96

Table 40. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study Atorvastatin (Excluding Subjects #48 and 49, n=74)

	Test (n=74)		Reference (n=74)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.17	564.50	162.08	506.31	175.34	1.11
0.25	3957.28	152.80	3614.89	137.22	1.09
0.33	11026.08	103.95	10954.18	113.48	1.01
0.42	19440.12	85.98	17460.07	97.53	1.11
0.50	24622.19	81.87	21820.72	95.37	1.13
0.58	25750.87	79.13	24728.15	85.42	1.04
0.67	25094.59	69.21	24634.51	75.19	1.02
0.83	22709.13	60.41	23481.15	74.34	0.97
1.00	20331.01	59.66	21705.86	71.23	0.94
1.25	18963.07	59.61	19889.20	69.54	0.95
1.50	17393.73	56.98	19729.39	84.90	0.88
1.75	16753.62	59.29	18855.52	105.81	0.89
2.00	17838.38	62.43	20284.87	133.42	0.88
2.50	15651.74	82.78	17668.91	123.08	0.89
3.00	14081.89	79.52	15301.60	129.41	0.92
4.00	10848.45	71.28	10991.07	91.96	0.99
5.00	10588.75	52.08	10575.57	58.96	1.00
6.00	7907.25	47.69	7879.40	46.99	1.00
8.00	5249.80	50.58	5275.72	47.35	1.00
10.00	3940.27	54.93	4004.28	50.13	0.98
12.00	3629.85	55.58	3546.39	46.99	1.02
16.00	1435.55	52.79	1460.66	53.28	0.98
20.00	984.98	53.83	1033.19	65.74	0.95
24.00	630.87	61.69	660.49	64.00	0.96
36.00	374.77	62.91	399.96	70.28	0.94
48.00	144.19	103.08	146.55	72.15	0.98
60.00	103.15	163.87	90.24	104.79	1.14
72.00	31.49	195.55	29.86	180.06	1.05
96.00	4.13	412.81	4.29	440.66	0.96

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study Atorvastatin (n=76)

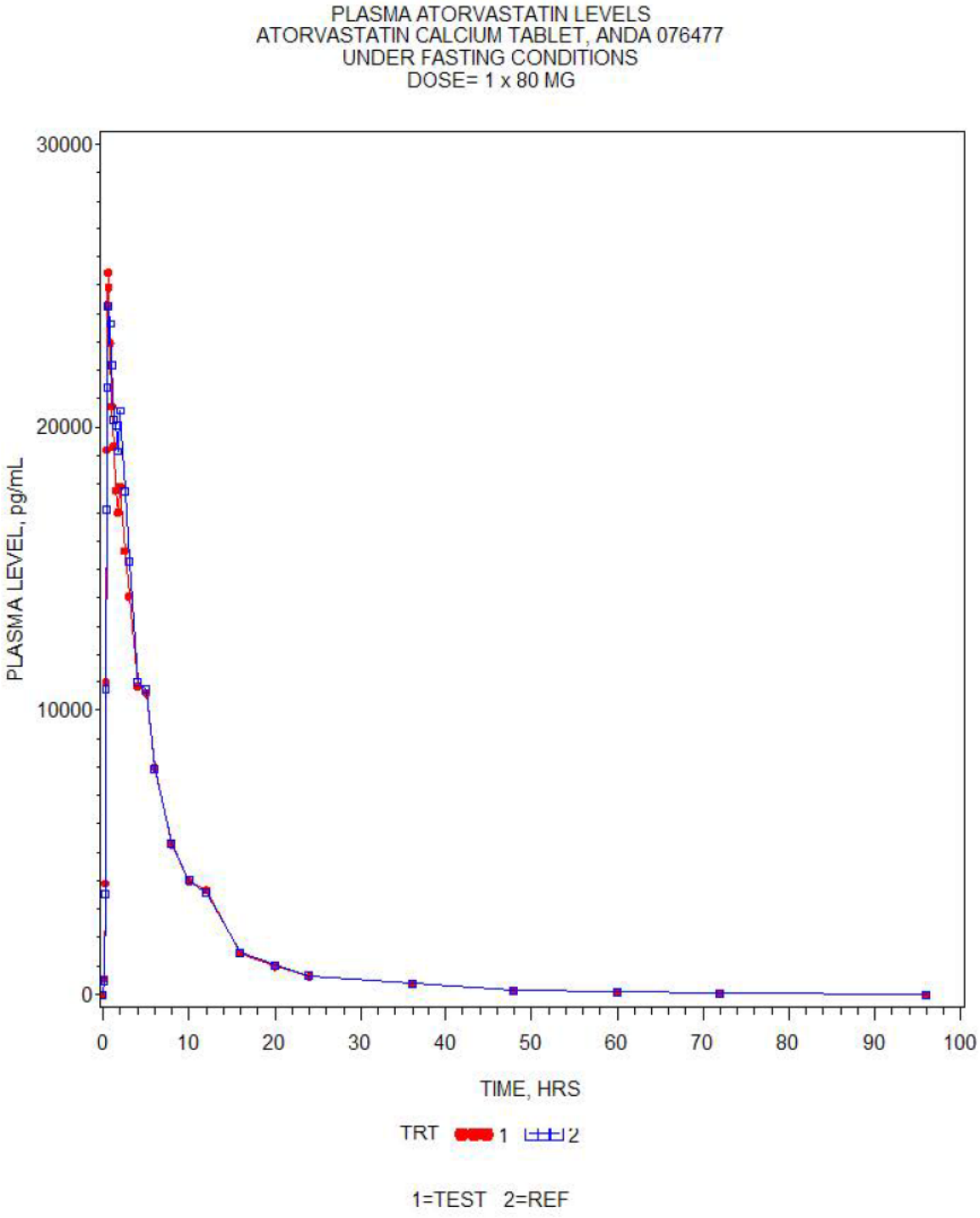


Table 41. Arithmetic Mean Pharmacokinetic Parameters-Ortho-hydroxy Atorvastatin (n=76)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	184760.5	41.73	87070.37	597359.8	184564.4	52.11	51868.37	812166.5	1.00
AUCI	pg hr/mL	186393.0	41.34	88251.40	598497.1	185902.5	52.50	53413.07	814426.4	1.00
CMAX	pg/mL	33005.19	52.14	8603.17	122429.2	34805.71	66.06	2962.56	185771.2	0.95
TMAX	hr	1.125	.	0.50	4.00	1.250	.	0.50	8.00	0.90
KE	hr-1	0.063	35.70	0.02	0.13	0.061	29.89	0.01	0.11	1.04
THALF	hr	12.381	34.86	5.38	29.09	12.751	43.36	6.54	46.49	0.97

* Tmax values are presented as median, range

Table 42. Geometric Means and 90% Confidence Intervals - Firm Calculated Ortho-hydroxy Atorvastatin

See firm's data for Atorvastatin above (Table 33).

Table 43. Geometric Means and 90% Confidence Intervals - Reviewer Calculated-Ortho-hydroxy Atorvastatin (n=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	172630.2	168593.4	1.02	96.44	108.72
LAUCI	174365.2	170216.5	1.02	96.41	108.85
LCMAX	29865.76	29897.59	1.00	89.65	111.31

Table 44. Additional Study Information, Fasting Study No. -Ortho-hydroxy Atorvastatin (n=76)

Root mean square error, AUC0-t	0.156742	
Root mean square error, AUC∞	0.156621	
Root mean square error, Cmax	0.283129	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	76	76
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	76	0.99	0.96	1.00
Reference	74	0.99	0.97	1.00

Table 45. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study Ortho-hydroxy Atorvastatin (n=76)

	Test (n=76)		Reference (n=76)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.17	22.19	279.28	15.39	349.40	1.44
0.25	616.39	229.97	558.75	200.69	1.10
0.33	3160.55	139.98	3340.33	160.00	0.95
0.42	7806.57	101.09	7496.01	121.98	1.04
0.50	13472.10	86.42	12175.27	106.55	1.11
0.58	17526.34	83.39	15946.31	92.25	1.10
0.67	20040.55	77.54	18035.55	81.48	1.11
0.83	22232.92	67.04	21010.26	71.71	1.06
1.00	22154.30	62.07	22096.79	70.83	1.00
1.25	22561.85	59.93	22167.78	68.18	1.02
1.50	21950.42	56.87	22246.01	66.34	0.99
1.75	21072.21	51.57	21847.18	71.27	0.96
2.00	22629.31	55.33	23064.82	91.07	0.98
2.50	20718.15	74.59	21448.92	96.58	0.97
3.00	19044.67	79.02	19486.83	110.95	0.98
4.00	15719.53	78.47	15288.98	89.21	1.03
5.00	13387.92	56.66	13184.48	63.33	1.02
6.00	10432.21	47.97	10305.95	54.04	1.01
8.00	7512.56	35.46	7514.21	44.23	1.00
10.00	5975.69	42.62	5985.78	40.89	1.00
12.00	5058.69	41.35	4998.98	41.60	1.01
16.00	2141.41	40.62	2129.73	41.99	1.01
20.00	1447.76	44.37	1466.59	46.19	0.99
24.00	936.73	50.32	939.96	46.16	1.00
36.00	560.67	47.19	580.44	48.52	0.97
48.00	224.50	62.15	243.50	53.59	0.92
60.00	166.17	95.99	157.89	63.51	1.05
72.00	68.52	99.83	69.71	107.27	0.98
96.00	15.37	240.67	17.59	253.22	0.87

Figure 2. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study Ortho-hydroxy Atorvastatin (n=76)

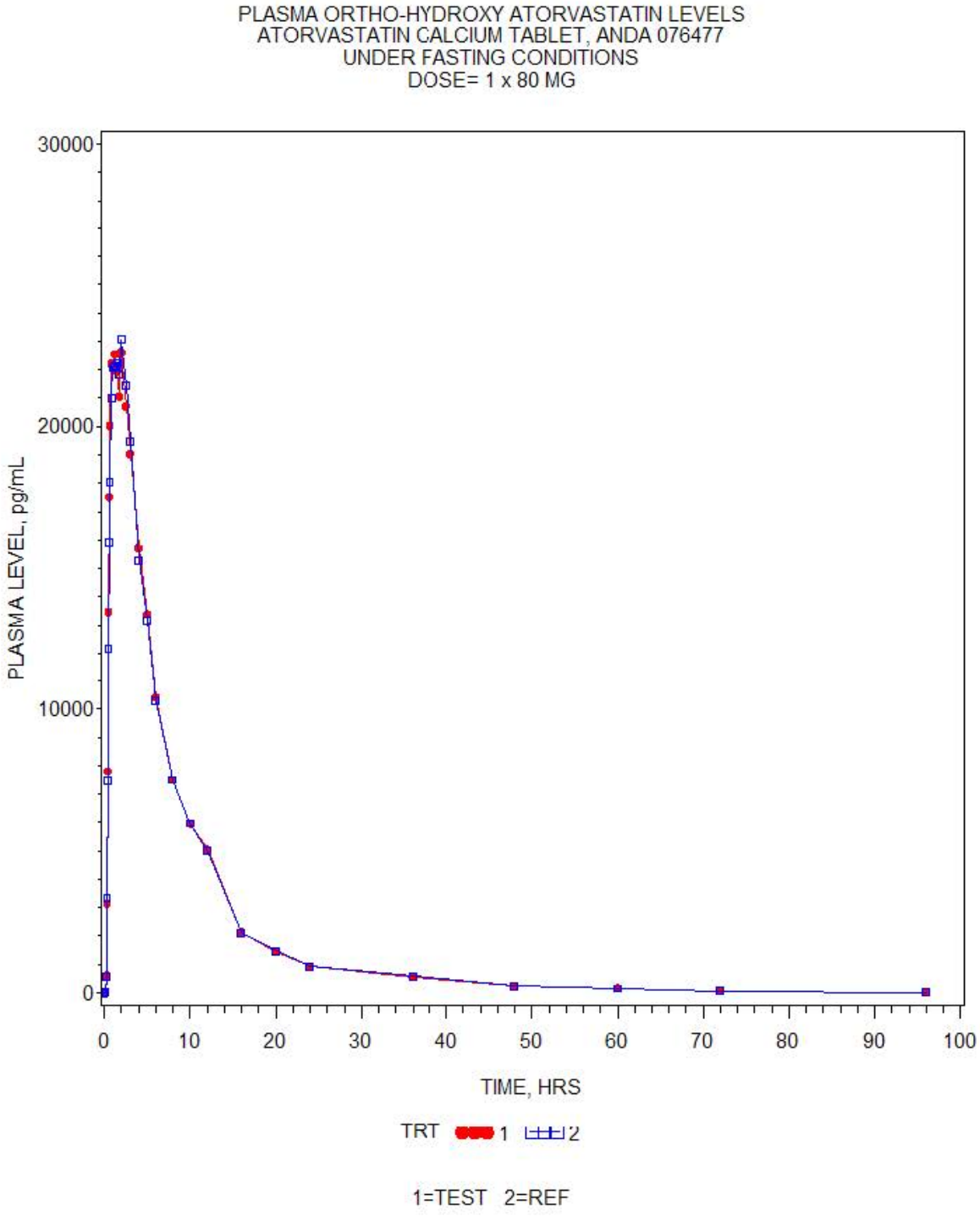


Table 46. Arithmetic Mean Pharmacokinetic Parameters- Para -hydroxy Atorvastatin (n=76)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	22375.81	61.73	5337.34	82282.47	22959.79	72.07	5865.00	112867.1	0.97
AUCI	pg hr/mL	26707.84	54.46	8679.30	83718.07	26993.07	65.40	6964.89	113777.2	0.99
CMAX	pg/mL	1256.251	117.31	188.41	11469.17	1388.316	180.69	180.70	21513.33	0.90
TMAX	hr	5.500	.	0.45	20.00	5.000	.	0.50	20.00	1.10
KE	hr-1	0.037	27.92	0.02	0.06	0.037	31.38	0.02	0.07	1.01
THALF	hr	20.291	29.95	10.91	39.40	20.799	32.83	10.32	40.43	0.98

* Tmax values are presented as median, range

Table 47. Geometric Means and 90% Confidence Intervals - Firm Calculated- Para hydroxy Atorvastatin

See firm's data for Atorvastatin above (Table 33).

Table 48. Geometric Means and 90% Confidence Intervals - Reviewer Calculated- Para -hydroxy Atorvastatin (n=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	19003.56	19153.00	0.99	91.57	107.51
LAUCI	22702.34	22582.77	1.01	92.26	109.54
LCMAX	926.56	920.80	1.01	91.02	111.24

Table 49. Additional Study Information, Fasting Study No. - Para -hydroxy Atorvastatin (n=76)

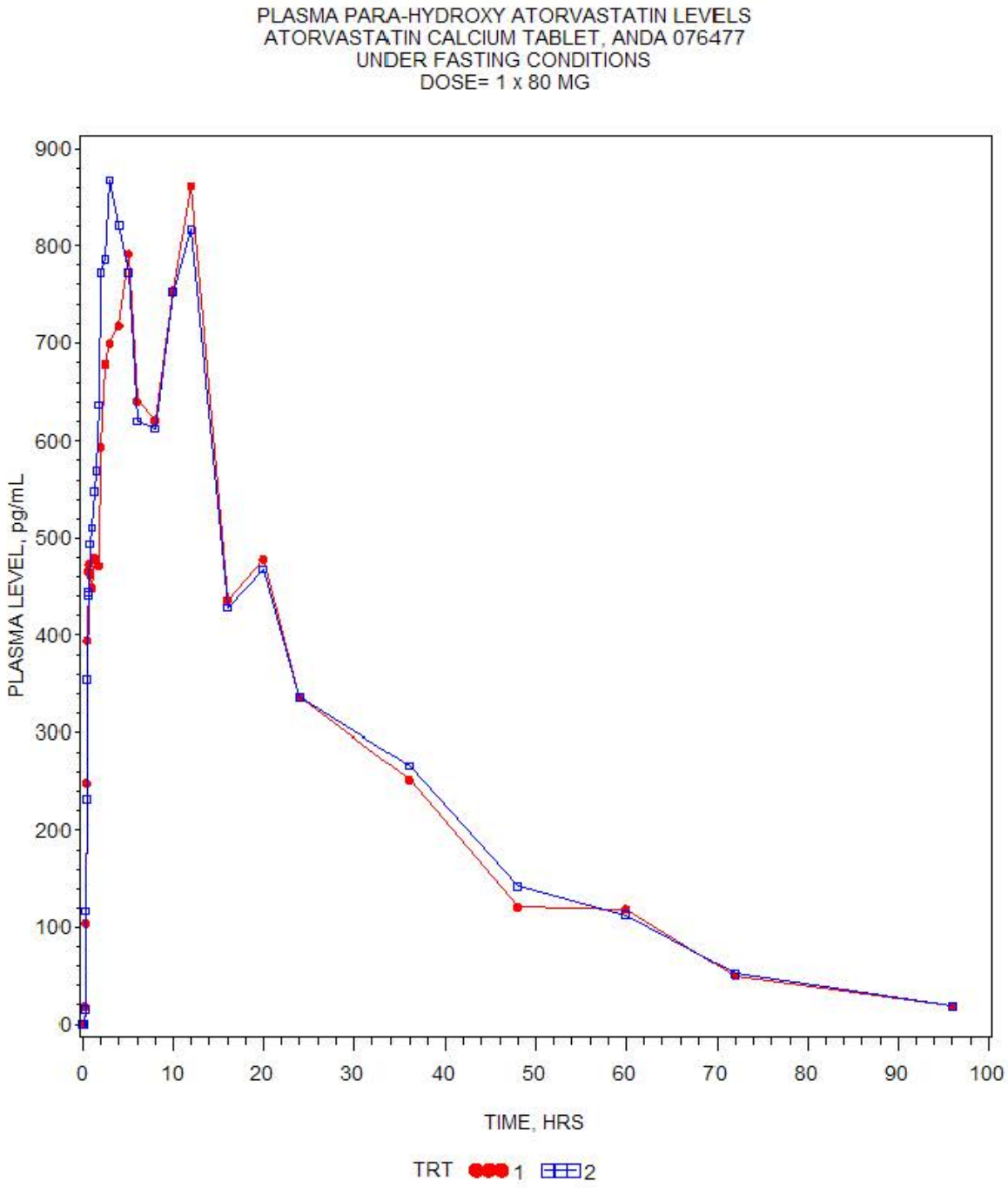
Root mean square error, AUC0-t	0.209911	
Root mean square error, AUC∞	0.186172	
Root mean square error, Cmax	0.262363	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	62	62
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	NO	NO

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	62	0.90	0.67	0.98
Reference	62	0.89	0.73	0.99

Table 50. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study-Para -hydroxy Atorvastatin (n=76)

	Test (n=76)		Reference (n=76)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.17	0.00	.	0.00	.	.
0.25	18.44	325.59	15.86	296.80	1.16
0.33	104.46	174.04	117.12	184.38	0.89
0.42	249.05	139.70	232.89	144.02	1.07
0.50	394.68	141.83	354.05	141.37	1.11
0.58	466.04	156.39	444.54	146.62	1.05
0.67	473.05	140.29	441.41	124.79	1.07
0.83	462.46	122.34	494.27	144.62	0.94
1.00	448.63	112.64	510.77	157.66	0.88
1.25	479.79	119.12	547.76	159.96	0.88
1.50	477.70	115.53	569.77	170.08	0.84
1.75	471.63	122.24	637.64	215.23	0.74
2.00	594.19	126.83	772.27	274.74	0.77
2.50	678.68	197.54	786.38	244.11	0.86
3.00	699.33	174.70	867.81	286.05	0.81
4.00	717.79	147.25	821.33	217.19	0.87
5.00	791.85	87.47	772.47	101.23	1.03
6.00	641.17	74.79	620.71	86.09	1.03
8.00	621.28	59.31	612.94	68.56	1.01
10.00	754.11	67.75	752.30	68.03	1.00
12.00	861.66	78.60	817.28	72.69	1.05
16.00	436.25	52.54	428.61	53.42	1.02
20.00	478.28	66.81	468.23	62.96	1.02
24.00	336.95	71.38	336.38	68.24	1.00
36.00	252.24	49.05	266.57	62.87	0.95
48.00	121.08	69.72	142.82	67.95	0.85
60.00	119.02	79.03	112.87	73.55	1.05
72.00	49.93	113.80	52.47	114.62	0.95
96.00	19.42	216.65	19.05	186.88	1.02

Figure 3. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study-Para-hydroxy Atorvastatin (n=76)



4.2.2. Single-dose Fed Bioequivalence Study

4.2.2.1.Study Design

Table 51. Study Information

Study Number	R09-1033
Study Title	A Bioequivalence Study of 80 mg Atorvastatin Calcium Tablets Versus 80 mg Lipitor® Tablets Under Fed Conditions.
Clinical Site (Name, Address, Phone #)	Clinical Services Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104 Phone: (701) 239-4750 Clinical Laboratory Facility Cetero Research – Fargo Clinical Laboratory 4801 Amber Valley Parkway Fargo, ND 58104 USA Phone: (701) 239-4750
Principal Investigator	Anthony R. Godfrey, Pharm.D. Cetero Research 4801 Amber Valley Parkway Fargo, ND 58104 USA Phone: (701) 239-4750
Dosing Dates	PERIOD I: 04 October 2009 PERIOD II: 18 October 2009
Analytical Site (Name, Address, Phone #)	(b) (4)
Analysis Dates	2009-10-26 to 2009-11-21
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	48 days (2009-10-04 to 2009-11-21)

Table 52. Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Atorvastatin calcium tablets 80 mg	Lipitor Tablets 80 mg
Manufactured by	OHM Laboratories INC.	Pfizer Ireland Pharmaceuticals,
Batch No.	RI560901	04558V
Manufacture Date	May 2009	-
Expiry Date	April 2012	Mar 2011
Strength	80 mg	80 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4) Tablets	-
Production Batch Size	Tablets	-
Potency	102.0%	97.3%
Content Uniformity (mean, %CV)	102.2%	97.7%
Dose Administered	1x80 mg	1x80 mg
Route of Administration	Oral	Oral

Table 53. Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	80 Enrolled, Subjects were dosed; 76 completed the study
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	14 days
Randomization Scheme	**TR:** 1, 3, 5, 7, 11, 12, 14, 16, 19, 20, 21, 22, 25, 27, 30, 31, 35, 36, 38, 40, 42, 43, 45, 46, 50, 51, 54, 55, 59, 60, 61, 62, 65, 67, 69, 71, 75, 76, 77, 80 **RT:** 2, 4, 6, 8, 9, 10, 13, 15, 17, 18, 23, 24, 26, 28, 29, 32, 33, 34, 37, 39, 41, 44, 47, 48, 49, 52, 53, 56, 57, 58, 63, 64, 66, 68, 70, 72, 73, 74, 78, 79
Blood Sampling Times	Pre-dose and at 0.333, 0.667, 1, 1.25, 1.5, 1.75, 2, 2.25, 2.5, 2.75, 3, 3.5, 4, 6, 8, 10, 12, 16, 24, 36, 48, 60, 72 and 96 hours post dose
Blood Volume Collected/Sample	3 mL in K2-EDTA was used.
Blood Sample Processing/Storage	After collection, blood samples were cooled; immediately centrifuged; plasma samples were separated, and stored at -80 ^{0}C until analysis.
IRB Approval	Yes
Informed Consent	Yes
Length of Fasting	Subjects fasted overnight for at least 10 hours. The subjects were given FDA standard high calorie high fat breakfast prior to drug administration. Lunch was served 4 hours following the drug administration.
Length of Confinement	Subjects were confined to clinical facility from at least 36 hours prior to each drug administration until after the 24-hour blood sample collection.
Safety Monitoring	Subjects were monitored throughout the study.
Drug Specific Information	None

Composition of Meal Used in Fed Bioequivalence Study		
Composition	**Percent of total Kcal**	**Kcal**
Fat	54.96%	507.6
Carbohydrate	30.32%	280.0
Protein	14.72%	136.0
Total		923.6

The composition of meal used here refers to the following FDA standardized high fat breakfast:

2 eggs fried in butter
4 oz hash brown potatoes
2 strips of bacon
2 slices of toast with butter
8 oz (240 ml) whole milk.

Comments on Study Design: The study design is **acceptable.**

4.2.2.2.Clinical Results

Table 54. Demographics Profile of Subjects Completing the Bioequivalence Study

		R09-1033 Treatment Groups	
		Test Product N=76[1]	Reference Product N=76[1]
Age (years)	Mean ± SD	31.5 ± 13.7	31.5 ± 13.7
	Range	18 - 66	18 - 66
Age Groups	< 18	-	-
	18 – 39	56 (73.7%)	56 (73.7%)
	40 – 64	19 (25.0%)	19 (25.0%)
	65 – 75	1 (1.3%)	1 (1.3%)
	> 75	-	-
Sex	Male	68 (89.5%)	68 (89.5%)
	Female	8 (10.5%)	8 (10.5%)
Hispanic or Latino Race	N	1 (1.3%)	1 (1.3%)
	A	-	-
	B	-	-
	I	-	-
	W	1 (1.3%)	1 (1.3%)
Not Hispanic or Latino Race	N	-	-
	A	3 (3.9%)	3 (3.9%)
	B	4 (5.3%)	4 (5.3%)
	I	-	-
	W	64 (84.2%)	64 (84.2%)
	BN	1 (1.3%)	1 (1.3%)
	WA	1 (1.3%)	1 (1.3%)
	WN	1 (1.3%)	1 (1.3%)
BMI	Mean ± SD	25.6 ± 3.4	25.6 ± 3.4
	Range	19.3 - 31.8	19.3 - 31.8
Other Factors			

[1]Subjects used in final statistical report

RACE:

American Indian or Alaskan Native	N
Asian	A
Black or African American	B
Native Hawaiian or Other Pacific Islander	I
White	W

Table 55. Dropout Information, Fed Bioequivalence Study

R09-1033				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
10	Withdrew consent prior to Period II check in.	I	No	N/A
11	Withdrew consent prior to Period II dosing due to AEs (abdominal discomfort, dizziness, feeling hot, and headache).	I	No	N/A
19	Withdrew consent prior to Period II check in.	I	No	N/A
77	Withdrew consent prior to Period II check in	I	No	N/A

Table 56. Study Adverse Events, Fed Bioequivalence Study

Body System/Adverse Event[1]	**Reported Incidence by Treatment Groups** R09-1033	
	Test N=79[2]	**Reference** N=77[2]
	n (%)[3]	**n (%)[3]**
Gastrointestinal disorders		
Abdominal discomfort	1 (1.27%)	-
Diarrhoea	-	1 (1.30%)
Nausea	-	1 (1.30%)
General disorders and administration site conditions		
Chills	-	1 (1.30%)
Feeling hot	1 (1.27%)	-
Musculoskeletal and connective tissue disorders		
Muscle spasms	-	1 (1.30%)
Muscular weakness	1 (1.27%)	-
Nervous system disorders		
Dizziness	2 (2.53%)	-
Headache	3 (3.80%)	3 (3.90%)
Sinus headache	-	1 (1.30%)
Respiratory, thoracic and mediastinal disorders		
Cough	2 (2.53%)	-
Nasal congestion	-	1 (1.30%)
Oropharyngeal pain	1 (1.27%)	1 (1.30%)
Pharyngeal erythema	1 (1.27%)	-
Rhinorrhoea	3 (3.80%)	-
Sinus congestion	-	2 (2.60%)
Skin and subcutaneous tissue disorders		
Hyperhidrosis	-	1 (1.30%)
Upper respiratory tract disorders (excl infections)		
Nasal congestion	1 (1.27%)	-
Total	7 (8.86%)	9 (11.69%)

[1] MedDRA Version 12.0
[2] N = Number of subjects dosed for each treatment
[3] n = Number of subjects reporting at least one incidence of respective adverse event;
(%) = percentage of subjects reporting at least one incidence of respective adverse event (i.e. 100*(n/N)%

Table 57. Protocol Deviations, Fed Bioequivalence Study

R09-1033		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Concomitant medications	42, 65	N/A
Pre-dose vitals completed outside of 90 minute window (128 minutes) (Subject 59)	N/A	N/A
Breakfast not served 30 minutes prior to dosing (24 minutes) (Subject 60)	N/A	N/A
Period I, sample processing information Day 1 0.333 hour (draw 2) not documented correctly	36	N/A
Period I, time to freezer Day 3 48 hour (draw 22) incorrectly documented, freezer time unknown	42	N/A
Period I, Day 3 48 hour (draw 22) freezer time inadvertently not documented	60, 61, 65, 69, 77	53, 57, 63, 74
Period I, Day 2, 36 hour Query and PK (draw 21) not completed	51	78
Period I, Day 3, 48 hour Query and PK (draw 22) not completed	05	N/A
Period I, Day 3, 60 hour Query and PK (draw 23) not completed	N/A	17, 44
Period II, Day 16, 36 hour Query and PK (draw 21) not completed	34, 78	N/A
Period II, Day 17, 48 hour Query and PK (draw 22) not completed	47, 73	N/A
Period II, Day 17, 60 hour Query and PK (draw 23) not completed	N/A	01
Period II, Day 18 72 hour (draw 24) sample not flash frozen	N/A	31

Comments on Adverse Events/Protocol Deviations: Subject #10, 11, 19 and 77 withdrew consent. Therefore, dropout is acceptable. The adverse events and protocol deviations were minor and did not compromise the outcome of the study.

4.2.2.3.Bioanalytical Results

Table 58. Assay Validation – Within the Fed BE Study: Atorvastatin

Bioequivalence Study No. R09-1033 Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	50.06	100.12	2002.40	5006.00	10012.00	20024.00	40048.00	50060.00
Mean (pg/ml)	49.96	100.33	2059.41	5100.65	10048.70	19952.47	39082.97	48915.18
Interday Precision (%CV)	6.12	4.36	3.90	3.25	3.73	4.12	3.44	3.52
Interday Accuracy (% bias)	-0.20	0.21	2.85	1.89	0.37	-0.36	-2.41	-2.29
Linearity	0.9865 to 0.9996							
Linearity Range (pg/mL)	50.06 to 50060.00							
Sensitivity/LOQ (pg/mL)	50.06							

Bioequivalence Study No. R09-1033 Atorvastatin				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	150.66	2511.00	15066.00	35154.00
Mean (pg/ml)	151.38	2597.07	15211.81	35715.22
Interday Precision (%CV)	5.04	3.87	4.24	4.20
Interday Accuracy (%)	100.48	103.43	100.97	101.60
Interday Accuracy (% bias)	0.48	3.43	0.97	1.60

Table 59. Assay Validation – Within the Fed BE Study: p-Hydroxy-atorvastatin

Bioequivalence Study No. R09-1033 p-Hydroxy-Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	50.30	100.60	201.20	503.00	1006.00	2012.00	4024.00	5030.00
Mean (pg/ml)	50.48	98.39	206.19	509.07	1001.28	2004.85	3974.03	5036.63
Interday Precision (%CV)	7.21	6.23	4.81	4.02	3.91	3.59	3.68	3.69
Interday Accuracy (% bias)	0.36	-2.20	2.48	1.21	-0.47	-0.36	-1.24	0.13
Linearity	0.9915 to 0.9985							
Linearity Range (pg/mL)	50.30 to 5030.00							
Sensitivity/LOQ (pg/mL)	50.30							

Bioequivalence Study No. R09-1033 p-Hydroxy-Atorvastatin				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	150.00	250.00	1500.00	3500.00
Mean (pg/ml)	144.64	257.14	1512.34	3557.75
Interday Precision (%CV)	8.02	5.78	4.36	4.17
Interday Accuracy (%)	96.43	102.86	100.82	101.65
Interday Accuracy (% bias)	-3.57	2.86	0.82	1.65

Table 60. Assay Validation – Within the Fed BE Study: o-Hydroxy-atorvastatin

Bioequivalence Study No. R09-1033 o-Hydroxy-Atorvastatin								
Parameter	**Standard Curve Samples**							
Concentration (pg/mL)	50.06	100.12	2002.40	5006.00	10012.00	20024.00	40048.00	50060.00
Mean (pg/ml)	50.50	98.22	2029.78	5051.62	9949.92	20111.14	39602.55	50003.56
Interday Precision (%CV)	8.57	6.94	3.59	3.16	2.62	3.20	3.14	2.98
Interday Accuracy (% bias)	0.88	-1.90	1.37	0.91	-0.62	0.44	-1.11	-0.11
Linearity	0.9926 to 0.9993							
Linearity Range (pg/mL)	50.06 to 50060.00							
Sensitivity/LOQ (pg/mL)	50.06							

Bioequivalence Study No. R09-1033 o-Hydroxy-Atorvastatin				
Parameter	**Quality Control Samples**			
Concentration (pg/mL)	150.42	2507.00	15042.00	35098.00
Mean (pg/ml)	149.70	2617.84	15235.07	36030.11
Interday Precision (%CV)	7.50	4.80	4.27	4.52
Interday Accuracy (%)	99.52	104.42	101.28	102.66
Interday Accuracy (% bias)	-0.48	4.42	1.28	2.66

Comments on Study Assay Validation: Acceptable.

Any interfering peaks in chromatograms?	No
Were 20% of chromatograms included?	Yes.
Were chromatograms serially or randomly selected?	Mixed, Runs #11-15 and 39-40 (Subject # 1-9, 12-18, 26, 27, 79, 80)

Comments on Chromatograms: Acceptable

Table 61. SOP's Dealing with Bioanalytical Repeats of Study Samples

SOP No.	Effective Date of SOP	SOP Title
ANI 156.12	2009-07-10	Sample Reassays and Reporting of Final Concentrations

Title: Preparation, Identification, Acceptance Criteria of Stock Solutions, Calibration Standards, Quality Controls and Reference Solutions		
Effective Date: 2009-07-06	**SOP & Version #** ANI 153_13	**Page** 1 of 19

Table 62. Additional Comments on Repeat Assays

Were all SOPs followed?	Yes
Did recalculation of PK parameters change the study outcome?	No PK repeats
Does the reviewer agree with the outcome of the repeat assays?	Yes
If no, reason for disagreement	N/A

Summary/Conclusions, Study Assays: The PK parameters were calculated from actual plasma concentration data using actual collection time. There were no PK repeats; however, the firm repeated samples to confirm values according to SOP. The original, repeat and accepted values are given in the Appendix (see Section 4.6, 4.7, Repeat Analysis – Fasting, Repeat Analysis – Fed). The firm's repeat analytical values because of mix-up, etc. for Subjects #47 are not acceptable (see below, Pharmacokinetic Results).

4.2.2.4.Pharmacokinetic Results

Comments on Pharmacokinetic and Statistical Analysis:

- The reviewer carried out the ANOVA analysis for 76 subjects for Atorvastatin, o-Hydroxy-atorvastatin and p-Hydroxy-atorvastatin using TWOWAY CONTINU.SAS (for firm's accepted repeat values for Sub #47) and TWOWAY CALCKE.SAS (for original values for Sub #47).

- There were no PK repeats. However, the firm suspected a sample mix-up between Sub 47-Per1-1.5h (Reference) and Sub 47-Per2-1.5h (Test), repeated the analyses and used the repeat values in statistical analysis. However, in a laboratory setting, sample mix-up can not be accurately verified. Therefore, the reviewer analyzed the Atorvastatin data using original and repeat values. ANOVA analysis for Atorvastatin was also carried out after excluding Subjects 47 (n=75).

- The summary of PK data and results are presented as follows: Atorvastatin in Tables 63-73 and Fig. 4; o-Hydroxy-atorvastatin in Tables 74-78 and Fig. 5; and p-Hydroxy-atorvastatin in Tables 79-83 and Fig. 6.

- The pharmacokinetic parameters and 90% confidence intervals for Atorvastatin in plasma (n=76) calculated by the reviewer agree with firm's calculations.

- The 90% CIs for LAUCt, LAUCi and LCmax parameters for Atorvastatin with original and repeat values, and after excluding Subjects #47 (n=75), are within the 80-125%. In order to save additional valuable data on the subject, the reviewer prefers the analysis with original values (n=76).

- The supporting data, i.e., the pharmacokinetic parameters and point-estimates for the metabolite, o-Hydroxy-atorvastatin and p-Hydroxy-atorvastatin in plasma (n=76), calculated by the reviewer agree with firm's calculations.

- The point estimates (n=76) for LAUCt, LAUCi and LCmax parameters for o-Hydroxy-atorvastatin and p-Hydroxy-atorvastatin are within the 80-125%.

Summary and Conclusions, Single-Dose Fed Bioequivalence Study: The study is **acceptable**.

Table 63. Arithmetic Mean Pharmacokinetic Parameters- Atorvastatin (n=76)

(Used repeat values for Subject #47)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	138560.3	40.87	50779.29	325603.8	139944.2	43.43	54928.71	322949.3	0.99
AUCI	pg hr/mL	140500.1	41.18	52417.57	326513.2	142007.6	43.63	55483.72	324179.0	0.99
CMAX	pg/mL	32951.43	62.47	8322.95	96825.04	34640.92	68.05	9601.73	119982.9	0.95
TMAX	hr	1.250	.	0.67	6.00	1.500	.	0.67	6.00	0.83
KE	hr-1	0.070	35.71	0.03	0.20	0.071	41.20	0.03	0.17	0.98
THALF	hr	11.010	34.64	3.53	26.60	10.999	32.42	4.04	21.07	1.00

* Tmax values are presented as median, range

Table 64. Arithmetic Mean Pharmacokinetic Parameters- Atorvastatin (n=76)

(Used original values for Subject #47)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	138611.4	40.84	50779.29	325603.8	139752.1	43.11	54928.71	322949.3	0.99
AUCI	pg hr/mL	139372.6	40.59	51705.15	325910.6	140431.7	42.91	55384.80	323413.7	0.99
CMAX	pg/mL	32951.43	62.47	8322.95	96825.04	34640.92	68.05	9601.73	119982.9	0.95
TMAX	hr	1.250	.	0.67	6.00	1.500	.	0.67	6.00	0.83
KE	hr-1	0.133	19.07	0.07	0.20	0.133	16.62	0.07	0.19	1.00
THALF	hr	5.409	21.08	3.53	9.47	5.374	17.94	3.61	9.47	1.01

Table 65. Arithmetic Mean Pharmacokinetic Parameters-Atorvastatin (n=75)

(Excluded Subjects #47)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	137864.7	41.11	50779.29	325603.8	137583.5	41.84	54928.71	322949.3	1.00
AUCI	pg hr/mL	139782.0	41.45	52417.57	326513.2	139528.9	42.07	55483.72	324179.0	1.00
CMAX	pg/mL	33073.68	62.57	8322.95	96825.04	34234.63	68.53	9601.73	119982.9	0.97
TMAX	hr	1.250	.	0.67	6.00	1.500	.	0.67	6.00	0.83
KE	hr-1	0.070	35.97	0.03	0.20	0.071	41.28	0.03	0.17	0.99
THALF	hr	11.053	34.59	3.53	26.60	11.066	32.05	4.04	21.07	1.00

Table 66. Geometric Means and 90% Confidence Intervals - Firm Calculated- Atorvastatin and metabolites (n=76)

Atorvastatin Dose (80 mg) Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)				
Fed Bioequivalence Study (Study No. R09-1033)				
Parameter	**Test**	**Reference**	**Ratio (%)**	**90% CI**
AUC_{0-t}	128437.49 pg.hr/ml	128865.94 pg.hr/ml	99.67	(96.00, 103.47)
$AUC_{0-\infty}$	130112.86 pg.hr/ml	130682.95 pg.hr/ml	99.56	(95.87, 103.40)
C_{max}	27847.28 pg/ml	29025.88 pg/ml	95.94	(86.75, 106.11)
2-Hydroxy Atorvastatin (o-Hydroxy Atorvastatin) **Least Square Geometric Means, Ratio of Means**				
Fed Bioequivalence Study (Study No. R09-1033)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	142055.40 pg.hr/ml	143318.73 pg.hr/ml	99.12	
$AUC_{0-\infty}$	143728.64 pg.hr/ml	145312.87 pg.hr/ml	98.91	
C_{max}	20093.50 pg/ml	20613.33 pg/ml	97.48	
4-Hydroxy Atorvastatin (p-Hydroxy Atorvastatin) **Least Square Geometric Means, Ratio of Means**				
Fed Bioequivalence Study (Study No. R09-1033)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	16282.37 pg.hr/ml	16691.03 pg.hr/ml	97.55	
$AUC_{0-\infty}$	20166.96 pg.hr/ml	21036.43 pg.hr/ml	95.87	
C_{max}	748.86 pg/ml	751.79 pg/ml	99.61	

Table 67. Geometric Means and 90% Confidence Intervals - Reviewer Calculated-Atorvastatin (n=76)

(Used repeat values for Subject #47)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	128437.5	128865.9	1.00	94.53	105.09
LAUCI	130112.9	130682.9	1.00	94.24	105.19
LCMAX	27847.28	29025.88	0.96	83.20	110.63

Table 68. Geometric Means and 90% Confidence Intervals - Reviewer Calculated-Atorvastatin (n=76)

(Used original values for Subject #47)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	128501.9	128788.4	1.00	94.67	105.16
LAUCI	129322.5	129512.3	1.00	94.76	105.22
LCMAX	27847.28	29025.88	0.96	83.20	110.63

Table 69. Arithmetic Mean Pharmacokinetic Parameters-Atorvastatin (n=75)

(Excluded Subjects #47)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	127697.8	127310.6	1.00	95.28	105.59
LAUCI	129313.2	129009.6	1.00	95.04	105.71
LCMAX	27882.98	28714.35	0.97	84.31	111.84

Table 70. Additional Study Information, Fed Study No. R09-1033- Atorvastatin

Root mean square error, AUC0-t	0.1386	
Root mean square error, AUC∞	0.1397	
Root mean square error, Cmax	0.3726	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	72	72
Do you agree or disagree with firm's decision?	AGREE	AGREE
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	NO	NO

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	72	0.99	0.95	1.00
Reference	72	0.99	0.98	1.00

Table 71. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study Atorvastatin (n=76)

	Test (n=76)		Reference (n=76)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.33	2049.29	356.03	1306.63	257.55	1.57
0.67	12089.18	146.59	11906.33	166.55	1.02
1.00	19259.09	98.23	20891.98	110.57	0.92
1.25	20871.02	79.97	23886.89	94.46	0.87
1.50	20916.03	75.89	24147.61	81.62	0.87
1.75	19455.74	70.87	21511.67	71.92	0.90
2.00	17929.63	74.92	19623.79	73.46	0.91
2.25	17076.44	75.81	18157.84	67.63	0.94
2.50	16612.85	76.14	17074.52	59.36	0.97
2.75	15876.09	68.44	16405.13	61.57	0.97
3.00	15175.36	66.27	15203.24	62.88	1.00
3.50	13579.61	57.46	13841.23	65.52	0.98
4.00	11868.57	56.17	12240.98	60.49	0.97
6.00	8764.51	50.22	8809.22	53.32	0.99
8.00	5237.46	64.64	5042.90	50.97	1.04
10.00	3747.04	64.43	3612.14	55.88	1.04
12.00	3353.84	54.57	3171.07	52.52	1.06
16.00	1394.66	51.13	1376.01	50.18	1.01
24.00	644.88	62.53	612.53	53.75	1.05
36.00	433.07	74.84	398.02	61.64	1.09
48.00	153.24	75.26	143.93	71.81	1.06
60.00	117.56	118.35	95.13	93.06	1.24
72.00	33.69	171.88	25.51	174.41	1.32
96.00	4.19	439.96	4.55	543.38	0.92

Table 72. Arithmetic Mean Pharmacokinetic Parameters-Atorvastatin (n=76) (Used Original Concentration Values for Subjects #47)

	Test (n=76)		Reference (n=76)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.33	2049.29	356.03	1306.63	257.55	1.57
0.67	12089.18	146.59	11906.33	166.55	1.02
1.00	19259.09	98.23	20891.98	110.57	0.92
1.25	20871.02	79.97	23886.89	94.46	0.87
1.50	20916.03	75.89	23394.26	82.77	0.89
1.75	19455.74	70.87	21511.67	71.92	0.90
2.00	17929.63	74.92	19623.79	73.46	0.91
2.25	17076.44	75.81	18157.84	67.63	0.94
2.50	16612.85	76.14	17074.52	59.36	0.97
2.75	15876.09	68.44	16405.13	61.57	0.97
3.00	15175.36	66.27	15203.24	62.88	1.00
3.50	13579.61	57.46	13841.23	65.52	0.98
4.00	11868.57	56.17	12240.98	60.49	0.97
6.00	8764.51	50.22	8809.22	53.32	0.99
8.00	5237.46	64.64	5042.90	50.97	1.04
10.00	3747.04	64.43	3612.14	55.88	1.04
12.00	3353.84	54.57	3171.07	52.52	1.06
16.00	1394.66	51.13	1376.01	50.18	1.01
24.00	644.88	62.53	612.53	53.75	1.05
36.00	433.07	74.84	398.02	61.64	1.09
48.00	153.24	75.26	143.93	71.81	1.06
60.00	117.56	118.35	95.13	93.06	1.24
72.00	33.69	171.88	25.51	174.41	1.32
96.00	4.19	439.96	4.55	543.38	0.92

Table 73. Arithmetic Mean Pharmacokinetic Parameters-Atorvastatin (n=75) (Excluded Subjects #47)

	Test (n=75)		Reference (n=75)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.33	2068.73	354.96	1308.63	258.88	1.58
0.67	12228.59	145.55	12014.71	165.97	1.02
1.00	19482.64	97.23	20942.57	111.03	0.93
1.25	21105.60	79.01	23337.22	95.12	0.90
1.50	21137.83	75.04	23652.77	81.86	0.89
1.75	19632.88	70.26	21129.34	71.98	0.93
2.00	18008.89	74.99	19354.62	73.98	0.93
2.25	17118.67	76.11	17889.61	67.86	0.96
2.50	16672.09	76.31	16813.94	59.14	0.99
2.75	15939.62	68.54	16126.25	61.20	0.99
3.00	15198.71	66.60	15010.99	63.12	1.01
3.50	13562.51	57.91	13619.05	65.49	1.00
4.00	11709.72	56.07	11919.13	57.88	0.98
6.00	8674.77	50.27	8662.35	52.52	1.00
8.00	5167.12	64.87	4937.46	48.94	1.05
10.00	3670.20	63.62	3515.84	52.56	1.04
12.00	3308.73	54.39	3108.61	50.98	1.06
16.00	1372.27	50.32	1341.16	46.54	1.02
24.00	634.77	62.41	603.91	53.43	1.05
36.00	433.80	75.22	396.17	62.22	1.09
48.00	153.24	75.26	143.57	72.45	1.07
60.00	118.25	118.34	94.93	93.90	1.25
72.00	34.14	170.37	25.85	172.89	1.32
96.00	4.24	436.95	4.61	539.71	0.92

Figure 4. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study-Atorvastatin (n=76)

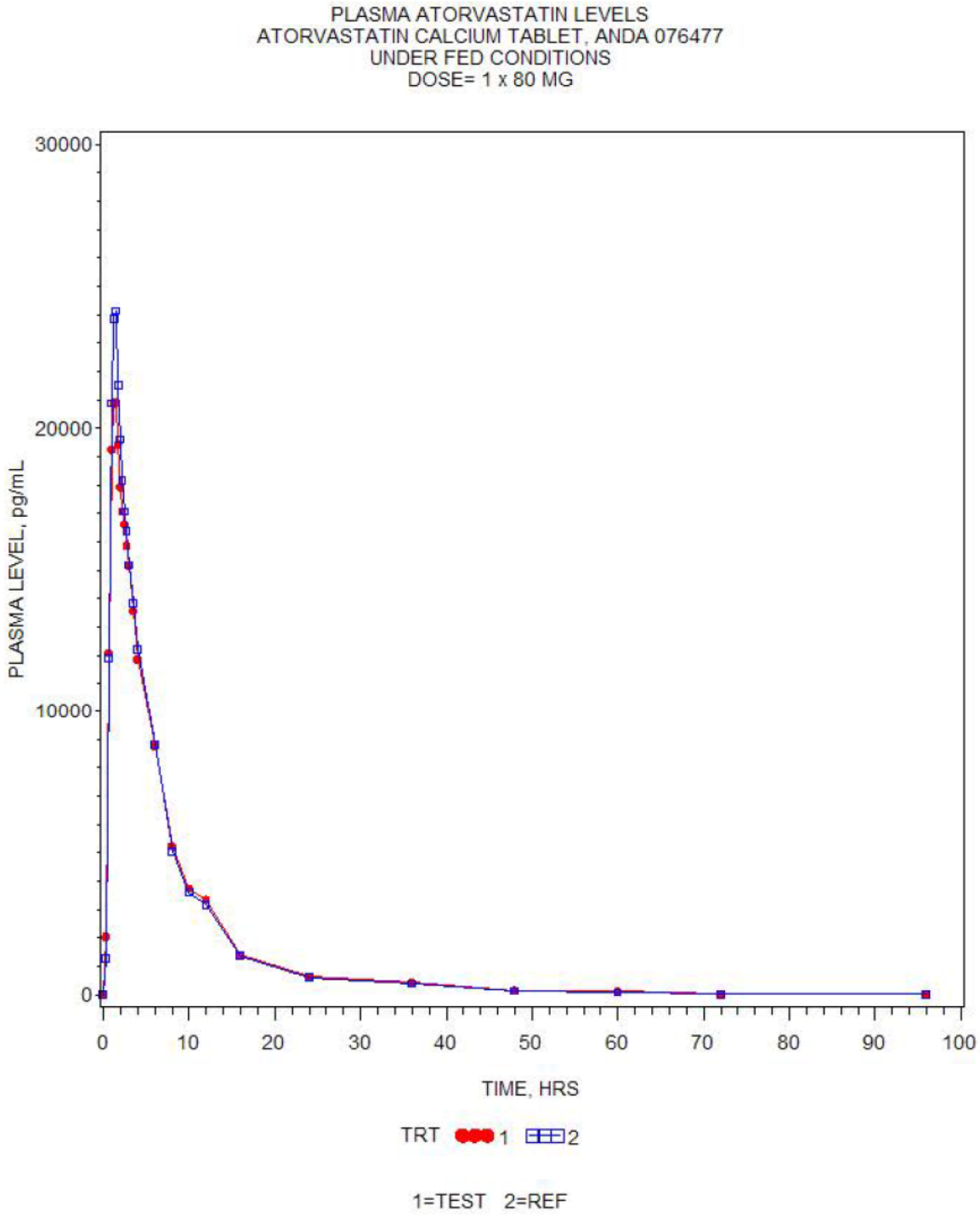


Table 74. Arithmetic Mean Pharmacokinetic Parameters- Ortho-hydroxy Atorvastatin (n=76)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	152698.6	42.90	69186.53	419633.1	153484.9	41.75	73452.78	405238.9	0.99
AUCI	pg hr/mL	154614.7	42.78	70350.51	422019.4	155658.1	41.44	74445.93	406577.0	0.99
CMAX	pg/mL	22919.48	57.78	7172.71	67988.44	23411.10	57.05	8759.64	79779.06	0.98
TMAX	hr	1.500	.	0.67	10.00	1.500	.	0.67	6.00	1.00
KE	hr-1	0.062	32.41	0.02	0.12	0.055	33.56	0.02	0.12	1.12
THALF	hr	12.957	47.93	5.64	46.21	14.164	37.92	5.79	33.31	0.91

* Tmax values are presented as median, range

Table 75. Geometric Means and 90% Confidence Intervals - Firm Calculated- Ortho-hydroxy Atorvastatin

See firm's data for Atorvastatin above (Table 66).

Table 76. Geometric Means and 90% Confidence Intervals - Reviewer Calculated- Ortho-hydroxy Atorvastatin (n=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	142055.4	143318.7	0.99	95.76	102.59
LAUCI	143728.6	145312.9	0.99	95.59	102.34
LCMAX	20093.50	20613.33	0.97	86.64	109.67

Table 77. Additional Study Information, Fed Study No. R09-1033- Ortho-hydroxy Atorvastatin (n=76)

Root mean square error, AUC0-t	0.0902	
Root mean square error, AUC∞	0.0886	
Root mean square error, Cmax	0.3082	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	75	75
Do you agree or disagree with firm's decision?	Agree	Agree
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	No	No

Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	75	0.99	0.95	1.00
Reference	75	0.99	0.96	1.00

Table 78. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study-Ortho-hydroxy Atorvastatin (n=76)

	Test (n=76)		Reference (n=76)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.33	364.49	444.53	244.20	397.85	1.49
0.67	5250.20	205.67	4646.30	182.44	1.13
1.00	11369.37	106.76	11768.33	111.31	0.97
1.25	14189.85	87.06	15191.77	94.96	0.93
1.50	15046.25	88.80	16094.98	80.57	0.93
1.75	14118.65	83.02	15188.41	76.80	0.93
2.00	13763.42	78.72	14652.72	73.32	0.94
2.25	13591.87	70.80	14485.86	70.95	0.94
2.50	13932.70	75.40	14183.05	62.20	0.98
2.75	14082.09	68.32	14276.64	59.79	0.99
3.00	13935.76	64.86	13956.92	60.65	1.00
3.50	13559.11	59.35	13965.90	61.30	0.97
4.00	13342.58	52.87	13595.06	54.70	0.98
6.00	10038.30	49.66	10175.19	50.50	0.99
8.00	7007.09	60.05	6997.55	49.81	1.00
10.00	5486.36	54.41	5414.46	50.79	1.01
12.00	4663.35	54.18	4475.75	52.31	1.04
16.00	2089.37	52.23	2053.02	45.45	1.02
24.00	921.76	52.19	908.87	46.30	1.01
36.00	623.48	53.00	601.49	48.40	1.04
48.00	248.85	56.60	253.75	56.80	0.98
60.00	175.69	75.81	167.01	60.32	1.05
72.00	74.05	107.33	78.77	81.07	0.94
96.00	18.70	196.21	14.79	200.26	1.26

Figure 5. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study-Ortho-hydroxy Atorvastatin (n=76)

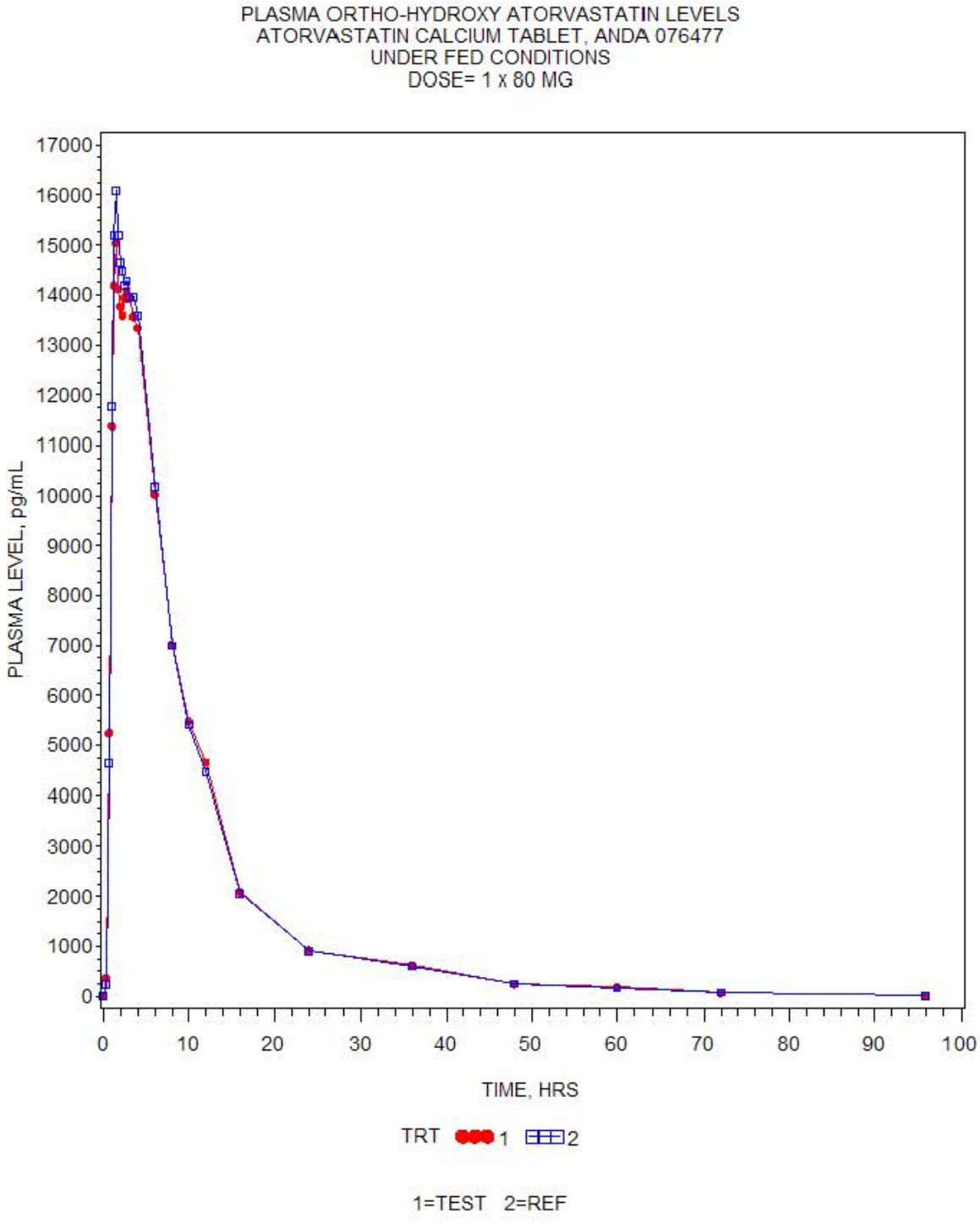


Table 79. Arithmetic Mean Pharmacokinetic Parameters

Para -hydroxy Atorvastatin (n=76)

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
AUCT	pg hr/mL	18596.20	55.07	3583.98	53417.98	18900.65	53.36	3895.78	53200.17	0.98
AUCI	pg hr/mL	22595.31	51.17	7269.48	56772.11	23405.18	48.97	7033.59	61224.60	0.97
CMAX	pg/mL	917.904	80.44	148.31	4511.88	900.634	66.97	198.15	3022.20	1.02
TMAX	hr	8.050	.	0.67	36.00	8.000	.	1.00	36.00	1.01
KE	hr-1	0.032	31.07	0.02	0.06	0.032	33.73	0.02	0.06	1.00
THALF	hr	23.813	32.34	11.60	42.02	24.542	37.71	12.03	46.23	0.97

* Tmax values are presented as median, range

Table 80. Geometric Means and 90% Confidence Intervals - Firm Calculated Para -hydroxy Atorvastatin

See firm's data for Atorvastatin above (Table 66).

Table 81. Geometric Means and 90% Confidence Intervals - Reviewer Calculated- Para -hydroxy Atorvastatin (n=76)

	Least Squares Geometric Mean		Ratio	90% Confidence Intervals	
Parameter	Test	Reference	(T/R)	Lower	Upper
LAUCT	16282.37	16691.03	0.98	92.86	102.48
LAUCI	20166.96	21036.43	0.96	90.16	101.93
LCMAX	748.86	751.79	1.00	91.79	108.09

Table 82. Additional Study Information, Fed Study

Para-hydroxy Atorvastatin (n=76)

Root mean square error, AUC0-t	0.1288	
Root mean square error, AUC∞	0.1304	
Root mean square error, Cmax	0.2138	
	Test	**Reference**
Kel and AUC∞ determined for how many subjects?	51	51
Do you agree or disagree with firm's decision?	AGREE	AGREE
Indicate the number of subjects with the following:		
measurable drug concentrations at 0 hr	0	0
first measurable drug concentration as Cmax	0	0
Were the subjects dosed as more than one group?	NO	NO

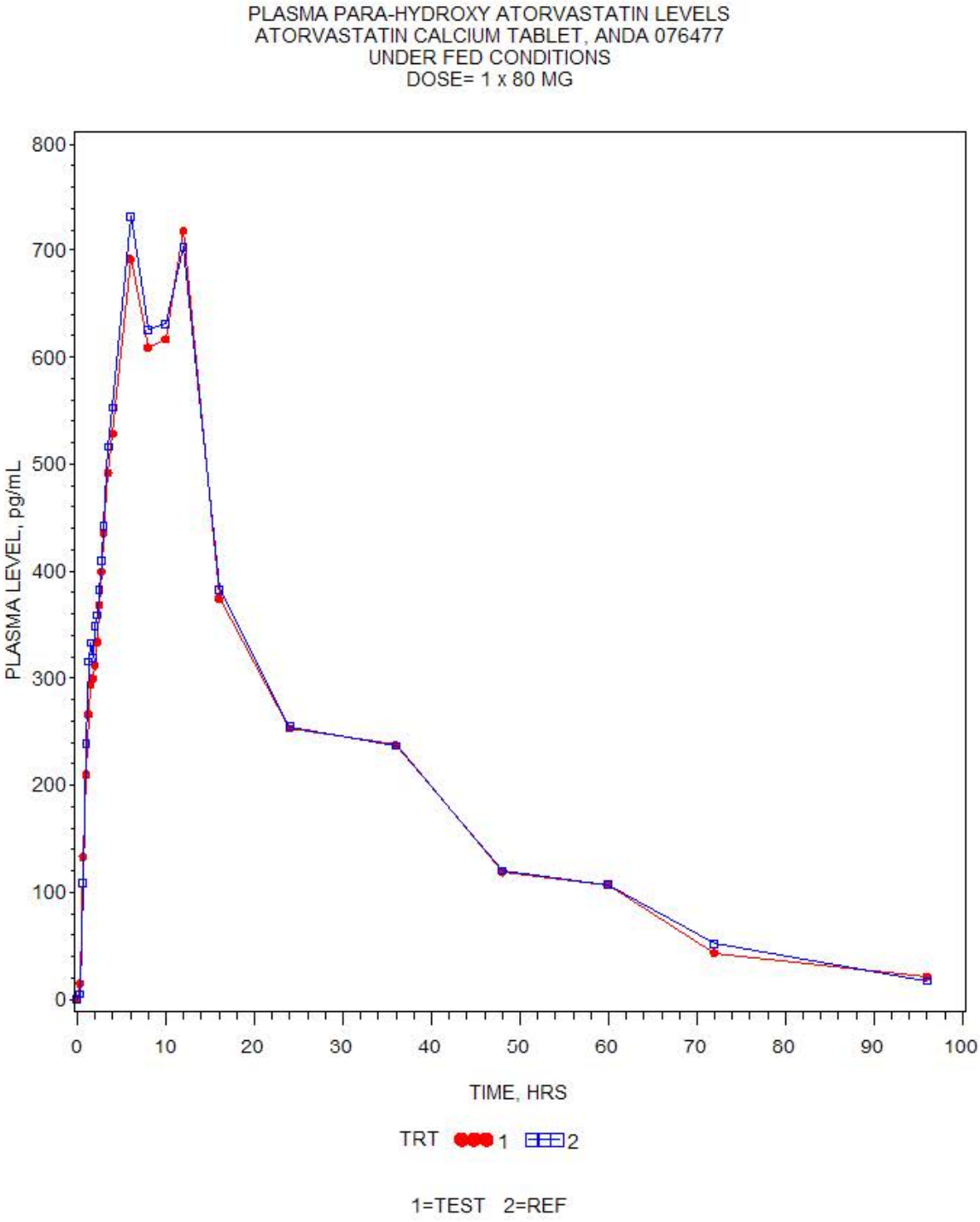
Ratio of AUC0-t/AUC∞				
Treatment	**n**	**Mean**	**Minimum**	**Maximum**
Test	51*	0.86	0.63	0.96
Reference	51*	0.86	0.73	0.97

*76 Subjects completed the study, but Kel could be determined for 51 subjects only.

Table 83. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study-Para-hydroxy Atorvastatin (n=76)

	Test (n=76)		Reference (n=76)		Ratio
Time (hr)	Mean (pg/mL)	CV%	Mean (pg/mL)	CV%	(T/R)
0.00	0.00	.	0.00	.	.
0.33	15.01	592.58	5.19	516.89	2.89
0.67	133.16	326.13	108.49	225.92	1.23
1.00	210.40	138.33	239.37	148.03	0.88
1.25	266.56	114.59	315.79	131.46	0.84
1.50	294.01	111.91	333.41	113.60	0.88
1.75	299.91	113.98	319.43	115.71	0.94
2.00	312.38	116.71	348.56	127.44	0.90
2.25	334.10	111.93	359.34	111.99	0.93
2.50	368.79	106.40	382.53	95.01	0.96
2.75	400.01	97.63	409.88	88.80	0.98
3.00	435.78	95.97	442.54	91.96	0.98
3.50	492.22	86.29	516.53	90.65	0.95
4.00	528.73	82.12	553.05	79.40	0.96
6.00	691.90	68.01	732.88	68.77	0.94
8.00	609.04	92.39	625.58	66.86	0.97
10.00	616.72	66.64	630.96	62.83	0.98
12.00	719.22	72.90	703.11	64.64	1.02
16.00	374.67	51.22	383.28	48.16	0.98
24.00	253.46	54.74	255.02	49.95	0.99
36.00	237.49	57.19	237.18	51.68	1.00
48.00	118.93	60.07	120.36	61.93	0.99
60.00	106.99	76.61	107.15	63.09	1.00
72.00	43.44	136.00	51.96	105.66	0.84
96.00	21.61	194.18	17.26	208.36	1.25

Figure 6. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study-Para-hydroxy Atorvastatin (n=76)



4.2.3. Pilot Studies

The firm has also conducted four pilot studies prior to conducting the pivotal studies. The formulations of the pilot and pivotal study lots are identical. The outline of the studies and PK results calculated and submitted by the firm are provided in the Appendix, 4.2.3, Pilot Studies. Brief summary of study results are provided below. Three pilot studies failed in meeting the 90% CI BE criteria of 80-125% for Atorvastatin for Cmax (see Tables 77, 81 and 85 below). In one fasting study (3023-ATORV-08), the study failed the 90% CI criteria for all three PK parameters (Table 89). Supporting data for ortho-hydroxy and para-hydroxy atorvastatin were within the 80-125% for all PK parameters.

1. Study no. BE-248-ATOR-2009

A single dose three way cross-over fasting study (Study No: BE-248-ATOR-2009) for Atorvastatin calcium tablet 80 mg with test batch no B204130 against US reference (Lipitor 80 mg tablet B.No. 22537V, Pfizer USA) and Canada reference (Lipitor 80 mg tablets B.No. 0378088, Pfizer Canada)

2. Study no BE-249-ATOR-2009

A single dose two way cross over fed study (Study No BE-249-ATOR-2009) for Atorvastatin calcium tablet 80 mg with test batch No. B204130 against reference (Lipitor 80 mg tablets, Pfizer USA) with batch no 22537V.

3. Study no 365_ATORV_09

A single dose three way cross-over fasting study (Study No. 365_Atorv_09) for Atorvastatin calcium tablet 80 mg with test batch no. ANK (3926)071A against reference (Lipitor 80 mg tablet, Pfizer USA) with batch no 04558V and Belgium reference (Lipitor 80 mg tablet) with batch no 0904118B.

4. Study no 3023_ATROV_08

A single dose two way cross over fasting study (Study No 3023_ATORV_08) for Atorvastatin calcium tablet 80 mg with test batch no. ANK (3926)049 against reference (Lipitor 80 mg tablets, Pfizer USA) with batch no 22537V.

4.2.3.1.Pilot BE Study (BE-248-ATOR-2009) - Fasting

Table 84. Study Information

Study Number	BE-248-ATOR-2009
Study Title	An open label, balanced, randomized, three-treatment, three-sequence, three-period, single-dose, cross-over, bioequivalence study comparing Atorvastatin Calcium Tablets 80 mg (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Ranbaxy Research Laboratories, India with two different formulations of LIPITOR 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Pfizer Ireland Pharmaceuticals, Dublin, Ireland, and LIPITOR 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Pfizer, Canada in healthy, adult human subjects, under fasting condition.
Clinical Site (Name, Address, Phone #)	**Clinical Services** Clinical Section Fortis Clinical Research Limited, Sunflag Hospital & Research Centre Sector-16A, Faridabad 121 002, Haryana, India Tel: 0129-409 0900 Fax: 0129-409 0924 **Clinical Laboratory** Ranbaxy Laboratories Limited Plot No. GP5, Sector-18, HSIDC Old Delhi- Gurgaon Road Gurgaon-122015 Haryana India
Principal Investigator	Deepak C. Chilkoti
Dosing Dates	Period I: March 19, 2009 Period II: April 2, 2009 Period III: April 16, 2009
Analytical Sites (Name, Address, Phone #)	(b) (4) (b) (4)
Analysis Dates	April 22, 2009 to April 27, 2009
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	34 days

Table 85. Product Information

Table 11 Product Information

BE-248-ATOR-2009			
Product	**Test**	**Reference**	**Reference**
Treatment ID	T	R1	R2
Product Name	Atorvastatin Calcium Tablets 80 mg	LIPITOR tablets 80 mg	LIPITOR tablets 80 mg
Manufacturer	Ohm Laboratories Inc., USA	Pfizer Ireland Pharmaceuticals, Dublin, Ireland	Pfizer Canada Inc., Licencie Kirkland (Quebec)
Batch/Lot No.	B204130	22537V	0378088
Manufacture Date	Feb-09	-	-
Expiration Date	Aug-09	Dec-10	Jul-11
Strength	80 mg	80 mg	80 mg
Dosage Form	Tablets	Tablets	Tablets
Bio-batch size	(b) (4) kg	-	-
Production Batch Size	-	-	-
Potency	100.5%	100.0%	100.1%
Content Uniformity (mean, % CV)	N/A	N/A	N/A
Dose Administered	80 mg	80 mg	80 mg
Route of Administration	Oral	Oral	Oral

Table 86. Summary of Fasting BE Study (Pilot)

Table 2 Summary of Bioavailability studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD/%CV)						Study Report Location
					C_{max} (ng/mL)	AUC_{0-t} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	T_{max}* (h)	T½ (h)	K_{el} (hr^{-1})	
BE-248-ATOR-2009	An open label, balanced, randomized, three-treatment, three-sequence, three-period, single-dose, cross-over, bioequivalence study comparing Atorvastatin Calcium Tablets 80 mg (containing atorvastatin calcium equivalent to 80 mg	An open label, balanced, randomized, three-treatment, three-sequence, three-period, single-dose, cross-over, bioequivalence study Study Type: Pilot	**Reference (R1)**	15 healthy adult male volunteers were enrolled out of which 13 completed the study. Data is reported on 13 subjects Mean age: 27.4 years Range: 19 – 34 years	**Reference (R1)**	**Reference (R1)**	**Reference (R1)**	**Reference (R1)**	**Reference (R1)**	**Reference (R1)**	Not Applicable
			Dose: 80 mg, Dosage Form: Tablet, Route: Oral, Batch/Lot No.: 22537V Expiry date: Dec-10		Atorvastatin: 60.2552 (± 20.90494/ 34.7), Ortho hydroxy atorvastatin: 51.2292 (±21.38429/ 41.7), Para hydroxy atorvastatin: 3.3066 (± 2.20493/ 66.7)	Atorvastatin: 285.8257 (± 128.07637/ 44.8), Ortho hydroxy atorvastatin: 411.7236 (±196.72759/ 47.8), Para hydroxy atorvastatin: 71.4485 (± 44.28401/ 62.0)	Atorvastatin: 295.4048 (± 132.86660/ 45.0), Ortho hydroxy atorvastatin: 426.0833 (±208.52268/ 48.9), Para hydroxy atorvastatin: 127.4048 (±167.74621/ 131.7)	Atorvastatin: 0.667 (0.500 - 2.000), Ortho hydroxy atorvastatin: 1.500 (0.667 - 5.000), Para hydroxy atorvastatin: 6.000 (1.500 - 10.000)	Atorvastatin: 17.5229 (±5.38395/ 30.7), Ortho hydroxy atorvastatin: 17.2815 (±5.74823/ 33.3), Para hydroxy atorvastatin: 46.7368 (±62.87520/ 134.5)	Atorvastatin: 0.0455 (±0.02338/ 51.4), Ortho hydroxy atorvastatin: 0.0441 (±0.01386/ 31.4), Para hydroxy atorvastatin: 0.0266 (±0.01444/ 54.2)	

Table 87. Summary of Fasting BE Study (Pilot)

	of atorvastatin) of Ranbaxy Research Laboratories, India with two different formulations of LIPITOR 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Pfizer Ireland Pharmaceuticals, Dublin, Ireland, and LIPITOR 80 mg tablets (containing atorvastatin calcium										
			Reference (R2)		**Reference (R2)**	**Reference (R2)**	**Reference (R2)**	**Reference (R2)**	**Reference (R2)**	**Reference (R2)**	
			Dose: 80 mg, Dosage Form: Tablet, Route: Oral, Batch/Lot No.: 0378088 Expiry date: Jul-11		Atorvastatin: 66.5232 (±31.46828/ 47.3), Ortho hydroxy atorvastatin: 50.6318 (±24.78951/ 49.0), Para hydroxy atorvastatin: 3.0192 (±2.24738/ 74.4)	Atorvastatin: 287.6338 (±150.98144/ 52.5), Ortho hydroxy atorvastatin: 400.8052 (±246.52150/ 61.5), Para hydroxy atorvastatin: 76.0169 (±52.14388/ 68.6)	Atorvastatin: 294.0527 (±152.74429/ 51.9), Ortho hydroxy atorvastatin: 410.8159 (±250.71905/ 61.0), Para hydroxy atorvastatin: 100.7985 (±67.37860/ 66.8)	Atorvastatin: 0.500 (0.417 - 2.500), Ortho hydroxy atorvastatin: 1.250 (0.583 - 2.500), Para hydroxy atorvastatin: 6.000 (0.500 - 12.000)	Atorvastatin: 15.8907 (±5.17627/ 32.6), Ortho hydroxy atorvastatin: 16.2657 (±4.53647/ 27.9), Para hydroxy atorvastatin: 38.0799 (±21.35354/ 56.1)	Atorvastatin: 0.0485 (±0.01677/ 34.6), Ortho hydroxy atorvastatin: 0.0456 (±0.01193/ 26.2), Para hydroxy atorvastatin: 0.0230 (±0.01140/ 49.5)	

Table 88. Summary of Fasting BE Study (Pilot)

	equivalent to 80 mg of atorvastatin) of Pfizer, Canada in healthy, adult, human subjects, under fasting condition		**Test**	**Test**	**Test**	**Test**	**Test**	**Test**	**Test**		
			Dose: 80 mg, Dosage Form: Tablet, Route: Oral, Batch/Lot No.: B204130 Expiry date: Aug-09	Atorvastatin: 71.2251 (±33.84404/ 47.5), Ortho hydroxy atorvastatin: 48.3807 (±21.50829/ 44.5), Para hydroxy atorvastatin: 3.8278 (±4.48338/ 117.1)	Atorvastatin: 294.0958 (±158.05890/ 53.7), Ortho hydroxy atorvastatin: 407.2113 (±263.87682/ 64.8), Para hydroxy atorvastatin: 73.2003 (±53.87286/ 73.6)	Atorvastatin: 301.7013 (±162.84104/ 54.0), Ortho hydroxy atorvastatin: 418.8964 (±275.40354/ 65.7), Para hydroxy atorvastatin: 91.3993 (±64.45777/ 70.5)	Atorvastatin: 0.583 (0.417 - 2.500), Ortho hydroxy atorvastatin: 1.000 (0.583 - 2.500), Para hydroxy atorvastatin: 6.000 (1.000 - 16.000)	Atorvastatin: 15.1981 (±4.76770/ 31.4), Ortho hydroxy atorvastatin: 16.2496 (±3.43193/ 21.1), Para hydroxy atorvastatin: 33.1087 (±14.35173/ 43.3)	Atorvastatin: 0.0516 (±0.02319/ 45.0), Ortho hydroxy atorvastatin: 0.0444 (±0.00912/ 20.5), Para hydroxy atorvastatin: 0.0239 (±0.00785/ 32.9)	

*** - Median (Range) is provided.**

Table 89. Statistical Summary of in vivo Bioequivalence Study – Fasting (Pilot)

Fasted Bioequivalence study (Study No. BE-248-ATOR-2009)

Parameter	Test	Reference (R1)	Reference (R2)	Ratio % (T/R1)	90 % C.I	Ratio (T/R2)	90 % C.I
AUC_{0-t} (ng.h/mL)	Atorvastatin: 260.4194, Ortho hydroxy atorvastatin: 350.8535, Para hydroxy atorvastatin: 60.8598	Atorvastatin: 258.8401, Ortho hydroxy atorvastatin: 367.2718, Para hydroxy atorvastatin: 58.0519	Atorvastatin: 257.4199, Ortho hydroxy atorvastatin: 348.6631, Para hydroxy atorvastatin: 62.3408	Atorvastatin: 100.61, Ortho hydroxy atorvastatin: 95.53, Para hydroxy atorvastatin: 104.84	Atorvastatin: 88.77 - 114.02, Ortho hydroxy atorvastatin: 85.81 - 106.35, Para hydroxy atorvastatin: 91.86 - 119.65	Atorvastatin: 101.17, Ortho hydroxy atorvastatin: 100.63, Para hydroxy atorvastatin: 97.62	Atorvastatin: 89.26 - 114.65, Ortho hydroxy atorvastatin: 90.39 - 112.02, Para hydroxy atorvastatin: 85.54 - 111.42
AUC_{inf} (ng.h/mL)	Atorvastatin: 267.4671, Ortho hydroxy atorvastatin: 360.7288, Para hydroxy atorvastatin: 77.6726	Atorvastatin: 267.7431, Ortho hydroxy atorvastatin: 379.1949, Para hydroxy atorvastatin: 81.2002	Atorvastatin: 264.1815, Ortho hydroxy atorvastatin: 358.4202, Para hydroxy atorvastatin: 83.0985	Atorvastatin: 99.90, Ortho hydroxy atorvastatin: 95.13, Para hydroxy atorvastatin: 95.66	Atorvastatin: 88.40 - 112.89, Ortho hydroxy atorvastatin: 85.92 - 105.33, Para hydroxy atorvastatin: 79.44 - 115.19	Atorvastatin: 101.24, Ortho hydroxy atorvastatin: 100.64, Para hydroxy atorvastatin: 93.47	Atorvastatin: 89.59 - 114.41, Ortho hydroxy atorvastatin: 90.90 - 111.44, Para hydroxy atorvastatin: 77.62 - 112.56

C_{max} (ng/mL)	Atorvastatin: 64.4997, Ortho hydroxy atorvastatin: 44.1504, Para hydroxy atorvastatin: 2.8436	Atorvastatin: 56.5192, Ortho hydroxy atorvastatin: 47.4915, Para hydroxy atorvastatin: 2.7447	Atorvastatin: 60.4934, Ortho hydroxy atorvastatin: 44.4694, Para hydroxy atorvastatin: 2.4195	Atorvastatin: 114.12, Ortho hydroxy atorvastatin: 92.96, Para hydroxy atorvastatin: 103.60	Atorvastatin: 98.09 - 132.77, Ortho hydroxy atorvastatin: 80.31 - 107.61, Para hydroxy atorvastatin: 79.10 - 135.71	Atorvastatin: 106.62, Ortho hydroxy atorvastatin: 99.28, Para hydroxy atorvastatin: 117.53	Atorvastatin: 91.65 - 124.05, Ortho hydroxy atorvastatin: 85.77 - 114.93, Para hydroxy atorvastatin: 89.73 - 153.95

4.2.3.2. Pilot BE Study (BE-249-ATOR-2009) - Fed

Table 90 Study Information

Study Number	BE-249-ATOR-2009
Study Title	An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, cross-over, bioequivalence study comparing Atorvastatin Calcium Tablets 80 mg (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Ranbaxy Research Laboratories, India with LIPITOR 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Pfizer Ireland Pharmaceuticals, Dublin, Ireland, in healthy, adult, human subjects, under fed condition
Clinical Site (Name, Address, Phone #)	**Clinical Services** Clinical Section Fortis Clinical Research Limited, Sunflag Hospital & Research Centre Sector-16A, Faridabad 121 002, Haryana, India Tel: 0129-409 0900 Fax: 0129-409 0924 **Clinical Laboratory** Ranbaxy Laboratories Limited Plot No. GP5, Sector-18, HSIDC Old Delhi- Gurgaon Road Gurgaon-122015 Haryana India
Principal Investigator	Deepak C. Chilkoti
Dosing Dates	Period I: March 19, 2009 Period II: April 02, 2009
Analytical Sites (Name, Address, Phone #)	(b) (4)
Analysis Dates	April 27, 2009 to May 1, 2009
Analytical Director	(b) (4)
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	39 days

Table 91. Product Information

BE-249-ATOR-2009		
Product	**Test**	**Reference**
Treatment ID	T	R
Product Name	Atorvastatin Calcium Tablets 80 mg	LIPITOR tablets 80 mg
Manufacturer	Ohm Laboratories Inc., USA	Pfizer Ireland Pharmaceuticals, Dublin, Ireland
Batch/Lot No.	B204130	22537V
Manufacture Date	Feb-09	-
Expiration Date	Aug-09	Dec-10
Strength	80 mg	80 mg
Dosage Form	Tablets	Tablets
Bio-batch size	(b) (4)	-
Production Batch Size	-	-
Potency	105%	100%
Content Uniformity (mean, % CV)	N/A	N/A
Dose Administered	80 mg	80 mg
Route of Administration	Oral	Oral

Table 92. Summary of in vivo Bioequivalence Study – Fed (Pilot)

Table 2 Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD/%CV)						
					C_{max} (ng/mL)	AUC_{0-t} (ng*h/mL)	$AUC_{0-\infty}$ (ng*h/mL)	T_{max}* (h)	T½ (h)	K_{el} (hr^{-1})	Study Report Location
BE-249-ATOR-2009	An open label, balanced, randomized, two-treatment,two-sequence, two-period, single-dose, cross-over, bioequivalence study comparing Atorvastatin Calcium Tablets 80 mg (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Ranbaxy Research Laboratories, India with LIPITOR 80 mg tablets	An open label, balanced, randomized, two-treatment, two-sequence, two-period, single-dose, cross-over, bioequivalence Study Type: Pilot	**Reference (R)**	14 healthy adult male volunteers were enrolled out of which 11 completed the study. Data is reported on 11 subjects	**Reference (R)**	**Reference (R)**	**Reference (R)**	**Reference (R)**	**Reference (R)**	**Reference (R)**	Not Applicable
			Dose: 80 mg, Dosage Form: Tablet, Route: Oral, Batch/Lot No.: 22537V Expiry date: Dec-10	Mean age: 26.3 years Range: 21 – 36 years	Atorvastatin: 51.8924 (± 33.83224/ 65.2), Ortho hydroxy atorvastatin: 26.9410 (±16.07981/ 59.7),	Atorvastatin: 296.7769 (± 151.75986/ 51.1), Ortho hydroxy atorvastatin: 312.6904 (± 192.81504/ 61.7),	Atorvastatin: 305.1659 (±157.72531/ 51.7), Ortho hydroxy atorvastatin: 326.7057 (±218.89399/ 67.0),	Atorvastatin: 2.250 (0.667 - 6.000), Ortho hydroxy atorvastatin: 6.000 (1.000 - 6.000) ,	Atorvastatin: 13.4403 (± 6.21426/ 46.2), Ortho hydroxy atorvastatin: 14.9483 (±5.71623/ 38.2),	Atorvastatin: 0.0580 (±0.01709/ 29.5), Ortho hydroxy atorvastatin: 0.0502 (±0.01174/ 23.4),	

	(containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Pfizer Ireland Pharmaceuticals , Dublin, Ireland, in healthy, adult,human subjects, under fed condition				Para hydroxy atorvastatin: 2.9994 (±1.88493/ 62.8)	Para hydroxy atorvastatin: 62.5255 (±35.21559/ 56.3)	Para hydroxy atorvastatin: 93.1260 (±104.91193 /112.7)	Para hydroxy atorvastatin: 6.000 (6.000 - 10.000)	Para hydroxy atorvastatin: 33.5409 (±35.92746/ 107.1)	Para hydroxy atorvastatin: 0.0318 (±0.01613/ 50.8)	
			Test (T)		**Test (T)**	**Test (T)**	**Test (T)**	**Test (T)**	**Test (T)**	**Test (T)**	
			Dose: 80 mg, Dosage Form: Tablet, Route: Oral, Batch/Lot No.: B204130 Expiry date: Aug-09		Atorvastatin: 41.3929 (± 24.77497/ 59.9), Ortho hydroxy atorvastatin: 24.3401 (±9.59595/ 39.4), Para hydroxy atorvastatin: 2.7154 (± 1.33853/ 49.3)	Atorvastatin: 267.9353 (±114.42772/ 42.7), Ortho hydroxy atorvastatin: 288.9993 (±158.81450/ 55.0), Para hydroxy atorvastatin: 58.1145 (±32.55040/ 56.0)	Atorvastatin: 273.3433 (±115.27245/ 42.2), Ortho hydroxy atorvastatin: 297.3915 (±163.25490/ 54.9), Para hydroxy atorvastatin: 72.9369 (±36.62455/ 50.2)	Atorvastatin: 2.500 (0.667 - 4.000) , Ortho hydroxy atorvastatin: 6.000 (1.000 - 10.000), Para hydroxy atorvastatin: 6.000 (3.000 - 10.000)	Atorvastatin: 12.7086 (± 2.15645/ 17.0), Ortho hydroxy atorvastatin: 13.9019 (±2.25998/ 16.3), Para hydroxy atorvastatin: 30.4012 (± 14.33076/ 47.1)	Atorvastatin: 0.0561 (±0.01058/ 18.8), Ortho hydroxy atorvastatin: 0.0509 (±0.00751/ 14.7), Para hydroxy atorvastatin: 0.0269 (±0.01010/ 37.5)	

*** - Median (Range) is provided.**

Table 93. Statistical Summary of in vivo Bioequivalence Study – Fed (Pilot)

Parameter	Test (T)	Reference (R)	Ratio% (T/R)	90 % C.I
AUC_{0-t} (ng.h/mL)	Atorvastatin: 242.9523, Ortho hydroxy atorvastatin: 259.1722, Para hydroxy atorvastatin: 50.0296	Atorvastatin: 259.9057, Ortho hydroxy atorvastatin: 274.2544, Para hydroxy atorvastatin: 54.6337	Atorvastatin: 93.48, Ortho hydroxy atorvastatin: 94.50, Para hydroxy atorvastatin: 91.57	Atorvastatin:83.17 - 105.06, Ortho hydroxy atorvastatin: 85.54 - 104.40, Para hydroxy atorvastatin: 79.47 - 105.52
AUC_{inf} (ng.h/mL)	Atorvastatin: 248.7460, Ortho hydroxy atorvastatin:266.8598, Para hydroxy atorvastatin: 65.8014	Atorvastatin: 267.2847, Ortho hydroxy atorvastatin: 282.7816, Para hydroxy atorvastatin: 69.4124	Atorvastatin: 93.06, Ortho hydroxy atorvastatin: 94.37, Para hydroxy atorvastatin: 94.80	Atorvastatin: 82.65 - 104.79, Ortho hydroxy atorvastatin: 84.79 - 105.03, Para hydroxy atorvastatin: 76.26 - 117.83
C_{max} (ng/mL)	Atorvastatin: 35.3815, Ortho hydroxy atorvastatin: 22.2420, Para hydroxy atorvastatin: 2.3538	Atorvastatin: 41.6543, Ortho hydroxy atorvastatin: 23.2850, Para hydroxy atorvastatin: 2.5498	Atorvastatin: 84.94, Ortho hydroxy atorvastatin: 95.52, Para hydroxy atorvastatin: 92.31	Atorvastatin: 67.25 - 107.29, Ortho hydroxy atorvastatin: 77.11 - 118.32, Para hydroxy atorvastatin: 74.86 - 113.84

4.2.3.3. Pilot BE Study (365-ATORV-09) - Fasting

Table 94 Study Information

Study Number	365_ATORV_09
Study Title	An open label, balanced, randomized, three-treatment, three-period, three sequence, single dose, crossover, bioequivalence study comparing atorvastatin calcium 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Ranbaxy Research Laboratories with Lipitor® 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Parke-Davis. and Lipitor 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Pfizer S.A., in healthy, adult, human, male subjects under fasting condition
Clinical Site (Name, Address, Phone #)	**Clinical Services** Clinical Pharmacology Unit Ranbaxy Laboratories Limited Majeedia Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062 India Tel: (91-11) 2995-8529 **Clinical Laboratory** Ranbaxy Laboratories Limited Plot No. GP5, Sector-18, HSIDC Old Delhi- Gurgaon Road Gurgaon-122015 Haryana India Tel: (91-124) 4768174
Principal Investigator	**Dr. Amit Marwah** Clinical Pharmacology Unit Ranbaxy Laboratories Limited Majeedia Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062 India. Tel: (91-11) 2995-8529 (Office) Fax: (91-11) 2605-9879
Dosing Dates	PERIOD I: June 10, 2009 PERIOD II: June 24, 2009 PERIDO III: July 07, 2009
Analytical Site (Name, Address, Phone #)	Clinical Pharmacology & Pharmacokinetics Ranbaxy Laboratories Limited Plot No. GP-5, Sector 18, HSIDC, Old Delhi –Gurgaon Road, Gurgaon 122 015, Haryana, India Tel: (+91-124) 4231001 Fax: (+91-124) 4231002
Analysis Dates	18 Jul 2009-27 Jul 2009
Analytical Director	Dr. Tausif Monif
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	47 days

Table 95. Product Information

Table 11 Product Information

Product	Test	Reference	Reference
Treatment ID	T	R1	R2
Product Name	Atorvastatin calcium 80 mg tablets	Lipitor® Tablets 80 mg	Lipitor Tablets 80 mg
Manufactured by	Ranbaxy Research Laboratories, Gurgaon	Pfizer Ireland Pharmaceuticals, Dublin, Ireland	Godecke Gmbh, Mooswalgallee 1-9, D-19090 Freiburg, Germany
Batch/Lot No.	ANK(3926)071A	04558V	0904118B
Manufacture Date	March-09	Not available	Not available
Expiry Date	Aug 2009	March 2011	October 2011
Strength	80 mg	80 mg	80 mg
Dosage Form	Tablet	Tablet	Tablet
Bio-batch Size **Production Batch Size**	- -	- -	- -
Potency	100.8%	101.9%	100.5%
Content Uniformity (mean, %CV)	Not available	Not available	Not available
Dose Administered	80 mg	80 mg	80 mg
Route of Administration	Oral	Oral	Oral

Table 96. Summary of in vivo Bioequivalence Study – Fasting (Pilot)

Table 2. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD/%CV) Atorvastatin						Study Report Location
					C_{max} (ng/mL)	T_{max}* (hr)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	T½ (hr)	K_{el} (hr^{-1})	
365_ATORV_09	To assess the bioequivalence of single oral dose of atorvastatin calcium 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Ranbaxy Research Laboratories with Lipitor® 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Parke-Davis and Lipitor 80 mg tablets (containing atorvastatin calcium equivalent to 80 mg of atorvastatin) of Pfizer S.A. in healthy, adult, human, male subjects under fasting condition	Open label, balanced, randomized, three-treatment, three -sequence, three -period, single-dose crossover bioequivalence study under fasting condition	T: Atorvastatin calcium tablets 80 mg ;[Batch no. ANK(3926) 071A; Expiry Date: 08/2009. 1 Tablet, Oral. R1: Lipitor® Tablets 80 mg; [Batch No.: 04558V; Expiry Date: 03/2011] 1 Tablet, Oral. R2: Lipitor Tablets 80 mg ;[Batch No.: 0904118B; Expiry Date: 10/2011] 1 Tablet, Oral.	A total of 18 healthy, male subjects were enrolled in the study. 17 subjects completed all the periods of the study. Mean age: 30.47 years (Completed Subjects) Range: 21-40 years	T 43.4043 (13.68593 /31.5) R1 50.7661 (27.01152 /53.2) R2 46.1574 (17.11071 /37.1)	T 0.583 (0.417-2.500) R1 0.583 (0.333-4.000) R2 0.667 (0.333-3.000)	T 157.1289 (66.87321/ 42.6) R1 163.4301 (81.06522/ 49.6) R2 168.5142 (84.75000/ 50.3)	T 162.3435 (68.41444/ 42.1) R1 167.5759 (85.16358 /50.8) R2 172.7066 (86.29799 /50.0)	T 11.95848 (5.726185 /47.9) R1 9.35131 (3.897337 /41.7) R2 10.43470 (4.956713/ 47.5)	T 0.07485 (0.042863 /57.3) R1 0.08859 (0.040025 /45.2) R2 0.08489 (0.042711 /50.3)	Not applicable
					2-Hydroxy Atorvastatin (o- Hydroxy Atorvastatin)						
					T 37.3242 (18.16716 /48.7) R1 38.5011 (16.36420 /42.5) R2 38.4786 (14.95326 /38.9)	T 0.866 (0.583 - 2.500) R1 1.000 (0.583 - 4.000) R2 1.000 (0.583 - 4.000)	T 219.2267 (106.98199/ 48.8) R1 218.4742 (76.31555/ 34.9) R2 228.7824 (82.59888/ 36.1)	T 224.7488 (108.65841/ 48.3) R1 223.3388 (79.14006 /35.4) R2 234.0706 (83.42314 /35.6)	T 12.44207 (4.401604 /35.4) R1 11.59599 (3.534435 /30.5) R2 12.82215 (4.120492/ 32.1)	T 0.06485 (0.029328 /45.2) R1 0.06700 (0.028502 /42.5) R2 0.06066 (0.024167 /39.8)	
					4-HydroxyAtorvastatin (p- Hydroxy Atorvastatin)						
					T 1.6195 (0.93992 /58.0) R1 1.8029 (1.15487 /64.1) R2 1.8257 (1.00202 /54.9)	T 8.000 (1.500-16.000) R1 5.000 (0.583 - 16.000) R2 6.000 (1.500-12.000)	T 33.1844 (17.02892/ 51.3) R1 35.0014 (17.39635/ 49.7) R2 35.6647 (16.61512/ 46.6)	T 53.3882 (15.23104/ 28.5) R1 47.5904 (18.93649 /39.8) R2 57.2676 (13.05205 /22.8)	T 19.42419 (5.220212 /26.9) R1 16.69360 (2.739693 /16.4) R2 23.82719 (9.184626/ 38.5)	T 0.03766 (0.008824 /23.4) R1 0.04258 (0.007449 /17.5) R2 0.03203 (0.009899 /30.9)	

Table 97. Statistical Summary of in vivo Bioequivalence Study – Fasting (Pilot)

Table 3 Statistical Summary of the Comparative Bioavailability Data

Atorvastatin **Dose (80 mg)** **Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)**							
Fasting Bioequivalence Study (Study No. 365_ATORV_09)							
Parameter	Test	Reference 1	Reference 2	Ratio T/R1(%)	Ratio T/R2(%)	90% CI T/R1	90% CI T/R2
AUC_{0-t}	141.6119 ng.h/mL	147.9674 ng.h/mL	149.7027 ng.h/mL	95.70	94.60	86.25 – 106.19	85.25 - 104.96
$AUC_{0-\infty}$	146.6073 ng.h/mL	151.1620 ng.h/mL	153.6251 ng.h/mL	96.99	95.43	87.09 – 108.00	85.70 - 106.27
C_{max}	40.9730 ng/mL	44.3465 ng/mL	43.1425 ng/mL	92.39	94.97	79.15 – 107.85	81.36 - 110.86
2-Hydroxy Atorvastatin (o- Hydroxy Atorvastatin) **Least Square Geometric Means, Ratio of Means**							
Fasting Bioequivalence Study (Study No. 365_ATORV_09)							
Parameter	Test	Reference 1	Reference 2	Ratio T/R1(%)	Ratio T/R2(%)		
AUC0-t	191.9256 ng.h/mL	203.9215 ng.h/mL	210.2465 ng.h/mL	94.12	91.29		
AUC0-∞	197.6475 ng.h/mL	207.6151 ng.h/mL	215.5512 ng.h/mL	95.20	91.69		
C max	32.8340 ng/mL	35.2029 ng/mL	35.4423 ng/mL	93.27	92.64		
4-Hydroxy Atorvastatin (p- Hydroxy Atorvastatin) **Least Square Geometric Means, Ratio of Means**							
Fasting Bioequivalence Study (Study No. 365_ATORV_09)							
Parameter	Test	Reference 1	Reference 2	Ratio T/R1(%)	Ratio T/R2(%)		
AUC0-t	28.6392 ng.h/mL	30.2964 ng.h/mL	30.8193 ng.h/mL	94.53	92.93		
AUC0-∞	44.9231 ng.h/mL	43.4509 ng.h/mL	44.1560 ng.h/mL	103.39	101.74		
C max	1.3516 ng/mL	1.4490 ng/mL	1.5280 ng/mL	93.28	88.45		

4.2.3.4. Pilot BE Study (3023-ATORV-08) - Fasting

Table 98 Study Information

Study Number	3023_ATORV_08
Study Title	An open label, balanced, randomized, two-treatment, two-period, two sequence, single dose, crossover, bioequivalence study comparing atorvastatin calcium 80 mg tablets of Ranbaxy Research Laboratories with Lipitor 80 mg tablets (containing atorvastatin calcium 80 mg) of Pfizer Ireland Pharmaceuticals, in healthy, adult, male human subjects under fasting condition
Clinical Site (Name, Address, Phone #)	**Clinical Services** Clinical Pharmacology Unit Ranbaxy Laboratories Limited Majeedia Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062 India Tel: (91-11) 2995-8529 **Clinical Laboratory** Ranbaxy Laboratories Limited Plot No. GP5, Sector-18, HSIDC Old Delhi- Gurgaon Road Gurgaon-122015 Haryana India Tel: (91-124) 4768174
Principal Investigator	**Dr. Amit Marwah** Clinical Pharmacology Unit Ranbaxy Laboratories Limited Majeedia Hospital (2nd Floor) Jamia Hamdard (Hamdard University) Hamdard Nagar New Delhi 110 062 India. Tel: (91-11) 2995-8529 (Office) Fax: (91-11) 2605-9879
Dosing Dates	PERIOD I: December 12, 2008 PERIOD II: January 08, 2009
Analytical Site (Name, Address, Phone #)	Clinical Pharmacology & Pharmacokinetics Ranbaxy Laboratories Limited Plot No. GP-5, Sector 18, HSIDC, Old Delhi –Gurgaon Road, Gurgaon 122 015, Haryana, India Tel: (+91-124) 4231001 Fax: (+91-124) 4231002
Analysis Dates	16 Jan 2009 – 24 Jan 2009
Analytical Director	Dr. Tausif Monif
Storage Period of Biostudy Samples (no. of days from the first day of sample collection to the last day of sample analysis)	43 days

Table 99. Product Information

Table 11 Product Information

Product	Test	Reference
Treatment ID	T	R
Product Name	Atorvastatin calcium tablets 80 mg	Lipitor Tablets 80 mg
Manufactured by	Ranbaxy Research Laboratories, Gurgaon	Pfizer Ireland Pharmaceuticals, Dublin, Ireland
Batch No.	ANK(3926)049	22537V
Manufacture Date	Not available	Not available
Expiry Date	05/2010	Dec 2010
Strength	80 mg	80 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	-	-
Production Batch Size	-	-
Potency	101.4%	100.0%
Content Uniformity (mean, %CV)	N/A	N/A
Dose Administered	80 mg	80 mg
Route of Administration	Oral	Oral

Table 100. Summary of in vivo Bioequivalence Study – Fasting (Pilot)

Table 2. Summary of Bioavailability Studies

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, route) [Product ID]	Subjects (No. (M/F) type Age: mean (range)	Mean Parameters (± SD/%CV) Atorvastatin						Study Report Location
					C_{max} (ng/mL)	T_{max}* (hr)	AUC_{0-t} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	T½ (hr)	K_{el} (hr^{-1})	
3023_ATROV_08	The objective of the study is to evaluate the single oral dose of atorvastatin calcium 80 mg tablets of Ranbaxy Research Laboratories with Lipitor 80 mg tablets (containing atorvastatin calcium 80 mg) of Pfizer Ireland Pharmaceuticals, in healthy, adult, human, male subjects under fasting condition.	An open label, balanced, randomized, two-treatment, two-period, two sequence, single dose, crossover, bioequivalence study Study Type: Pilot	**T:** Atorvastatin calcium tablets 80 mg; [Batch no. ANK(3926)049; Expiry Date: May 2009 1 Tablet, Oral. **R:** Lipitor Tablets 80 mg; [Batch No.: 22537V; Expiry Date: Dec 2010] 1 Tablet, Oral.	A total of fourteen (14) healthy, male subjects were enrolled in the study. Twelve (12) subjects completed both the periods of the study. Mean age: 28.83 years (Completed Subjects) Range: 22-38 years	**Test** 52.9079 (18.01929 / 34.1) **Ref.** 55.1299 (23.73944 / 43.1	**Test** 1.250 (0.500-4.033) **Ref.** 0.625 (0.417 – 2.000)	**Test** 192.4689 (47.41795/ 24.6) **Ref.** 168.8847 (56.61308/ 33.5)	**Test** 197.6843 (47.28607 / 23.9) **Ref.** 172.2837 (56.48389 / 32.8)	**Test** 11.63396 (6.051591 / 52.0) **Ref.** 9.38748 (3.451533 / 36.8)	**Test** 0.07634 (0.039126 / 51.3) **Ref.** 0.08360 (0.029927 / 35.8)	Not Applicable
					2-Hydroxy Atorvastatin (o-Hydroxy Atorvastatin)						
					Test 24.1779 (8.15750 / 33.7) **Ref.** 23.6249 (12.46710 / 52.8)	**Test** 1.375 (0.667 - 4.033) **Ref.** 1.167 (0.533 – 3.000)	**Test** 158.9703 (50.91973 / 32.0) **Ref.** 144.3720 (63.00413 / 43.6)	**Test** 162.9204 (50.90853 / 31.2) **Ref.** 149.7457 (62.27115 / 41.6)	**Test** 10.08995 (3.275919 / 32.5) **Ref.** 12.24093 (5.442694 / 44.5)	**Test** 0.07504 (0.022406 / 29.9) **Ref.** 0.06699 (0.029055 / 43.4)	
					4-Hydroxy Atorvastatin (p-Hydroxy Atorvastatin)						
					Test 1.5866 (0.76139 / 48.0) **Ref.** 1.5302 (1.39705 / 91.3)	**Test** 7.000 (3.000 - 10.000) **Ref.** 5.500 (2.000 – 12.000)	**Test** 31.6690 (14.09657 / 44.5) **Ref.** 28.9925 (16.81861 / 58.0)	**Test** 44.3441 (16.39740 / 37.0) **Ref.** 52.4202 (18.44796 / 35.2)	**Test** 19.49459 (8.892236 / 45.6) **Ref.** 16.51341 (6.519763 / 39.5)	**Test** 0.04764 (0.034332 / 72.1) Ref. 0.04756 (0.019260 / 40.5)	

Table 101. Statistical Summary of in vivo Bioequivalence Study – Fasting (Pilot)

Atorvastatin Dose (80 mg) Least Square Geometric Means, Ratio of Means, and 90% Confidence Intervals (CI)				
Fasting Bioequivalence Study (Study No. 3023_ATORV_08)				
Parameter	**Test**	**Reference**	**Ratio (%)**	**90% CI**
AUC_{0-t}	188.3614 ng.h/mL	161.6684 ng.h/mL	116.51	102.58 – 132.33
$AUC_{0-\infty}$	193.5338 ng.h/mL	165.1965 ng.h/mL	117.15	103.36 – 132.79
C_{max}	50.9534 ng/mL	51.2247 ng/mL	99.47	77.73 – 127.30
2-Hydroxy Atorvastatin (o-Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means				
Fasting Bioequivalence Study (Study No. 3023_ATORV_08)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	151.7430 ng.h/mL	132.1667 ng.h/mL	114.81	
$AUC_{0-\infty}$	155.9941 ng.h/mL	138.1402 ng.h/mL	112.92	
C_{max}	22.4071 ng/mL	20.8814 ng/mL	107.31	
4-Hydroxy Atorvastatin (p-Hydroxy Atorvastatin) Least Square Geometric Means, Ratio of Means				
Fasting Bioequivalence Study (Study No. 3023_ATORV_08)				
Parameter	**Test**	**Reference**	**Ratio (%)**	
AUC_{0-t}	29.0862 ng.h/mL	25.5404 ng.h/mL	113.88	
$AUC_{0-\infty}$	41.5592 ng.h/mL	40.5781 ng.h/mL	102.42	
C_{max}	1.3957 ng/mL	1.1826 ng/mL	118.02	

4.3.Formulation Data

From its original acceptable formulation, the firm has made major changes in polymorphic form, components and composition, manufacturing process and manufacturing site (see the tables below).

4.3.1. Revised Formulation

NOT FOR RELEASE UNDER FOI

Quantitative composition (Unit Composition)
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg & 80 mg

S.No.	Ingredient	mg/tab							
		10mg	%	20mg	%	40mg	%	80mg	%

(b) (4)

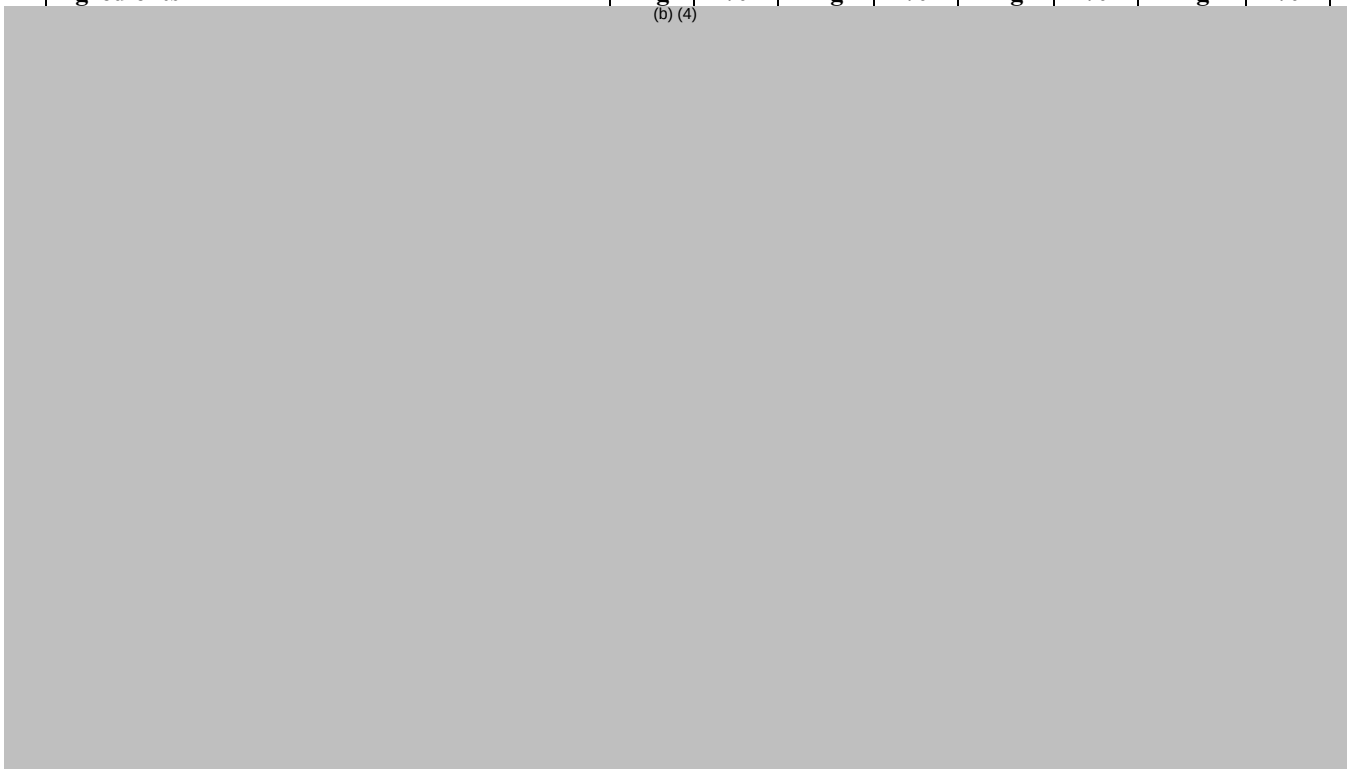
4.3.2. Original Formulation (Reviewed before)

NOT FOR RELEASE UNDER FOI

Formulations of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

	10 mg		20 mg		40 mg		80 mg	
Ingredients	**mg**	**%**	**mg**	**%**	**mg**	**%**	**mg**	**%**

(b) (4)



Is there an overage of the active pharmaceutical ingredient (API)?	No
If the answer is yes, has the appropriate chemistry division been notified?	N/A
If it is necessary to reformulate to reduce the overage, will bioequivalence be impacted?	N/A
Comments on the drug product formulation:	See Comments below.

Comments

- From its original acceptable formulation, the firm has made major changes in the polymorphic form, components and composition, manufacturing process and manufacturing site.
- (b) (4)
- As per labeling, one 10, 20, 40 or 80 mg dose per day is recommended. The daily intake of each inactive ingredient is calculated based on this information and is given in the table below.
- The excipients used in the formulation are within the IIG/MDD limits.
- The formulation is **acceptable**.

Excipient	Test Product		IIG Limit and Reference		Acceptable?
	Daily Intake, mg	mg/Unit dose	Daily Intake, mg	NDA/ANDA	
Lactose Monohydrate	(b) (4)				Yes
Microcrystalline Cellulose					Yes
Calcium Carbonate					Yes
Croscarmellose Sodium					Yes
Hydroxy-propyl Cellulose					Yes
Polysorbate-80					Yes
Magnesium Stearate					Yes
(b) (4)					Yes
Simethicone Emulsion (b) (4)					Yes
Candelilla Wax					Yes

4.4.Dissolution Data

Dissolution Review Path	See Tables below

Table 102. Dissolution Data – 10 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus: II
	Speed of Rotation:	75 rpm
	Medium:	pH 6.8 Phosphate buffer
	Volume:	900 ml
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	NLT (b) (4) (Q) of labeled amount of Atorvastatin is released in 15 minutes	
Dissolution Testing Site (Name, Address)	Ohm Laboratories, Inc. PO Box 7397 1385 Livingston Avenue **North Brunswick, New Jersey 08902** USA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date/Expiration Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**				**Study Report Location**
						5 min.	**10 min.**	**15 min.**	**30 min.**	
-	May 2009	Atorvastatin Calcium Tablets, 10 mg Batch No. RI530902 Manufacturing date – May, 2009 Expiration date – April, 2012	10 mg Tablet	12	Mean	91	97	98	99	NA
					Range	84-98	92-100	95-101	96-101	
					%CV	4.7	2.4	1.8	1.3	
-	June 2009	LIPITOR 10 mg Tablets (Innovator), Batch No. 20637V, Expiration date: November, 2010	10 mg Tablet	12	Mean	91	95	98	100	
					Range	84-95	88-99	92-101	97-102	
					%CV	4.0	3.3	2.2	1.4	

Table 103. Dissolution Data – 20 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus: II
	Speed of Rotation:	75 rpm
	Medium:	pH 6.8 Phosphate buffer
	Volume:	900 ml
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	NLT (b) (4) (Q) of labeled amount of Atorvastatin is released in 15 minutes	
Dissolution Testing Site (Name, Address)	Ohm Laboratories, Inc. PO Box 7397 1385 Livingston Avenue **North Brunswick, New Jersey 08902** USA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date/Expiration Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**				**Study Report Location**
						5 min.	**10 min.**	**15 min.**	**30 min.**	
-	May 2009	Atorvastatin Calcium Tablets, 20 mg Batch No. RI540901, Manufacturing date – May, 2009 Expiration date – April, 2012	20 mg Tablet	12	Mean	94	98	99	100	NA
					Range	91-99	94-101	96-101	98-102	
					%CV	2.6	2.2	1.6	1.3	
-	June 2009	LIPITOR 20 mg Tablets (Innovator), Batch No. 0509117, Expiration date: October, 2010	20 mg Tablet	12	Mean	91	97	98	100	
					Range	85-96	95-100	97-100	98-101	
					%CV	3.2	1.6	0.9	1.1	

Table 104. Dissolution Data – 40 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus: II
	Speed of Rotation:	75 rpm
	Medium:	pH 6.8 Phosphate buffer
	Volume:	900 ml
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	NLT (b) (4) (Q) of labeled amount of Atorvastatin is released in 15 minutes	
Dissolution Testing Site (Name, Address)	Ohm Laboratories, Inc. PO Box 7397 1385 Livingston Avenue **North Brunswick, New Jersey 08902** USA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date/Expiration Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**				**Study Report Location**
						5 min.	**10 min.**	**15 min.**	**30 min.**	
-	May 2009	Atorvastatin Calcium Tablets, 40 mg Batch No. RI550901, Manufacturing date – May, 2009 Expiration date – April, 2012	40 mg Tablet	12	Mean	89	96	97	98	NA
					Range	84-92	92-98	94-100	97-100	
					%CV	2.9	1.9	1.5	1.0	
-	June 2009	LIPITOR 40 mg Tablets (Innovator), Batch No. 0431117, Expiration date: October, 2010	40 mg Tablet	12	Mean	90	93	94	97	
					Range	85-95	91-96	92-96	95-98	
					%CV	3.4	2.0	1.5	1.2	

Table 105. Dissolution Data – 80 mg

Dissolution Conditions	**Apparatus:**	USP Apparatus: II
	Speed of Rotation:	75 rpm
	Medium:	pH 6.8 Phosphate buffer
	Volume:	900 ml
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	NLT (b) (4) (Q) of labeled amount of Atorvastatin is released in 15 minutes	
Dissolution Testing Site (Name, Address)	Ohm Laboratories, Inc. PO Box 7397 1385 Livingston Avenue **North Brunswick, New Jersey 08902** USA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date/Expiration Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**				**Study Report Location**
						5 min.	**10 min.**	**15 min.**	**30 min.**	
-	May 2009	Atorvastatin Calcium Tablets, 80 mg Batch No. RI560901, Manufacturing date – May, 2009 Expiration date – April, 2012	80 mg Tablet	12	Mean	88	96	99	100	NA
					Range	84-93	94-99	97-101	99-102	
					%CV	3.9	1.7	1.2	1.2	
-	June 2009	LIPITOR 80 mg Tablets (Innovator), Batch No. 04558V, Expiration date: March, 2011	80 mg Tablet	12	Mean	79	92	94	97	
					Range	71-85	87-95	90-96	94-100	
					%CV	6.0	2.4	1.8	1.9	

4.5.DSI Inspection Audit of the Clinical Site, Cetero Research, Fargo, ND

At the request of Division of Metabolic and Endocrine Products, the Division of Scientific Investigations conducted an audit of the following bioequivalence study:

Study Number: MPC-028-07-1007: A Single-Dose, Bioequivalence Study of 105 mg Fenofibric Acid Tablets Versus 145 mg TriCor® (Fenofibrate) Tablets Under Fasting Conditions

The clinical portion of the study was conducted at PRACS Institute-Cetero Research, Ltd., Fargo, ND. The analytical portion was conducted at (b) (4). Following the inspection at (b) (4), no Form FDA-483 was issued. Following the inspection at PRACS Institute-Cetero Research (March 24-26, 2009), Form FDA-483 was issued. The firm's response to Form FDA-483 was not received as of the date of this review. Our evaluation of the significant findings is as follows:

PRACS Institute-Cetero Research, Ltd., Fargo, ND

1. The firm failed to report to the IRB all unanticipated problems involving risk to human subjects.

For study MPC-028-07-1007, source records showed that subject #04 had a positive pregnancy test on November 3, 2007 at period II check in, and was dropped from the study prior to the start of period II.

During a post-study follow-up with subject #04, the firm was notified that the subject had a miscarriage, at which time the firm documented this as a serious adverse event (SAE). However, this SAE was never reported to the PRACS Institute, Ltd. IRB.

It is objectionable that this SAE (subject #04's miscarriage) was not reported to the IRB. Subject #04's discontinuation and miscarriage was discussed in the study report.

It should be noted that subject #04 participated in period I, however she tested negative for pregnancy at screening and period I check in. Furthermore, the firm's SAE report indicates that subject #04 received the reference drug (TriCor®) during period I.

2. Failure to prepare or maintain accurate case histories with respect to observations and data pertinent to the investigation.

For study MPC-028-07-1007, the firm changed 50 of the 54 subjects' case report forms (CRFs) from meeting inclusion/exclusion criteria to not meeting inclusion/exclusion criteria for medical history, physical examinations, clinical laboratory test results, clinically significant vital sign measurements and ECG parameters. Changes to the CRFs were done on 7/25/08, more than 8 months after those 50 subjects completed the study.

Additionally, a protocol deviation log was created on 7/28/08 indicating that the 50 CRFs were changed due to "Misinterpretation of protocol". However, the firm's records do not indicate how this assessment was made. Furthermore, the firm's records do not indicate any correspondence with the sponsor regarding these changes.

As per the protocol, subjects not meeting health screening criteria can not be included in the study. Therefore, it is objectionable that:

- 50 out of 54 subjects not meeting the eligibility criteria were allowed to participate in the study
- The case report forms were modified more than 8 months after completion of the study without documented justification
- The site created a protocol deviation log for those 50 subjects citing "misinterpretation of protocol" without further clarification

It should be noted that the 50 subjects deviating from inclusion/exclusion criteria are listed in the final report.

Conclusion:

Following the above inspections, the Division of Scientific Investigations concludes the following:

- It is objectionable that PRACS Institute-Cetero Research failed to report subject #04's miscarriage to the IRB and failed to completely assure subject safety. As per the protocol, the IRB should be notified of all SAEs.[1] Furthermore, DSI plans to follow-up and determine if the firm has implemented corrective actions by reporting all SAEs to the IRB.
- It is objectionable that the firm changed 50 of the 54 subjects' CRFs from being study eligible to being study ineligible without clarification, more than 8 months after study completion. DSI recommends that the review division evaluate the extent of these subject deviations, and also consider the impact of enrolling these ineligible subjects.

4.6.DSI Inspection of Analytical Site, (b) (4) (b) (4)

Study (b) (4) was in NDA (b) (4) and Studies (b) (4) were in NDA (b) (4) The clinical portion of Study (b) (4) was conducted by (b) (4) (b) (4). The clinical portions of Studies (b) (4) and the analytical portions of all three studies were conducted by (b) (4) (b) (4). It should be noted that in 2007, the clinical and analytical facilities of (b) (4) were moved from (b) (4) (b) (4)

Following the inspections, no Form FDA-483 was issued at (b) (4) and no significant finding in the clinical conduct of Study (b) (4) was found. At (b) (4), no significant clinical observation was identified. However, an objectionable analytical finding was uncovered and Form FDA-483 was issued to (b) (4) (Attachment 1). The Form FDA-483 item and DSI evaluation follow.

(b) (4)

1. Failure to investigate discrepancies in stability data generated during method validation. For example, (b) (4) was found stable at -20°C for 402 days but was found unstable after storage at -80°C for the same time period. (b) (4) in plasma was found stable at room temperature for 25 hours, but another experiment showed (b) (4) was unstable after storage at 4°C for 24 hours.

(b) (4) acknowledged the observation and conducted an investigation during the FDA inspection to examine the discrepancies. No documented errors in the stability experiments were identified. Consequently, (b) (4) decided to re-evaluate the long term storage stability of (b) (4) using samples stored previously at -80°C. A second experiment for confirmation purpose was also conducted. The results of both experiments showed (b) (4) were stable at -80°C for up to 585 days. Similarly, another two new experiments (i.e., one for repeat evaluation and one for confirmation) were conducted for short-term storage stability, and the results showed (b) (4) was stable in plasma samples stored at 4°C for up to 24 hours.

Conclusion:

3. The analytical observation cited in the Form FDA-483 should not have significant impact on the outcomes of the studies.

4.11. Additional Attachments

NOTE for PM

The firm is under AIP for products manufactured at Paonta Saheb facilities and for unapproved products. Therefore, please hold the letter until the firm obtains clearance from the FDA. Thanks.

BIOEQUIVALENCE DEFICIENCY

ANDA:	076477
APPLICANT:	Ranbaxy Laboratories Ltd.
DRUG PRODUCT:	Atorvastatin Calcium Tablet 10, 20 , 40 and 80 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

Your dissolution testing data using the FDA-recommended method are insufficiently discriminating, with greater than 85% of the drug in the dosage form dissolved in 10 minutes. Therefore, please conduct additional dissolution testing for 12 units of each strength of the test and reference products using the decreased paddle speed of 50 rpm, as follows:

Medium: 0.05M Phosphate Buffer, pH 6.8 at 37^{0}C
Volume: 900 mL
USP Apparatus: II (Paddle) at 50 rpm
Recommended Sampling Times: 10, 15, 20, 30, 45 minutes and until at least (b) (4) dissolved.

[NOTE: The method should use conventional USP II Vessels, and not (b) (4) Vessels]

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.12. Outcome Page

ANDA: 076477

5. COMPLETED ASSIGNMENT FOR 076477 ID: 13597

Reviewer: Shrivastava, Surendra **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Atorvastatin Calcium Tablets

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal		
13597	12/9/2009	Bioequivalence Study	Fasting Study	1	1	Edit	Delete
13597	12/9/2009	Bioequivalence Study	Fed Study	1	1	Edit	Delete
13597	12/9/2009	Other	Dissolution Review	1	1	Edit	Delete
13597	12/9/2009	Other	Dissolution Waiver	1	1	Edit	Delete
13597	12/9/2009	Other	Dissolution Waiver	1	1	Edit	Delete
13597	12/9/2009	Other	Dissolution Waiver	1	1	Edit	Delete
13597	12/9/2009	Bioequivalence Study	Fasting Study	1	1	Edit	Delete
13597	12/9/2009	Bioequivalence Study	Fed Study	1	1	Edit	Delete
13597	12/9/2009	Bioequivalence Study	Fasting Study	1	1	Edit	Delete
13597	12/9/2009	Bioequivalence Study	Fasting Study	1	1	Edit	Delete
13597	12/9/2009	Other	DSI Inspection Report	1	1	Edit	Delete
13597	12/9/2009	Other	DSI Inspection Report	1	1	Edit	Delete
				Bean Total:	12		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURENDRA P SHRIVASTAVA
04/19/2011

YIH CHAIN HUANG
05/03/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
05/04/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	076477					
Drug Product Name	Atorvastatin Calcium Tablets					
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg					
Applicant Name	Ranbaxy Laboratories Ltd., India					
Address	Plot # GP-5, Sector 18, HSIDC, Old Delhi, Gurgaon Road, Gurgaon, 122015, Hariyana, India					
Applicant's Point of Contact	Usha Sankaran, US Agent, 600 College Road East, Ranbaxy Inc., Princeton, NJ 08540					
Contact's Telephone Number	609-720-5304					
Contact's Fax Number	609-514-9797					
Original Submission Date(s)	August 19, 2002 December 9, 2009					
Submission Date(s) of Amendment(s) Under Review	**November 12, 2010** **(API Change-Additional Dissolution Data for all Strengths)**					
Reviewer	S. P. Shrivastava, Ph.D.					
Study Number (s)	**R09-1032**	**R09-1033**	**BE-248-ATOR-2009**	**BE-249-ATOR-2009**	**365-ATORV-09**	**3023-ATORV-08**
Study Type (s)	Fasting	Fed	Fasting	Fed	Fasting	Fed
Strength (s)	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg
Clinical Site	**Cetero Research**		**Clinical Services Fortis Clinical Research Ltd.**		**Ranbaxy Labs. Ltd.**	
Clinical Site Address	4801 Amber Valley Pkwy. Fargo, ND 58104		Ltd., Sunflag Hospital & Research Centre Sector-16A, Faridabad 121 002, Haryana, India		Majeedia Hospital, Hamdard Nagar New Delhi India	
Analytical Site	(b) (4)				**Ranbaxy Labs. Ltd**	
Analytical Site Address					Plot No. GP-5, Sector 18, HSIDC, Gurgaon, Haryana, India	
Dissolution Testing Site	Ranbaxy Laboratory Ltd.					
DSI Inspection Status	No DSI inspection is pending or necessary					
Overall Review Result	**INADEQUATE**					
Waiver Request Result	**INADEQUATE :** 10, 20 and 40 mg					
DSI Report Result	**Clinical: ADEQUATE.** **Analytical: ADEQUATE**					

Bioequivalence Study Tracking/Supporting Document #	**Study/Test Type**	**Strength**	**Review Result**
Supporting Document #57, 58	**Dissolution**	80 mg	**INADEQUATE**
	Dissolution	40 mg	**INADEQUATE**
	Dissolution	20 mg	**INADEQUATE**
	Dissolution	10 mg	**INADEQUATE**
Supporting Document	**Fasting (Pivotal)**	80 mg	**ADEQUATE**

# 57			
	Fed (Pivotal)	80 mg	**ADEQUATE**
	Pilot Fasting (BE-248-ATOR-2009)	80 mg	**INADEQUATE**
	Pilot Fed (BE-249-ATOR-2009)	80 mg	**INADEQUATE**
	Pilot Fasting (365-ATORV-09)	80 mg	**INADEQUATE**
	Pilot Fasting (3023-ATORV-08)	80 mg	**INADEQUATE**
	Permeability Study	**N/A**	**N/A**
	Solubility Study	**N/A**	**N/A**

1. EXECUTIVE SUMMARY

This application references Atorvastatin Calcium Tablets, 10, 20, 40 and 80 mg [Lipitor®, Pfizer, NDA 020702, Approved 10, 20 mg, 40 mg-12/17/1996; 80 mg-4/7/2000 (RLD)]. The firm had previously conducted acceptable single-dose fasting and fed studies on 80 mg tablets, and dissolution testing results on all strengths [see JEChaney, C:\Documents and Settings\shrivastavas\My Documents\076477A1110.doc, C:\Documents and Settings\shrivastavas\My Documents\076477A1110.doc, SHRIVASTAVA, SURENDRA P 09/27/2007 N/A 09/27/2007 REV-BIOEQ-01(General Review) Original-1, SHRIVASTAVA, SURENDRA P 06/19/2008 N/A 06/19/2008 REV-BIOEQ-01(General Review) Original-1]. In the 12/09/2009 amendment, the firm made CMC changes (polymorphic form, component and composition, manufacturing process and manufacturing site). In support of the CMC changes the firm submitted additional single-dose fasting and fed studies on 80 mg strength and requested waivers of BE studies for 10, 20 and 40 mg tablets. The fasting and fed studies were found acceptable [see DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1]. NOTE: The test product in these additional BE studies used the API from (b) (4) (crystalline form). The dissolution testing was found inadequate due to insufficiently discriminatory method. In this amendment, the firm has proposed additional source of APIs (Ranbaxy Labs., DMF 24139) for Atorvastatin Calcium, USP (crystalline), manufactured by two different processes. In support of these changes, the firm has provided comparative dissolution data for Test (Ranbaxy's APIs by Process-I and Process-II) and Reference ((b) (4) API) products.

There is an FDA-recommended dissolution method (900 mL of 0.05 Phosphate buffer at pH 6.8 and Paddle at 75 rpm). In the original application (submission date 08/19/2002), the firm used the conventional USP vessels, and in 09/13/22006 amendment, it proposed to use (b) (4) Vessels instead of USP-2 Vessels for dissolution testing, which was found acceptable (see the reviews -v:\firmsnz\ranbaxy\ltrs&rev\76477n0802.doc; v:\firmsnz\ranbaxy\ltrs&rev\76477a0503.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0906.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0807.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0108.doc). In the 12/09/2009 amendment, the firm submitted dissolution testing comparing its newly formulated test product ((b) (4) API) and the RLD using the FDA-recommended method [USP Apparatus-II (Paddle) at 75 rpm, instead of the (b) (4) Vessels]. As indicated above, firm's dissolution testing with the FDA recommended method was found inadequate due to insufficiently discriminatory method [see DARRTS, ANDA 076477, Submission date

12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

The firm's dissolution testing method is non-discriminatory. Thus, >85% of the drug in the dosage form dissolves in 10 minutes. Therefore, the firm is requested to conduct dissolution testing as follows using the Paddle speed at 50 rpm:

Medium:	0.05M Phosphate Buffer, pH 6.8 at 37 ^{0}C
Volume:	900 mL
USP Apparatus:	II (Paddle) at 50 rpm
Dosage Units:	12 each for Test and Reference

[NOTE: The method should use conventional USP Apparatus II Vessels (Paddle), and not (b) (4) Vessels]

Since the firm has not been informed of the deficiency found in the previous submission [see DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1], and deficiencies from both the submissions (dated 12/09/2009 and 11/12/2010) are similar, deficiencies are combined in the same letter attached to the current review.

2. TABLE OF CONTENTS

3. SUBMISSION SUMMARY

3.1. Drug Product Information

[See DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

3.2.PK/PD Information

[See DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

3.3.Contents of Submission

Study Types	Yes/No?	How many?
Single-dose fasting	No	---
Single-dose fed	No	---
Steady-state	No	--
In vitro dissolution	Yes	8
Waiver requests	No	---
BCS Waivers	No	--
Clinical Endpoints	No	--
Failed Studies	---	---
Amendments	No	---
Pilot Studies	No	---

3.4. In Vitro Dissolution

In the current amendment, the firm has used the FDA recommended method as follows:

Location of DBE Dissolution Review	See Appendix, Section 4.1, Dissolution Data
Source of Method (USP, FDA or Firm)	**FDA**
Medium	0.05 M Phosphate buffer, pH 6.8 @ 37°C
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
Firm's specification	NLT (b) (4) (Q) in 15 minutes
DBE-recommended specification	Will be set based on complete data.
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	No
If no, reason why F2 not calculated	Fast dissolving (>85% in 10 minutes)
Is method acceptable?	No
If not then why?	Method non-discriminatory. Requesting additional data.

F2 metric, biostudy strengths compared to other strength(s)			
Biostudy Strength	**Other Strength**	**F2 metric for test**	**F2 metric for RLD**
Fast dissolving (>85% in 15 minutes)			

There is an FDA-recommended dissolution method (900 mL of 0.05 Phosphate buffer at pH 6.8 and Paddle at 75 rpm). In the original application (submission date 08/19/2002), the firm used the conventional USP vessels, and in 09/13/22006 amendment, it proposed to use (b) (4) Vessels instead of USP-2 Vessels for dissolution testing, which was found acceptable (see the reviews -v:\firmsnz\ranbaxy\ltrs&rev\76477n0802.doc; v:\firmsnz\ranbaxy\ltrs&rev\76477a0503.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0906.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0807.doc; V:\firmsnz\ranbaxy\ltrs&rev\76477a0108.doc).

It should be noted that since the time the above dissolution method with (b) (4) vessels was accepted, the DBE has changed its recommendation regarding the use of (b) (4) vessels. Currently, (b) (4) vessels are not recommended for release and stability dissolution testing since (b) (4) vessels are not compendial vessels and have not been adequately standardized.

In the 12/09/2009 amendment, the firm submitted dissolution testing comparing its newly formulated test product (b) (4) API) and the RLD using the FDA-recommended method [USP Apparatus-II (Paddle) at 75 rpm, and conventional USP Vessels instead of the (b) (4) Vessels]. Firm's dissolution testing with the FDA recommended method was found inadequate due to insufficiently discriminatory method [see DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

The dissolution testing on lots manufactured with Ranbaxy APIs (Process-I and Process-II) with the FDA recommended method is also inadequate because the method is not sufficiently discriminatory. Therefore, the firm is requested to conduct additional dissolution testing with the reduced paddle speed of 50 rpm (see Deficiency Comments).

3.5.Deficiency Comments

Since the firm has not been informed of the deficiency found in the previous submission [see DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1], and deficiencies from both the submissions, dated 12/9/2009 and 11/12/2010, are similar, deficiencies are combined in the same letter for the three Test products manufactured with three different APIs (b) (4) API (12/9/2009 submission), Ranbaxy Process-I and Ranbaxy Process-II APIs (current 11/12/2010 submission). The deficiency letter related to both amendments is attached in the current review.

1. The dissolution testing data based on the FDA-recommended method were insufficiently discriminating with greater than 85% of the drug in the dosage form dissolved in 10 minutes. Therefore, the firm is requested to conduct additional dissolution testing with the decreased paddle speed of 50 rpm:

   Medium: 0.05M Phosphate Buffer, pH 6.8 at 37 ^{0}C
   Volume: 900 mL
   USP Apparatus: II (Paddle) at 50 rpm
   Dosage Units: 12 each for Test and Reference of all strengths
   Recommended Sampling Times: 10, 15, 20, 30, 45 minutes and until at least (b) (4) is dissolved.

3.6.Recommendations

1. The dissolution testing conducted by Ranbaxy Laboratories Ltd. on its Atorvastatin Calcium, 10, 20, 40 and 80 mg Tablets, manufactured with Ranbaxy's APIs, comparing them with its original products manufactured with (b) (4) API Tablets, 10, 20, 40 and 80 mg Tablets, respectively, is **inadequate** due to deficiency #1 cited above.

2. The Division of Bioequivalence has previously **accepted** the fasting BE study (R09-1032) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #R1560901 (with (b) (4) API) comparing it to Pfizer, Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V.

3. The Division of Bioequivalence has previously **accepted** the fed BE study (R09-1033) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #R1560901 (with (b) (4) API) comparing it to Pfizer, Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V.

4. The Division of Bioequivalence has previously acknowledged the pilot fasting BE study (BE-248-ATOR-2009) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #B204130 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA), and Canada Lipitor®, 80 mg, Lot # B0378088 (Pfizer, Canada).

5. The Division of Bioequivalence has previously acknowledged the pilot fed BE study (BE-249-ATOR-2009) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #B204130 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA).

6. The Division of Bioequivalence has previously acknowledged the pilot fasting BE study (365-_ATORV_09) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #ANK (3926)071A comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V (Pfizer, USA), and Belgium Lipitor®, 80 mg, Lot # 0904118B (Pfizer, Belgium).

7. The Division of Bioequivalence has previously acknowledged the pilot fasting BE study (3023-_ATORV_08) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #ANK (3926)049 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA).

8. The dissolution testing previously conducted by Ranbaxy Laboratories Ltd. on its Atorvastatin Calcium, 10, 20, 40 and 80 mg Tablets, manufactured with (b) (4) API, comparing it with Pfizer's Lipitor® Tablets, 10, 20, 40 and 80 mg Tablets, respectively, was also found inadequate due to deficiency #1 cited above.

9. The formulations for the 10, 20 and 40 mg strengths were found (b) (4) to the 80 mg strength of the test product which underwent bioequivalence testing. The waivers of in vivo bioequivalence study requirements for 10, 20 and 40 mg strength Tablets of the test product cannot be granted at this time due to inadequate dissolution data.

3.7.Comments for Other OGD Disciplines

Discipline	Comment
Chemistry	From its original acceptable formulation, the firm has made major changes in polymorphic form, components and composition, manufacturing process and manufacturing site. Therefore, the Chemistry should look into the CMC aspects.

4. APPENDIX

4.1.Dissolution Data

Dissolution Review Path	See Tables below

Comparative dissolution testing results for Test products (Ranbaxy's API Process-I and II), and Reference ((b) (4) API) products are provided in Tables 1-8. The summary of comparative dissolution data for the reformulated Test products ((b) (4) API) and Reference (Pfizer's Lipitor®) is also included here from the previous review for completeness [see DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1; Tables 9-12].

Table 1. Dissolution Data – 10 mg (Ranbaxy's API , Process-1)

COMPARATIVE DISSOLUTION PROFILES OF ATORVASTATIN CALCIUM TABLETS AND ATORVASTATIN CALCIUM TABLETS

Product	:Atorvastatin Calcium Tablets,10mg	Product	:Atorvastatin Calcium Tablets,10mg
B.No	:RI530902-Composite-Coated	B.No	:RI531002-Composite-Coated
Mfg. Date	:05/2009	Mfg. Date	:02/2010
Expiry Date	:04/2011	Expiry Date	:01/2012

	Atorvastatin Calcium Tablets; B.No:RI530902,10mg Manufactured by: OHM Laboratories Inc. % Atorvastatin dissolved in				Atorvastatin Calcium Tablets; B.No:RI531002,10mg Manufactured by: OHM Laboratories Inc. % Atorvastatin dissolved in			
Vessel #	**5min**	**10min**	**15 min**	**30 min**	**5min**	**10min**	**15 min**	**30 min**
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	**91**	**97**	**98**	**99**	**84**	**90**	**93**	**96**
%RSD	4.7	2.4	1.8	1.3	3.2	1.3	1.8	1.5
Maximum	(b) (4)							
Minimum								
Date of Analysis	05/20/09				02/18/10			
Reference	B:2015, P:12-13				B:2146, P:240-241			

Dissolution Parameters

Apparatus	:USP Apparatus II(Paddles)
Medium	:0.05M Phosphate Buffer(pH 6.8)
Volume	:900 mL
Rotational Speed	:75 rpm
Temparature	:37±0.5°C
Specification:	NLT (b) (4) (Q) of the labeled claim of Atorvastatin dissolved in 15 minutes.

04/07/10 04/08/10

Table 2. Dissolution Data – 20 mg (Ranbaxy's API , Process-1)

COMPARATIVE DISSOLUTION PROFILES OF ATORVASTATIN CALCIUM TABLETS AND ATORVASTATIN CALCIUM TABLETS

Product	:Atorvastatin Calcium Tablets,20mg	Product	:Atorvastatin Calcium Tablets,20mg
B.No	:RI540901-Composite-Coated	B.No	:RI541001-Composite-Coated
Mfg. Date	:05/2009	Mfg. Date	:02/2010
Expiry Date	:04/2011	Expiry Date	:01/2012

	Atorvastatin Calcium Tablets; B.No:RI540901,20mg				Atorvastatin Calcium Tablets; B.No:RI541001,20mg			
	Manufactured by: OHM Laboratories Inc.				Manufactured by: OHM Laboratories Inc.			
	% Atorvastatin dissolved in				% Atorvastatin dissolved in			
Vessel #	**5min**	**10min**	**15 min**	**30 min**	**5min**	**10min**	**15 min**	**30 min**
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	**94**	**98**	**99**	**100**	**82**	**89**	**92**	**96**
%RSD	2.6	2.2	1.6	1.3	5.8	2.8	1.6	2.7
Maximum	(b) (4)							
Minimum								
Date of Analysis	05/26/09				02/22/10			
Reference	B:2015,P:32-33				B:2246, P:59-60			

Dissolution Parameters

Apparatus	:USP Apparatus II(Paddles)
Medium	:0.05M Phosphate Buffer(pH 6.8)
Volume	:900 mL
Rotational Speed	:75 rpm
Temparature	:37±0.5°C
Specification:	NLT (b) (4) (Q) of the labeled claim of Atorvastatin dissolved in 15 minutes.

04/07/10 04/08/10

Table 3. Dissolution Data – 40 mg (Ranbaxy's API , Process-1)

COMPARATIVE DISSOLUTION PROFILES OF ATORVASTATIN CALCIUM TABLETS AND ATORVASTATIN CALCIUM TABLETS

Product	:Atorvastatin Calcium Tablets,40mg	Product	:Atorvastatin Calcium Tablets,40mg
B.No	:RI550901-Composite-Coated	B.No	:RI551001-Composite-Coated
Mfg. Date	:05/2009	Mfg. Date	:02/2010
Expiry Date	:04/2011	Expiry Date	:01/2012

	Atorvastatin Calcium Tablets; B.No:RI550901,40mg Manufactured by: OHM Laboratories Inc. % Atorvastatin dissolved in				Atorvastatin Calcium Tablets; B.No:RI551001,40mg Manufactured by: OHM Laboratories Inc. % Atorvastatin dissolved in			
Vessel #	**5min**	**10min**	**15 min**	**30 min**	**5min**	**10min**	**15 min**	**30 min**
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	**89**	**96**	**97**	**98**	**77**	**87**	**91**	**94**
%RSD	2.9	1.9	1.5	1.0	5.6	2.5	1.9	0.8
Maximum	(b) (4)							
Minimum								
Date of Analysis	05/28/09				02/23/10			
Reference	B:2015,P:38-39				B:2246, P:65-66			

Dissolution Parameters

Apparatus	:USP Apparatus II(Paddles)
Medium	:0.05M Phosphate Buffer(pH 6.8)
Volume	:900 mL
Rotational Speed	:75 rpm
Temparature	:37±0.5°C
Specification:	NLT (b) (4) (Q) of the labeled claim of Atorvastatin dissolved in 15 minutes.

04/07/10 04/08/10

Table 4. Dissolution Data – 80 mg (Ranbaxy's API , Process-1)

COMPARATIVE DISSOLUTION PROFILES OF ATORVASTATIN CALCIUM TABLETS AND ATORVASTATIN CALCIUM TABLETS

Product	:Atorvastatin Calcium Tablets,80mg	Product	:Atorvastatin Calcium Tablets,80mg
B.No	:RI560901-Composite-Coated	B.No	:RI561001-Composite-Coated
Mfg. Date	:05/2009	Mfg. Date	:02/2010
Expiry Date	:04/2011	Expiry Date	:01/2012

	Atorvastatin Calcium Tablets; B.No:RI560901,80mg				Atorvastatin Calcium Tablets; B.No:RI561001,80mg			
	Manufactured by: OHM Laboratories Inc.				Manufactured by: OHM Laboratories Inc.			
	% Atorvastatin dissolved in				% Atorvastatin dissolved in			
Vessel #	**5min**	**10min**	**15 min**	**30 min**	**5min**	**10min**	**15 min**	**30 min**
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	**88**	**96**	**99**	**100**	**76**	**86**	**89**	**93**
%RSD	3.9	1.7	1.2	1.2	6.9	2.2	1.4	1.4
Maximum	(b) (4)							
Minimum								
Date of Analysis	05/28/09				02/24/10			
Reference	B:2015,P:44-45				B:2246, P:72-73			

Dissolution Parameters

Apparatus	:USP Apparatus II(Paddles)
Medium	:0.05M Phosphate Buffer(pH 6.8)
Volume	:900 mL
Rotational Speed	:75 rpm
Temparature	:37±0.5°C
Specification:	NLT (b) (4) (Q) of the labeled claim of Atorvastatin dissolved in 15 minutes.

04/07/10 04/08/10

Table 5. Dissolution Data – 10 mg (Ranbaxy's API , Process-I1)

COMPARATIVE DISSOLUTION PROFILES OF ATORVASTATIN CALCIUM TABLETS AND ATORVASTATIN CALCIUM TABLETS

Product	:Atorvastatin Calcium Tablets,10mg	Product	:Atorvastatin Calcium Tablets,10mg
B.No	:RI530902-Composite-Coated	B.No	:RI531004-Composite-Coated
Mfg. Date	:05/2009	Mfg. Date	:03/2010
Expiry Date	:04/2011	Expiry Date	:02/2012

	Atorvastatin Calcium Tablets; B.No:RI530902,10mg Manufactured by: OHM Laboratories Inc. % Atorvastatin dissolved in				Atorvastatin Calcium Tablets; B.No:RI531004,10mg Manufactured by: OHM Laboratories Inc. % Atorvastatin dissolved in			
Vessel #	**5min**	**10min**	**15 min**	**30 min**	**5min**	**10min**	**15 min**	**30 min**
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	**91**	**97**	**98**	**99**	**91**	**97**	**98**	**99**
%RSD	4.7	2.4	1.8	1.3	4.5	1.4	1.1	0.9
Maximum								
Minimum								
Date of Analysis	05/20/09				03/19/10 and 03/26/10			
Reference	B:2015, P:12-13				B:2246, P:134 and B:2259, P:104			

(b) (4)

Dissolution Parameters

Apparatus	:USP Apparatus II(Paddles)
Medium	:0.05M Phosphate Buffer(pH 6.8)
Volume	:900 mL
Rotational Speed	:75 rpm
Temparature	:37±0.5°C
Specification:	NLT (b) (4) (Q) of the labeled claim of Atorvastatin dissolved in 15 minutes.

04/07/10 04/08/10

Table 6. Dissolution Data – 20 mg (Ranbaxy's API , Process-I1)

COMPARATIVE DISSOLUTION PROFILES OF ATORVASTATIN CALCIUM TABLETS AND ATORVASTATIN CALCIUM TABLETS

Product	:Atorvastatin Calcium Tablets,20mg	Product	:Atorvastatin Calcium Tablets,20mg
B.No	:RI540901-Composite-Coated	B.No	:RI541002-Composite-Coated
Mfg. Date	:05/2009	Mfg. Date	:03/2010
Expiry Date	:04/2011	Expiry Date	:02/2012

	Atorvastatin Calcium Tablets; B.No:RI540901,20mg				Atorvastatin Calcium Tablets; B.No:RI541002,20mg			
	Manufactured by: OHM Laboratories Inc.				Manufactured by: OHM Laboratories Inc.			
	% Atorvastatin dissolved in				% Atorvastatin dissolved in			
Vessel #	**5min**	**10min**	**15 min**	**30 min**	**5min**	**10min**	**15 min**	**30 min**
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	**94**	**98**	**99**	**100**	**92**	**98**	**98**	**99**
%RSD	2.6	2.2	1.6	1.3	3.5	2.3	1.5	1.1
Maximum	(b) (4)							
Minimum								
Date of Analysis	05/26/09				03/25/10 and 04/06/10			
Reference	B:2015,P:32-33				B:2246, P:146 and B:2258, P:54			

Dissolution Parameters

Apparatus	:USP Apparatus II(Paddles)
Medium	:0.05M Phosphate Buffer(pH 6.8)
Volume	:900 mL
Rotational Speed	:75 rpm
Temparature	:37±0.5°C
Specification:	NLT (b) (4) (Q) of the labeled claim of Atorvastatin dissolved in 15 minutes.

04/07/10 04/08/10

Table 7. Dissolution Data – 40 mg (Ranbaxy's API , Process-I1)

COMPARATIVE DISSOLUTION PROFILES OF ATORVASTATIN CALCIUM TABLETS AND ATORVASTATIN CALCIUM TABLETS

Product	:Atorvastatin Calcium Tablets,40mg	Product	:Atorvastatin Calcium Tablets,40mg
B.No	:RI550901-Composite-Coated	B.No	:RI551002-Composite-Coated
Mfg. Date	:05/2009	Mfg. Date	:03/2010
Expiry Date	:04/2011	Expiry Date	:02/2012

	Atorvastatin Calcium Tablets; B.No:RI550901,40mg Manufactured by: OHM Laboratories Inc. % Atorvastatin dissolved in				Atorvastatin Calcium Tablets; B.No:RI551002,40mg Manufactured by: OHM Laboratories Inc. % Atorvastatin dissolved in			
Vessel #	**5min**	**10min**	**15 min**	**30 min**	**5min**	**10min**	**15 min**	**30 min**
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	**89**	**96**	**97**	**98**	**87**	**94**	**97**	**98**
%RSD	2.9	1.9	1.5	1.0	5.8	2.8	1.0	1.1
Maximum	(b) (4)							
Minimum								
Date of Analysis	05/28/09				03/25/10 and 04/04/10			
Reference	B:2015,P:38-39				B:2246, P:147 and B:2258, P:55			

Dissolution Parameters

Apparatus	:USP Apparatus II(Paddles)
Medium	:0.05M Phosphate Buffer(pH 6.8)
Volume	:900 mL
Rotational Speed	:75 rpm
Temparature	:37±0.5°C
Specification:	NLT (b) (4) (Q) of the labeled claim of Atorvastatin dissolved in 15 minutes.

04/07/10 04/08/10

Table 8. Dissolution Data – 80 mg (Ranbaxy's API , Process-I1)

COMPARATIVE DISSOLUTION PROFILES OF ATORVASTATIN CALCIUM TABLETS AND ATORVASTATIN CALCIUM TABLETS

Product	:Atorvastatin Calcium Tablets,80mg	Product	:Atorvastatin Calcium Tablets,80mg
B.No	:RI560901-Composite-Coated	B.No	:RI561002-Composite-Coated
Mfg. Date	:05/2009	Mfg. Date	:03/2010
Expiry Date	:04/2011	Expiry Date	:02/2012

	Atorvastatin Calcium Tablets; B.No:RI560901,80mg				Atorvastatin Calcium Tablets; B.No:RI561002,80mg			
	Manufactured by: OHM Laboratories Inc.				Manufactured by: OHM Laboratories Inc.			
	% Atorvastatin dissolved in				% Atorvastatin dissolved in			
Vessel #	**5min**	**10min**	**15 min**	**30 min**	**5min**	**10min**	**15 min**	**30 min**
1	(b) (4)							
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
Mean	**88**	**96**	**99**	**100**	**80**	**92**	**96**	**98**
%RSD	3.9	1.7	1.2	1.2	4.9	2.4	1.4	1.3
Maximum	(b) (4)							
Minimum								
Date of Analysis	05/28/09				03/25/10 and 04/02/10			
Reference	B:2015,P:44-45				B:2246, P:148 and B:2258, P:64			

Dissolution Parameters

Apparatus	:USP Apparatus II(Paddles)
Medium	:0.05M Phosphate Buffer(pH 6.8)
Volume	:900 mL
Rotational Speed	:75 rpm
Temparature	:37±0.5°C
Specification:	NLT (b) (4) (Q) of the labeled claim of Atorvastatin dissolved in 15 minutes.

04/07/10 04/08/10

Table 9. Dissolution Data – 10 mg ((b) (4) API)

Dissolution Conditions	**Apparatus:**	USP Apparatus: II
	Speed of Rotation:	75 rpm
	Medium:	pH 6.8 Phosphate buffer
	Volume:	900 ml
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	NLT (b) (4) (Q) of labeled amount of Atorvastatin is released in 15 minutes	
Dissolution Testing Site (Name, Address)	Ohm Laboratories, Inc. PO Box 7397 1385 Livingston Avenue **North Brunswick, New Jersey 08902** USA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date/Expiration Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**				**Study Report Location**
						5 min.	**10 min.**	**15 min.**	**30 min.**	
-	May 2009	Atorvastatin Calcium Tablets, 10 mg Batch No. RI530902 Manufacturing date – May, 2009 Expiration date – April, 2012	10 mg Tablet	12	Mean	91	97	98	99	NA
					Range	84-98	92-100	95-101	96-101	
					%CV	4.7	2.4	1.8	1.3	
-	June 2009	LIPITOR 10 mg Tablets (Innovator), Batch No. 20637V, Expiration date: November, 2010	10 mg Tablet	12	Mean	91	95	98	100	
					Range	84-95	88-99	92-101	97-102	
					%CV	4.0	3.3	2.2	1.4	

Table 10. Dissolution Data – 20 mg (b) (4) API)

Dissolution Conditions	**Apparatus:**	USP Apparatus: II
	Speed of Rotation:	75 rpm
	Medium:	pH 6.8 Phosphate buffer
	Volume:	900 ml
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	NLT (b) (4) (Q) of labeled amount of Atorvastatin is released in 15 minutes	
Dissolution Testing Site (Name, Address)	Ohm Laboratories, Inc. PO Box 7397 1385 Livingston Avenue **North Brunswick, New Jersey 08902** USA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date/Expiration Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours) 5 min.**	**10 min.**	**15 min.**	**30 min.**	**Study Report Location**
-	May 2009	Atorvastatin Calcium Tablets, 20 mg Batch No. RI540901, Manufacturing date – May, 2009 Expiration date – April, 2012	20 mg Tablet	12	Mean	94	98	99	100	NA
					Range	91-99	94-101	96-101	98-102	
					%CV	2.6	2.2	1.6	1.3	
-	June 2009	LIPITOR 20 mg Tablets (Innovator), Batch No. 0509117, Expiration date: October, 2010	20 mg Tablet	12	Mean	91	97	98	100	
					Range	85-96	95-100	97-100	98-101	
					%CV	3.2	1.6	0.9	1.1	

Table 11. Dissolution Data – 40 mg ((b) (4) API)

Dissolution Conditions	**Apparatus:**	USP Apparatus: II
	Speed of Rotation:	75 rpm
	Medium:	pH 6.8 Phosphate buffer
	Volume:	900 ml
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	NLT (b) (4) (Q) of labeled amount of Atorvastatin is released in 15 minutes	
Dissolution Testing Site (Name, Address)	Ohm Laboratories, Inc. PO Box 7397 1385 Livingston Avenue **North Brunswick, New Jersey 08902** USA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date/Expiration Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**				**Study Report Location**
						5 min.	**10 min.**	**15 min.**	**30 min.**	
-	May 2009	Atorvastatin Calcium Tablets, 40 mg Batch No. RI550901, Manufacturing date – May, 2009 Expiration date – April, 2012	40 mg Tablet	12	Mean	89	96	97	98	NA
					Range	84-92	92-98	94-100	97-100	
					%CV	2.9	1.9	1.5	1.0	
-	June 2009	LIPITOR 40 mg Tablets (Innovator), Batch No. 0431117, Expiration date: October, 2010	40 mg Tablet	12	Mean	90	93	94	97	
					Range	85-95	91-96	92-96	95-98	
					%CV	3.4	2.0	1.5	1.2	

Table 12. Dissolution Data – 80 mg ((b) (4) API)

Dissolution Conditions	**Apparatus:**	USP Apparatus: II
	Speed of Rotation:	75 rpm
	Medium:	pH 6.8 Phosphate buffer
	Volume:	900 ml
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	NLT (b) (4) (Q) of labeled amount of Atorvastatin is released in 15 minutes	
Dissolution Testing Site (Name, Address)	Ohm Laboratories, Inc. PO Box 7397 1385 Livingston Avenue **North Brunswick, New Jersey 08902** USA	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test - Manufacture Date/Expiration Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times (minutes or hours)**				**Study Report Location**
						5 min.	**10 min.**	**15 min.**	**30 min.**	
-	May 2009	Atorvastatin Calcium Tablets, 80 mg Batch No. RI560901, Manufacturing date – May, 2009 Expiration date – April, 2012	80 mg Tablet	12	Mean	88	96	99	100	NA
					Range	84-93	94-99	97-101	99-102	
					%CV	3.9	1.7	1.2	1.2	
-	June 2009	LIPITOR 80 mg Tablets (Innovator), Batch No. 04558V, Expiration date: March, 2011	80 mg Tablet	12	Mean	79	92	94	97	
					Range	71-85	87-95	90-96	94-100	
					%CV	6.0	2.4	1.8	1.9	

4.2.Polymorphic Consideration for Atorvastatin Calcium Tablet Drug Products

Due to the OGD's recent concern of the effect of polymorphism on in vitro and in vivo performance of a drug product, polymorphic identification of an API compound with multiple polymorphs such as atorvastatin, would contribute toward the process of determining an appropriate and discriminatory dissolution method for use in the quality program of the drug product. Polymorphism has been linked to a product's stability, impurity profile, and solubility of the active ingredient. Following is a list of ANDAs of atorvastatin calcium tablet products which have been reviewed by the DBE and the polymorph(s) identified by the respective DBE reviewer for each product. The evaluation of the polymorphic form and/or composition of the API is primarily carried out by the OGD Division of Chemistry. The polymorphic identification list below is for the information purpose of the DBE reviewers only.

Application Number	Submitter	Reviewer	Polymorph (s)
ANDA-091650	DR REDDYS LABORATORIES LTD	Johnetta Walters	(b) (4)
ANDA-202357	DR REDDYS LABORATORIES LTD	Not Assigned	
(b) (4)		Not Assigned	
(b) (4)		Not Assigned	
(b) (4)		Haritha Mandula	(b) (4)
ANDA-091226	MATRIX LABORATORIES LTD	Hongling Zhang	
ANDA-078773	TEVA PHARMACEUTICALS USA	Suman Dandamudi	
ANDA-077575	SANDOZ INC	Li Gong	
ANDA-091624	KUDCO IRELAND LTD	Johnetta Walters	
ANDA-090548	APOTEX INC	Li Gong	
ANDA-076477	RANBAXY LABORATORIES LIMITED	Surendra Shrivastava	
NDA 020702 (Lipitor)	Pfizer		

NOTE for PM

1. The firm is under AIP for products manufactured at Paonta Saheb facilities and for unapproved products. Therefore, please hold the letter until the firm obtains clearance from the FDA.

2. This letter includes deficiencies for both 12/9/2009 and 11/12/2010 amendment submissions. Deficiencies are similar. Therefore, they are combined in the letter below. Thanks.

ANDA:	076477
APPLICANT:	Ranbaxy Laboratories Ltd.
DRUG PRODUCT:	Atorvastatin Calcium Tablet 10, 20 , 40 and 80 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

In the amendments dated December 9, 2009 and November 12, 2010, you submitted the dissolution data for all strengths of the reference product and the test products with the (b) (4) Active Pharmaceutical Ingredient (API), and Ranbaxy's API (manufactured from Process I and Process II) to support the API and other manufacturing changes. Your dissolution testing data using the FDA-recommended method are insufficiently discriminating, with greater than 85% of the drug in the dosage form dissolved in 10 minutes. Therefore, please conduct additional dissolution testing for 12 units of each strength of each of the three proposed test products manufactured with (b) (4) API, Ranbaxy Process-1 API, and Ranbaxy Process-II API, compared to the respective strengths of the reference (Lipitor®) products, using the reduced paddle speed of 50 rpm, as follows:

Medium: 0.05M Phosphate Buffer, pH 6.8 at 37^{0}C
Volume: 900 mL
USP Apparatus: II (Paddle) at 50 rpm
Recommended Sampling Times: 10, 15, 20, 30, 45 minutes and until at least (b) (4) is dissolved.

[NOTE: The method should use conventional USP II Vessels, and not (b) (4) Vessels.]

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.3.Outcome Page

ANDA: 076477

5. COMPLETED ASSIGNMENT FOR 076477 ID: 13718

Reviewer:	Shrivastava, Surendra	**Date Completed:**	
Verifier:	,	**Date Verified:**	
Division:	Division of Bioequivalence		
Description:	Atorvastatin Calcium Tabs		

Productivity:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Productivity***	***Subtotal***		
13718	11/12/2010	Other	Dissolution Review	1	1	Edit	Delete
13718	11/12/2010	Other	Dissolution Review	1	1	Edit	Delete
13718	11/12/2010	Other	Dissolution Review	1	1	Edit	Delete
13718	11/12/2010	Other	Dissolution Review	1	1	Edit	Delete
13718	11/12/2010	Other	Dissolution Review	1	1	Edit	Delete
13718	11/12/2010	Other	Dissolution Review	1	1	Edit	Delete
13718	11/12/2010	Other	Dissolution Review	1	1	Edit	Delete
13718	11/12/2010	Other	Dissolution Review	1	1	Edit	Delete
				Bean Total:	8		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURENDRA P SHRIVASTAVA
05/10/2011

YIH CHAIN HUANG
05/10/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
05/12/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	076477					
Drug Product Name	Atorvastatin Calcium Tablets					
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg					
Applicant Name	Ranbaxy Laboratories Ltd., India					
Address	Plot # GP-5, Sector 18, HSIDC, Old Delhi, Gurgaon Road, Gurgaon, 122015, Hariyana, India					
Applicant's Point of Contact	Scott D. Tomsky, US Agent, 600 College Road East, Ranbaxy Inc., Princeton, NJ 08540					
Contact's Telephone Number	609-720-5609					
Contact's Fax Number	609-514-9797					
Original Submission Date(s)	August 19, 2002 December 9, 2009 November 12, 2010 (additional API – Ranbaxy Process 1 and Process 2)					
Submission Date(s) of Amendment(s) Under Review	**July 18, 2011** **(Additional Dissolution Data for all Strengths)**					
Reviewer	S. P. Shrivastava, Ph.D.					
Study Number (s)	**R09-1032**	**R09-1033**	**BE-248-ATOR-2009**	**BE-249-ATOR-2009**	**365-ATORV-09**	**3023-ATORV-08**
Study Type (s)	Fasting	Fed	Fasting	Fed	Fasting	Fed
Strength (s)	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg
Clinical Site	**Cetero Research**		**Clinical Services Fortis Clinical Research Ltd.**		**Ranbaxy Labs. Ltd.**	
Clinical Site Address	4801 Amber Valley Pkwy. Fargo, ND 58104		Ltd., Sunflag Hospital & Research Centre Sector-16A, Faridabad 121 002, Haryana, India		Majeedia Hospital, Hamdard Nagar New Delhi India	
Analytical Site	(b) (4)				**Ranbaxy Labs. Ltd**	
Analytical Site Address					Plot No. GP-5, Sector 18, HSIDC, Gurgaon, Haryana, India	
Dissolution Testing Site	Ranbaxy Laboratory Ltd.					
DSI Inspection Status	No DSI inspections of pivotal study sites, Cetero Research (Clinical) or (b) (4) (Analytical) is pending or necessary					
Overall Review Result	**INADEQUATE**					
Waiver Request Result	**INADEQUATE :** 10, 20 and 40 mg					
DSI Report Result	**Clinical: ADEQUATE.** **Analytical: ADEQUATE** (Details covered in 12/9/2009 submission review)					
Bioequivalence Study Tracking/Supporting Document #	**Study/Test Type**		**Strength**		**Review Result**	
Supporting Document	**Dissolution**		80 mg		**INADEQUATE**	

#57, 58			
	Dissolution	40 mg	**INADEQUATE**
	Dissolution	20 mg	**INADEQUATE**
	Dissolution	10 mg	**INADEQUATE**
Supporting Document # 57	**Fasting (Pivotal) - using (b) (4) API**	80 mg	**ADEQUATE**
	Fed (Pivotal) – using (b) (4) API	80 mg	**ADEQUATE**
	Pilot Fasting (BE-248-ATOR-2009**)**	80 mg	**INADEQUATE**
	Pilot Fed (BE-249-ATOR-2009**)**	80 mg	**INADEQUATE**
	Pilot Fasting (365-ATORV-09**)**	80 mg	**INADEQUATE**
	Pilot Fasting (3023-ATORV-08)	80 mg	**INADEQUATE**
	Permeability Study	**N/A**	**N/A**
	Solubility Study	**N/A**	**N/A**

1. EXECUTIVE SUMMARY

This application references Atorvastatin Calcium Tablets, 10, 20, 40 and 80 mg [Lipitor®, Pfizer, NDA 020702, Approved 10, 20 mg, 40 mg-12/17/1996; 80 mg-4/7/2000 (RLD)]. The firm had previously conducted acceptable single-dose fasting and fed studies on 80 mg tablets, and dissolution testing results on all strengths [see JEChaney, C:\Documents and Settings\shrivastavas\My Documents\076477A0711.doc, C:\Documents and Settings\shrivastavas\My Documents\076477A0711.doc, SHRIVASTAVA, SURENDRA P 09/27/2007 N/A 09/27/2007 REV-BIOEQ-01(General Review) Original-1, SHRIVASTAVA, SURENDRA P 06/19/2008 N/A 06/19/2008 REV-BIOEQ-01(General Review) Original-1].

In the 12/09/2009 amendment, the firm made CMC pre-approval changes (polymorphic form, component and composition, manufacturing process and manufacturing site). The firm did not provide specific reason for the proposed changes. It is probably due to the regulatory issues related to the original manufacturing site (Ranbaxy Lab, Paonta Sahib's API). In support of the CMC changes the firm submitted additional single-dose fasting and fed studies on 80 mg strength and requested waivers of BE studies for 10, 20 and 40 mg tablets. The fasting and fed studies were found acceptable [see DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1]. The test product in these additional BE studies used the API from (b) (4) (crystalline form). However, in a subsequent amendment dated 11/12/2010, the firm proposed an additional source of API (Ranbaxy Labs., DMF 24139) for Atorvastatin Calcium, USP (crystalline), manufactured by two different processes. In support of these changes, the firm provided comparative dissolution data for Test (Ranbaxy's APIs by Process-I and Process-II) and Reference (b) (4) API) products using the FDA-recommended dissolution method (900 mL of 0.05 M Phosphate buffer at pH 6.8 and Paddle at 75 rpm) The dissolution testing was

found inadequate due to an insufficiently discriminatory method[1] and therefore the firm was requested to repeat the testing using a modified version of the FDA recommended method (Paddle speed of 50 rpm instead of 75 rpm). In the current amendment, the firm has provided additional dissolution data as requested.

Dissolution data on Ranbaxy Process-I and Process-II API products are acceptable. However, there is a discrepancy in the Expiration Dates reported for the (b) (4) API Test products. Thus, the Expiration Date for each of (b) (4) API Test products, 10, 20, 40 and 80 mg, Lot #s RI530902, RI540901, RI550901 and RI560901, is 4/2012 in the current submission, whereas in the previous submission, dated 11/12/2010, the Expiration Date for each of these lots was indicated as 4/2011. It is not clear how the firm determined the expiration date(s) for the test product without dissolution stability data. Based on the manufacturing date of 5/2009, the dissolution testing in the current amendment for the above (b) (4) API products were conducted on expired lots (i.e., based on the test dates between 6/28/2011-7/12/2011, the testing was conducted when these lots were more than 24 months old), and therefore not valid. It should be noted that the firm's test product used in the pivotal fasting and fed BE studies, 80 mg, were manufactured with (b) (4) API.

Therefore, the firm is requested to repeat the dissolution testing on unexpired lots of Atorvastatin Calcium Tablets (b) (4) API), 10, 20, 40 and 80 mg, using the modified FDA method as follows:

Medium:	0.05M Phosphate Buffer, pH 6.8 at 37^0C
Volume:	900 mL
USP Apparatus:	II (Paddle) at 50 rpm

The deficiency response is **incomplete**.

The application is **inadequate**.

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[1] [See DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

2. TABLE OF CONTENTS

3. SUBMISSION SUMMARY

3.1. Drug Product Information

[See DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

3.2. PK/PD Information

[See DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

3.3. Contents of Submission

Response to information request – Additional dissolution data.

3.4. In Vitro Dissolution

Location of DBE Dissolution Review	See Appendix, Section 4.1, Dissolution Data (current review)
Source of Method (USP, FDA or Firm)	**FDA**
Medium	0.05 M Phosphate buffer, pH 6.8 @ 37°C
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	50 rpm
Firm's specification	Not provided
DBE-recommended specification	NLT (b) (4) % (Q) is dissolved in 75 minutes
If a modified-release tablet, was testing done on ½ tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	No (see comment)
If not then why?	See Deficiency Comment

3.5. Deficiencies, Firm's Response and Conclusion

DEFICIENCY-1: *In the amendments dated December 9, 2009 and November 12, 2010, you submitted the dissolution data for all strengths of the reference product and the test products with the* (b) (4) *Active Pharmaceutical Ingredient (API), and Ranbaxy's API (manufactured from Process I and Process II) to support the API and other manufacturing changes. Your dissolution testing data using the FDA-recommended method are insufficiently discriminating, with greater than 85% of the drug in the dosage form dissolved in 10 minutes. Therefore, please conduct additional dissolution testing for 12 units of each strength of each of the three proposed test products manufactured with* (b) (4) *API, Ranbaxy Process-1 API, and Ranbaxy Process-II API, compared to the respective strengths of the reference (Lipitor®) products, using the reduced paddle speed of 50 rpm, as follows:*

Medium: *0.05M Phosphate Buffer, pH 6.8 at 37^{0}C*
Volume: *900 mL*
USP Apparatus: *II (Paddle) at 50 rpm*
Recommended Sampling Times: 10, 15, 20, 30, 45 minutes and until at least (b) (4) *is dissolved.*
[NOTE: The method should use conventional USP II Vessels, and not (b) (4) *Vessels.]*

Firm's Response:

As per Agency's recommendation, additional dissolution testing for 12 units of each strength of each of the three proposed test products manufactured with (b) (4) API, Ranbaxy Process-I API, and Ranbaxy Process-II API compared to the respective strengths of the reference (Lipitor®) products using the reduced paddle speed of 50 rpm at 10, 15, 20, 30, 45, 60 and 75 minutes have been performed. The **comparative dissolution data** are provided through this amendment.

The dissolution testing results are provided in Tables 1-12 in the Appendix.

Summary:

- There is no USP method for this product, but there is an FDA-recommended dissolution method (900 mL of 0.05 Phosphate buffer at pH 6.8 and Paddle at 75 rpm). Since firm's dissolution testing with the FDA recommended method (Paddles at 75 rpm) was found inadequate due to an insufficiently discriminatory method, the firm was requested to conduct dissolution testing using a modified FDA method as follows:

Medium:	0.05M Phosphate Buffer, pH 6.8 at 37 ^{0}C
Volume:	900 mL
USP Apparatus:	II (Paddle) at 50 rpm

- The dissolution method submitted in this submission with Paddle speed at 50 rpm is more discriminatory than submitted earlier with Paddle speed at 75 rpm.
- The F2 values (Similarity Factor) were calculated by the reviewer using all time points (10-75 minutes, n=7) and are provided in Table 13-15. F2 values were calculated for, 1) 80 mg Test batch vs. 10, 20 and 40 mg Test batches (all 3 APIs) and 80 mg Reference batch vs. 10, 20 and 40 mg batches (Table 13); 2) 80 mg Test biobatch (b) (4) API) vs. all other Test batches (Table 14); and 3) 80 mg Reference biobatch (Lipitor®) vs. all other Test batches (Table 15). All F2 values are >50 indicating similar dissolution profiles for all Test (manufactured with (b) (4) Ranbaxy Process-I or Ranbaxy Process-II API) and reference products.
- There is a discrepancy in the Expiration Dates indicated for the Test products in the current amendment and in previous submissions. Thus, the Expiration Date for each of (b) (4) API Test products, 10, 20, 40 and 80 mg, Lot #s RI530902, RI540901, RI550901 and RI560901, is 4/2012 in the current submission, whereas in the previous submission, dated 11/12/2010, the Expiration Date for each of these lots was indicated as 4/2011. Based on the 4/2011 Expiration Date (Manuf. Date 5/2009), the dissolution testing for the above (b) (4) API products were conducted on expired lots, and therefore not valid. The 24 months Expiry Period was also accepted by the he Chemistry Division [DARRTS, ANDA 076477, CMC Review, Section 29, Stability, page 69; LI, HAITAO 06/14/2011 N/A 06/14/2011 REV-QUALITY-03 (General Review) Original-1; Also see

Appendix, Section 4.2,]. Therefore, the firm should repeat the dissolution testing on Atorvastatin Calcium Tablets ((b) (4) API).

- Since the DBE does not set expiration dates for the test products, the expiration date discrepancy is communicated to the Division of Chemistry for consideration.

3.6.Deficiency Comments

1. There is a discrepancy in the Expiration Dates indicated for the Test products in the current amendment and in previous submissions. Thus, the Expiration Date for each of (b) (4) API Test products, 10, 20, 40 and 80 mg, Lot #s RI530902, RI540901, RI550901 and RI560901, is 4/2012 in the current submission, whereas in the previous submission, dated 11/12/2010, the Expiration Date for each of these lots was indicated as 4/2011. It is not clear how the firm determined the expiration date(s) for the test product without dissolution stability data. Based on the manufacturing date of 5/2009, the dissolution testing in the current amendment for the above (b) (4) API products were conducted on expired lots (i.e., based on the test dates between 6/28/2011-7/12/2011, the testing was conducted when these lots were more than 24 months old), and therefore not valid. It should be noted that the firm's test product used in the pivotal fasting and fed BE studies, 80 mg, were manufactured with (b) (4) API. It also should be noted that the 24 months Expiry Period was accepted by the Chemistry Division [DARRTS, ANDA 076477, CMC Review, Section 29, Stability, page 69; LI, HAITAO 06/14/2011 N/A 06/14/2011 REV-QUALITY-03 (General Review) Original-1; Also see Appendix, Section 4.2,].

   Therefore, the firm is requested to repeat the dissolution testing on unexpired batches of Atorvastatin Calcium Tablets (b) (4) API), 10, 20, 40 and 80 mg using the modified FDA method as follows:

Medium:	0.05M Phosphate Buffer, pH 6.8 at 37^0C
Volume:	900 mL
USP Apparatus:	II (Paddle) at 50 rpm

3.7.Recommendations

1. The dissolution testing conducted by Ranbaxy Laboratories Ltd. on its Atorvastatin Calcium, 10, 20, 40 and 80 mg Tablets, manufactured with Ranbaxy's APIs (process 1 and process 2), comparing them with its original products manufactured with (b) (4) API (crystalline form) , 10, 20, 40 and 80 mg Tablets, respectively, remains **inadequate** due to deficiency #1 cited above.

2. The Division of Bioequivalence has previously **accepted** the fasting BE study (R09-1032) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #R1560901 (with (b) (4) API) comparing it to Pfizer, Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V.

3. The Division of Bioequivalence has previously **accepted** the fed BE study (R09-1033) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #R1560901 (with (b) (4) API) comparing it to Pfizer, Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V.

4. The Division of Bioequivalence has previously acknowledged the pilot fasting BE study (BE-248-ATOR-2009) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #B204130 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA), and Canada Lipitor®, 80 mg, Lot # B0378088 (Pfizer, Canada).

5. The Division of Bioequivalence has previously acknowledged the pilot fed BE study (BE-249-ATOR-2009) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #B204130 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA).

6. The Division of Bioequivalence has previously acknowledged the pilot fasting BE study (365-_ATORV_09) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #ANK (3926)071A comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V (Pfizer, USA), and Belgium Lipitor®, 80 mg, Lot # 0904118B (Pfizer, Belgium).

7. The Division of Bioequivalence has previously acknowledged the pilot fasting BE study (3023-_ATORV_08) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #ANK (3926)049 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA).

8. The formulations for the 10, 20 and 40 mg strengths (b) (4) API) were found (b) (4) to the 80 mg strength of the test product (b) (4) API), which underwent bioequivalence testing. The waivers of in vivo bioequivalence study requirements for 10, 20 and 40 mg strength Tablets of the test product (b) (4) API) cannot be granted at this time pending the firm's acknowledgement of the FDA-recommended dissolution method and specification.

3.8. Comments for Other OGD Disciplines

Discipline	Comment
Chemistry	• From its originally acceptable formulation, the firm has made major changes in polymorphic form, components and composition, manufacturing process and manufacturing site. Therefore, the Chemistry should look into the CMC aspects. • The Chemistry should check into the Expiration Date for Test products manufactured with (b) (4) API. The firm quoted the Expiration Date for all Test products, 10, 20, 40 and 80 mg (b) (4) API), Lot #s RI530902, RI540901, RI550901 and RI560901, as 4/2012 in the current submission, whereas in the previous submission, dated 11/12/2010, the Expiration Date was indicated as 4/2011.

4. APPENDIX

4.1. Dissolution Data

Dissolution Review Path	See Tables below

Comparative dissolution testing results for Test products (Ranbaxy's API Process-I and II), and Reference ((b) (4) API) products are provided in Tables 1-15.

Table 1. Dissolution Data (b) (4) API vs. Lipitor®, 10 mg

Product: Atorvastatin Calcium Tablets, 10mg
Batch No.: RI530902
Mfg & Exp Date: 05/2009 & 04/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium) Tablets, 10mg
Batch No.: V101289
Mfg & Exp Date: NA & 08/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, I

	Batch No.: RI530902							Batch No.: V101289						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	55	68	74	82	82	82	83	66	73	79	84	88	91	95
2	58	71	78	79	79	85	86	62	68	71	81	89	92	91
3	59	70	74	79	86	87	89	60	69	76	84	87	90	92
4	70	76	80	83	84	85	92	60	69	78	88	91	94	93
5	63	66	78	83	83	86	90	71	80	86	91	94	95	94
6	60	67	72	80	83	87	96	63	70	79	88	92	94	95
7	66	75	74	76	82	81	93	68	72	74	80	89	90	91
8	68	75	81	88	89	90	91	57	59	62	72	78	84	85
9	71	69	71	78	80	89	91	60	63	66	76	80	84	90
10	72	68	73	76	75	80	93	72	73	75	78	85	87	90
11	70	71	72	80	87	84	94	74	77	79	83	85	86	88
12	68	78	73	77	85	93	94	63	66	68	74	81	88	90
Mean	**65**	**71**	**75**	**80**	**83**	**86**	**91**	**65**	**70**	**74**	**82**	**87**	**90**	**91**
%RSD	**8.9**	**5.5**	**4.5**	**4.3**	**4.6**	**4.4**	**4.0**	**8.4**	**8.2**	**9.0**	**7.2**	**5.7**	**4.2**	**3.2**
Minimum	**55**	**66**	**71**	**76**	**75**	**80**	**83**	**57**	**59**	**62**	**72**	**78**	**84**	**85**
Maximum	**72**	**78**	**81**	**88**	**89**	**93**	**96**	**74**	**80**	**86**	**91**	**94**	**95**	**95**
Date of Analysis	06-28-11 & 07-01-11							07-01-11& 07-13-11						
Book Reference	B#2763/P#44 & B#2776/P#17							B#2776, P#18 & B#2763/ Pg#58,59						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :**37±0.5**
RPM :**50**

Prepared By: VM 07-15-11 **Checked By:** Jiva Leuders 07/15/11 **Approved By:** 07/15/11

Expiry date for the Test lot was previously reported: 4/2011

Table 2. Dissolution Data –Ranbaxy Process-1 vs. Lipitor®, 10 mg

Product: Atorvastatin Calcium Tablets, 10mg
Batch No.: RI531002
Mfg & Exp Date: 02/2010 & 01/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium)Tablets, 10mg
Batch No.: V101289
Mfg & Exp Date: NA & 08/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI531002							Batch No.: V101289						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	54	58	63	67	72	78	81	66	73	79	84	88	91	95
2	59	64	67	71	75	83	86	62	68	71	81	89	92	91
3	56	66	74	81	85	88	88	60	69	76	84	87	90	92
4	62	72	76	82	85	86	88	60	69	78	88	91	94	93
5	60	73	80	86	88	91	90	71	80	86	91	94	95	94
6	61	67	73	78	84	87	88	63	70	79	88	92	94	95
7	62	71	74	80	82	85	86	68	72	74	80	89	90	91
8	64	74	80	84	86	88	89	57	59	62	72	78	84	85
9	60	71	78	83	86	89	89	60	63	66	76	80	84	90
10	66	76	80	84	86	88	89	72	73	75	78	85	87	90
11	68	77	85	87	89	90	90	74	77	79	83	85	86	88
12	72	80	83	87	89	93	91	63	66	68	74	81	88	90
Mean	**62**	**71**	**76**	**81**	**84**	**87**	**88**	**65**	**70**	**74**	**82**	**87**	**90**	**91**
%RSD	**8.0**	**8.6**	**8.4**	**7.7**	**6.3**	**4.5**	**3.0**	**8.4**	**8.2**	**9.0**	**7.2**	**5.7**	**4.2**	**3.2**
Minimum	**54**	**58**	**63**	**67**	**72**	**78**	**81**	**57**	**59**	**62**	**72**	**78**	**84**	**85**
Maximum	**72**	**80**	**85**	**87**	**89**	**93**	**91**	**74**	**80**	**86**	**91**	**94**	**95**	**95**
Date of Analysis	06-30-11							07-01-11 & 07-13-11						
Book Reference	B#2776/ Pg#11,12							B#2776, P#18 & B# 2763/ Pg# 58,59						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :37±0.5
RPM :**50**

Prepared By: VM 07-14-11 **Checked By:** Trivu Vaidya 07/15/11 **Approved By:** LG 07/15/11

Table 3. Dissolution Data –Ranbaxy Process-II API vs. Lipitor®, 10 mg

Product: Atorvastatin Calcium Tablets, 10mg
Batch No.: RI531004
Mfg & Exp Date: 03/2010 & 02/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium) Tablets 10mg
Batch No.: V101289
Mfg & Exp Date: NA & 08/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI531004							Batch No.: V101289						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	75	79	80	84	88	88	88	66	73	79	84	88	91	95
2	69	71	71	76	81	82	83	62	68	71	81	89	92	91
3	64	67	69	73	80	81	88	60	69	76	84	87	90	92
4	73	74	75	81	82	92	94	60	69	78	88	91	94	93
5	78	81	82	85	87	88	94	71	80	86	91	94	95	94
6	71	73	75	78	78	83	87	63	70	79	88	92	94	95
7	72	75	82	82	82	84	83	68	72	74	80	89	90	91
8	71	79	83	88	90	90	90	57	59	62	72	78	84	85
9	65	70	79	81	81	84	90	60	63	66	76	80	84	90
10	65	69	75	81	83	83	84	72	73	75	78	85	87	90
11	73	80	85	88	88	90	89	74	77	79	83	85	86	88
12	77	82	84	90	91	93	94	63	66	68	74	81	88	90
Mean	**71**	**75**	**78**	**82**	**84**	**87**	**89**	**65**	**70**	**74**	**82**	**87**	**90**	**91**
%RSD	**6.5**	**6.8**	**6.7**	**6.2**	**5.1**	**4.8**	**4.5**	**8.4**	**8.2**	**9.0**	**7.2**	**5.7**	**4.2**	**3.2**
Minimum	**64**	**67**	**69**	**73**	**78**	**81**	**83**	**57**	**59**	**62**	**72**	**78**	**84**	**85**
Maximum	**78**	**82**	**85**	**90**	**91**	**93**	**94**	**74**	**80**	**86**	**91**	**94**	**95**	**95**
Date of Analysis	07-05-11							07-01-11& 07-13-11						
Book Reference	B#2776/ Pg# 23 ,24							B#2776, P#18 & B#2763/ Pg#58,59						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :37±0.5
RPM :50

Prepared By: VM 07-14-11 **Checked By:** Srinivas Reddy 07/15/11 **Approved By:** LG 07/15/11

Table 4. Dissolution Data (b) (4) **API vs. Lipitor®, 20 mg**

Product: Atorvastatin Calcium Tablets, 20mg
Batch No.: RI540901
Mfg & Exp Date: 05/2009 & 04/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium)Tablets, 20mg
Batch No.: 0820011
Mfg & Exp Date: NA & 12/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI540901							Batch No.: 0820011						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	72	75	81	79	80	83	83	75	77	78	81	83	88	88
2	69	72	75	77	78	81	80	69	74	81	84	87	93	93
3	73	75	76	78	78	81	83	70	77	82	86	88	92	90
4	70	75	77	80	82	84	82	69	77	79	85	89	92	92
5	73	75	77	79	80	80	82	64	70	75	82	89	94	94
6	73	76	78	79	80	81	82	66	70	74	76	81	84	86
7	73	78	78	81	85	85	81	83	85	88	88	88	88	88
8	69	71	72	76	80	85	83	75	78	80	85	86	87	88
9	71	74	75	80	81	88	87	70	76	81	86	91	94	94
10	66	68	70	76	78	84	81	73	75	78	83	85	88	96
11	70	74	74	77	84	88	86	70	72	77	82	85	90	94
12	81	83	85	85	90	87	86	79	81	82	84	85	86	90
Mean	**72**	**75**	**77**	**79**	**81**	**84**	**83**	**72**	**76**	**80**	**84**	**86**	**90**	**91**
%RSD	**5.1**	**4.9**	**5.1**	**3.2**	**4.4**	**3.3**	**2.7**	**7.5**	**5.7**	**4.6**	**3.7**	**3.3**	**3.7**	**3.5**
Minimum	**66**	**68**	**70**	**76**	**78**	**80**	**80**	**64**	**70**	**74**	**76**	**81**	**84**	**86**
Maximum	**81**	**83**	**85**	**85**	**90**	**88**	**87**	**83**	**85**	**88**	**88**	**91**	**94**	**96**
Date of Analysis	07-06-11 & 07-07-11							07-06-11 & 07-07-11						
Book Reference	B#2776/ Pg# 30,39							B#2776/ Pg# 33, 42						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :**37±0.5**
RPM :**50**

Prepared By: [illegible] 07-15-11 **Checked By:** [illegible] 07/15/11 **Approved By:** [illegible] 07/15/11

Expiry date for Test lot previously reported: 4/2011

Table 5. Dissolution Data –Ranbaxy Process-I API vs. Lipitor®, 20 mg

Product: Atorvastatin Calcium Tablets, 20mg
Batch No.: RI541001
Mfg & Exp Date: 02/2010 & 01/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium) Tablets, 20mg
Batch No.: 0820011
Mfg & Exp Date: NA & 12/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI541001							Batch No.: 0820011						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	66	68	70	77	79	80	82	75	77	78	81	83	88	88
2	64	66	72	77	77	78	80	69	74	81	84	87	93	93
3	60	66	70	77	79	80	82	70	77	82	86	88	92	90
4	66	70	73	77	79	82	82	69	77	79	85	89	92	92
5	63	71	77	82	87	87	89	64	70	75	82	89	94	94
6	59	64	67	72	75	78	81	66	70	74	76	81	84	86
7	60	67	75	76	77	81	82	83	85	88	88	88	88	88
8	65	67	74	76	78	80	83	75	78	80	85	86	87	88
9	73	74	79	80	81	82	84	70	76	81	86	91	94	94
10	68	69	76	77	81	83	85	73	75	78	83	85	88	96
11	64	67	70	72	76	82	82	70	72	77	82	85	90	94
12	67	71	73	75	78	82	82	79	81	82	84	85	86	90
Mean	**65**	**68**	**73**	**77**	**79**	**81**	**83**	**72**	**76**	**80**	**84**	**86**	**90**	**91**
%RSD	**6.0**	**4.1**	**4.7**	**3.7**	**3.9**	**3.0**	**2.8**	**7.5**	**5.7**	**4.6**	**3.7**	**3.3**	**3.7**	**3.5**
Minimum	**59**	**64**	**67**	**72**	**75**	**78**	**80**	**64**	**70**	**74**	**76**	**81**	**84**	**86**
Maximum	**73**	**74**	**79**	**82**	**87**	**87**	**89**	**83**	**85**	**88**	**88**	**91**	**94**	**96**
Date of Analysis	07-06-11 & 07-07-11							07-06-11 & 07-07-11						
Book Reference	B#2776/ Pg# 31,40							B#2776/ Pg# 33, 42						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :**37±0.5**
RPM :**50**

Prepared By: VM 07-15-11 **Checked By:** Irina Feerdis 07/15/11 **Approved By:** LG 07/15/11

Table 6. Dissolution Data –Ranbaxy Process-II API vs. Lipitor®, 20 mg

Product: Atorvastatin Calcium Tablets, 20mg
Batch No.: RI541002
Mfg & Exp Date: 03/2010 & 02/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium)Tablets, 20mg
Batch No.: 0820011
Mfg & Exp Date: NA & 12/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI541002							Batch No.: 0820011						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	72	83	90	90	93	92	91	75	77	78	81	83	88	88
2	67	76	85	88	91	91	91	69	74	81	84	87	93	93
3	69	74	81	86	91	93	92	70	77	82	86	88	92	90
4	68	73	80	84	90	91	90	69	77	79	85	89	92	92
5	76	82	87	92	95	95	95	64	70	75	82	89	94	94
6	69	79	84	89	91	93	94	66	70	74	76	81	84	86
7	71	77	81	85	86	89	89	83	85	88	88	88	88	88
8	68	75	78	83	84	85	86	75	78	80	85	86	87	88
9	73	78	79	80	84	85	84	70	76	81	86	91	94	94
10	79	85	88	97	95	94	95	73	75	78	83	85	88	96
11	81	88	89	92	91	91	91	70	72	77	82	85	90	94
12	69	79	81	88	89	89	90	79	81	82	84	85	86	90
Mean	**72**	**79**	**84**	**88**	**90**	**91**	**91**	**72**	**76**	**80**	**84**	**86**	**90**	**91**
%RSD	**6.4**	**5.8**	**4.9**	**5.3**	**4.1**	**3.5**	**3.6**	**7.5**	**5.7**	**4.6**	**3.7**	**3.3**	**3.7**	**3.5**
Minimum	**67**	**73**	**78**	**80**	**84**	**85**	**84**	**64**	**70**	**74**	**76**	**81**	**84**	**86**
Maximum	**81**	**88**	**90**	**97**	**95**	**95**	**95**	**83**	**85**	**88**	**88**	**91**	**94**	**96**
Date of Analysis	07-06-11 & 07-07-11							07-06-11 & 07-07-11						
Book Reference	B#2776/ Pg# 32,41							B#2776/ Pg# 33, 42						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :**37±0.5**
RPM :**50**

Prepared By: VM 07-15-11 **Checked By:** Trina Fowler 07/15/11 **Approved By:** LG 07/15/11

Table 7. Dissolution Data – (b) (4) API vs. Lipitor®, 40 mg

Product: Atorvastatin Calcium Tablets, 40mg
Batch No.: RI550901
Mfg & Exp Date: 05/2009 & 04/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium)Tablets, 40mg
Batch No.: 0903011
Mfg & Exp Date: NA & 12/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI550901							Batch No.: 0903011						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	79	85	88	92	93	93	93	68	74	76	82	85	86	86
2	73	77	80	81	83	82	82	69	73	75	78	81	82	83
3	71	77	80	83	84	87	84	76	80	82	85	87	89	89
4	75	78	80	83	88	90	91	78	81	84	86	88	88	89
5	83	86	89	91	92	94	93	71	77	80	84	87	88	89
6	78	83	87	91	93	94	93	72	77	80	85	88	90	91
7	71	74	78	80	96	95	96	71	78	81	82	90	88	92
8	71	75	78	81	97	96	96	74	77	83	81	87	88	89
9	76	79	83	84	96	96	96	76	79	83	84	87	88	90
10	72	74	78	80	98	98	95	75	79	81	84	86	88	89
11	75	77	81	84	93	94	96	74	79	83	84	85	89	89
12	72	74	78	81	97	97	95	71	76	81	82	84	87	87
Mean	**75**	**78**	**82**	**84**	**93**	**93**	**93**	**73**	**78**	**81**	**83**	**86**	**88**	**89**
%RSD	**5.1**	**5.4**	**5.0**	**5.4**	**5.4**	**4.9**	**5.1**	**4.2**	**3.0**	**3.4**	**2.6**	**2.7**	**2.3**	**2.6**
Minimum	**71**	**74**	**78**	**80**	**83**	**82**	**82**	**68**	**73**	**75**	**78**	**81**	**82**	**83**
Maximum	**83**	**86**	**89**	**92**	**98**	**98**	**96**	**78**	**81**	**84**	**86**	**90**	**90**	**92**
Date of Analysis	07-08-11 & 07-11-11							07-08-11 & 07-11-11						
Book Reference	B#2777, P#6, 7 & B#2776 /P# 49							B#2777, P#12,13 &B# 2776/ P# 50						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :**37±0.5**
RPM :**50**

Prepared By: VM 07-15-11 **Checked By:** [illegible] 07/15/11 **Approved By:** 07/15/11

Expiry date for Test lot previously reported: 4/2011

Table 8. Dissolution Data –Ranbaxy Process-I API vs. Lipitor®, 40 mg

Product: Atorvastatin Calcium Tablets, 40mg
Batch No.: RI551001
Mfg & Exp Date: 02/2010 & 01/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium) Tablets, 40mg
Batch No.: 0903011
Mfg & Exp Date: NA & 12/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI551001							Batch No.: 0903011						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	64	69	73	75	80	80	81	68	74	76	82	85	86	86
2	70	75	78	81	83	84	84	69	73	75	78	81	82	83
3	72	77	79	81	82	83	83	76	80	82	85	87	89	89
4	72	77	79	81	82	84	83	78	81	84	86	88	88	89
5	74	78	81	82	83	85	85	71	77	80	84	87	88	89
6	76	81	81	83	84	85	84	72	77	80	85	88	90	91
7	74	79	81	83	83	86	83	71	78	81	82	90	88	92
8	74	79	82	83	84	85	83	74	77	83	81	87	88	89
9	76	80	83	84	84	85	85	76	79	83	84	87	88	90
10	72	80	82	84	83	84	85	75	79	81	84	86	88	89
11	75	79	82	84	82	84	85	74	79	83	84	85	89	89
12	74	79	83	84	85	86	86	71	76	81	82	84	87	87
Mean	**73**	**78**	**80**	**82**	**83**	**84**	**84**	**73**	**78**	**81**	**83**	**86**	**88**	**89**
%RSD	**4.5**	**4.1**	**3.5**	**3.1**	**1.6**	**1.9**	**1.6**	**4.2**	**3.0**	**3.4**	**2.6**	**2.7**	**2.3**	**2.6**
Minimum	**64**	**69**	**73**	**75**	**80**	**80**	**81**	**68**	**73**	**75**	**78**	**81**	**82**	**83**
Maximum	**76**	**81**	**83**	**84**	**85**	**86**	**86**	**78**	**81**	**84**	**86**	**90**	**90**	**92**
Date of Analysis	07-08-11 & 07-11-11							07-08-11 & 07-11-11						
Book Reference	B#2777, P#8, 9 &B# 2776/ P# 51							B#2777, P#12,13 & B#2776/ P#50						

Dissolution Parameters:
Apparatus : USP Apparatus II (Paddle)
Medium : 0.05M Phosphate Buffer, pH 6.8 ,900mL
Temperature(°C) :37±0.5
RPM :50

Prepared By: VM 07-15-11 **Checked By:** Trivedi 07/15/11 **Approved By:** 07/15/11

Table 9. Dissolution Data –Ranbaxy Process-II API vs. Lipitor®, 40 mg

Product: Atorvastatin Calcium Tablets, 40mg
Batch No.: RI551002
Mfg & Exp Date: 03/2010 & 02/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium) Tablets 40mg
Batch No.: 0903011
Mfg & Exp Date: NA & 12/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI551002							Batch No.: 0903011						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	78	85	88	92	95	95	96	68	74	76	82	85	86	86
2	73	82	86	89	91	93	93	69	73	75	78	81	82	83
3	77	81	84	87	89	91	91	76	80	82	85	87	89	89
4	70	75	78	83	86	91	93	78	81	84	86	88	88	89
5	82	84	86	89	92	93	93	71	77	80	84	87	88	89
6	82	88	91	94	96	96	97	72	77	80	85	88	90	91
7	80	86	91	93	87	97	95	71	78	81	82	90	88	92
8	75	86	84	93	87	98	96	74	77	83	81	87	88	89
9	74	87	85	91	87	97	96	76	79	83	84	87	88	90
10	75	85	85	93	87	93	91	75	79	81	84	86	88	89
11	76	85	89	93	90	94	92	74	79	83	84	85	89	89
12	78	85	89	93	93	94	96	71	76	81	82	84	87	87
Mean	**77**	**84**	**86**	**91**	**90**	**94**	**94**	**73**	**78**	**81**	**83**	**86**	**88**	**89**
%RSD	**4.7**	**4.1**	**4.2**	**3.6**	**3.8**	**2.5**	**2.3**	**4.2**	**3.0**	**3.4**	**2.6**	**2.7**	**2.3**	**2.6**
Minimum	**70**	**75**	**78**	**83**	**86**	**91**	**91**	**68**	**73**	**75**	**78**	**81**	**82**	**83**
Maximum	**82**	**88**	**91**	**94**	**96**	**98**	**97**	**78**	**81**	**84**	**86**	**90**	**90**	**92**
Date of Analysis	07-08-11 & 07-11-11							07-08-11 & 07-11-11						
Book Reference	B#2777, P#10,11 & B#2776,P#52							B#2777, P#12,13 & B#2776/P#52						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :**37±0.5**
RPM :**50**

Prepared By: YM 07-15-11 **Checked By:** Trina Leudes 07/15/11 **Approved By:** LG 07/15/11

Table 10. Dissolution Data (b) (4) API vs. Lipitor®, 80 mg

Product: Atorvastatin Calcium Tablets, 80mg
Batch No.: RI560901
Mfg & Exp Date: 05/2009 & 04/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium) Tablets, 80mg
Batch No.: V101806
Mfg & Exp Date: NA & 11/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI560901							Batch No.: V101806						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	68	74	76	80	85	87	86	77	82	84	87	87	88	88
2	71	76	79	83	84	84	84	70	79	83	86	86	86	87
3	76	80	82	84	86	90	91	73	77	79	81	83	84	85
4	76	81	84	88	91	93	93	75	81	82	86	86	86	87
5	77	85	88	90	92	93	93	69	73	75	79	81	84	87
6	76	81	84	88	91	91	92	77	79	80	82	83	85	86
7	71	77	80	83	84	84	86	68	75	78	81	84	85	86
8	79	83	86	88	90	89	89	76	80	83	85	86	87	86
9	72	78	83	89	91	91	91	78	86	88	89	90	90	89
10	78	82	85	88	89	89	90	69	73	78	80	83	84	85
11	82	84	85	86	86	86	88	80	83	84	86	87	88	87
12	79	80	81	82	82	82	84	76	79	81	83	84	85	85
Mean	**75**	**80**	**83**	**86**	**88**	**88**	**89**	**74**	**79**	**81**	**84**	**85**	**86**	**87**
%RSD	**5.5**	**4.1**	**4.0**	**3.7**	**3.9**	**4.1**	**3.7**	**5.5**	**5.0**	**4.3**	**3.8**	**2.9**	**2.2**	**1.4**
Minimum	**68**	**74**	**76**	**80**	**82**	**82**	**84**	**68**	**73**	**75**	**79**	**81**	**84**	**85**
Maximum	**82**	**85**	**88**	**90**	**92**	**93**	**93**	**80**	**86**	**88**	**89**	**90**	**90**	**89**
Date of Analysis	06-28-11 & 07-12-11							07-12-11 & 07-13-11						
Book Reference	B#2763/ Pg# 45 & B# 2777/ Pg# 23,24							B#2777/ Pg# 25,26 & B# 2763/ Pg# 64,65						

Dissolution Parameters:
Apparatus : USP Apparatus II (Paddle)
Medium : 0.05M Phosphate Buffer, pH 6.8 ,900mL
Temperature(°C) :37±0.5
RPM :50

Prepared By: VM 07-14-11 **Checked By:** Gina Fendler 07/15/11 **Approved By:** LG 07/15/11

Expiry date for Test lot previously reported: 4/2011

Table 11. Dissolution Data –Ranbaxy Process-I API vs. Lipitor®, 80 mg

Product: Atorvastatin Calcium Tablets, 80mg
Batch No.: RI561001
Mfg & Exp Date: 02/2010 & 01/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium) Tablets 80mg
Batch No.: V101806
Mfg & Exp Date: NA & 11/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI561001							Batch No.: V101806						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	72	76	77	81	82	84	85	77	82	84	87	87	88	88
2	64	69	72	75	78	83	84	70	79	83	86	86	86	87
3	68	72	74	77	79	81	84	73	77	79	81	83	84	85
4	69	73	76	79	81	83	83	75	81	82	86	86	86	87
5	73	79	81	83	85	87	86	69	73	75	79	81	84	87
6	71	78	80	83	86	87	87	77	79	80	82	83	85	86
7	61	67	70	77	78	81	82	68	75	78	81	84	85	86
8	70	75	78	80	84	85	85	76	80	83	85	86	87	86
9	68	74	76	79	83	85	84	78	86	88	89	90	90	89
10	75	79	81	82	83	84	85	69	73	78	80	83	84	85
11	67	69	72	74	77	80	81	80	83	84	86	87	88	87
12	69	73	75	78	80	82	82	76	79	81	83	84	85	85
Mean	**69**	**74**	**76**	**79**	**81**	**84**	**84**	**74**	**79**	**81**	**84**	**85**	**86**	**87**
%RSD	**5.5**	**5.4**	**4.8**	**3.7**	**3.7**	**2.7**	**2.1**	**5.5**	**5.0**	**4.3**	**3.8**	**2.9**	**2.2**	**1.4**
Minimum	**61**	**67**	**70**	**74**	**77**	**80**	**81**	**68**	**73**	**75**	**79**	**81**	**84**	**85**
Maximum	**75**	**79**	**81**	**83**	**86**	**87**	**87**	**80**	**86**	**88**	**89**	**90**	**90**	**89**
Date of Analysis	07-12-11 & 07-13-11							07-12-11 & 07-13-11						
Book Reference	B#2777/ Pg# 19,20 & B# 2763/ Pg# 60,61							B#2777/ Pg# 25,26 & B# 2763/ Pg# 64,65						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :**37±0.5**
RPM :**50**

Prepared By: 07-15-11 **Checked By:** 07/15/11 **Approved By:** 07/15/11

Table 12. Dissolution Data –Ranbaxy Process-II API vs. Lipitor®, 80 mg

Product: Atorvastatin Calcium Tablets, 80mg
Batch No.: RI561002
Mfg & Exp Date: 03/2010 & 02/2012
Manufactured By: OHM LABORATORIES INC., NJ

Product: Lipitor(atorvastatin calcium)Tablets 80mg
Batch No.: V101806
Mfg & Exp Date: NA & 11/2013
Manufactured By: Pfizer Ireland Pharmaceuticals, Dublin, Ireland

	Batch No.: RI561002							Batch No.: V101806						
	% Atorvastatin dissolved in							% Atorvastatin dissolved in						
Vessel #	10min	15min	20min	30min	45min	60 min	75 min	10min	15min	20min	30min	45min	60 min	75 min
1	78	85	86	89	90	91	90	77	82	84	87	87	88	88
2	72	78	81	84	86	87	87	70	79	83	86	86	86	87
3	83	87	89	91	92	91	91	73	77	79	81	83	84	85
4	72	77	80	84	87	88	88	75	81	82	86	86	86	87
5	67	74	79	83	85	86	86	69	73	75	79	81	84	87
6	79	83	85	87	88	88	88	77	79	80	82	83	85	86
7	78	82	86	87	90	89	89	68	75	78	81	84	85	86
8	74	80	83	85	86	85	87	76	80	83	85	86	87	86
9	76	79	82	83	84	83	85	78	86	88	89	90	90	89
10	79	80	82	91	93	92	92	69	73	78	80	83	84	85
11	81	84	87	91	93	92	92	80	83	84	86	87	88	87
12	81	83	85	87	88	87	88	76	79	81	83	84	85	85
Mean	77	81	84	87	89	88	89	74	79	81	84	85	86	87
%RSD	6.0	4.6	3.6	3.6	3.5	3.3	2.6	5.5	5.0	4.3	3.8	2.9	2.2	1.4
Minimum	67	74	79	83	84	83	85	68	73	75	79	81	84	85
Maximum	83	87	89	91	93	92	92	80	86	88	89	90	90	89
Date of Analysis	07-12-11 & 07-13-11							07-12-11 & 07-13-11						
Book Reference	B#2777/ Pg# 21,22 & B# 2763/ Pg# 62,63							B#2777/ Pg# 25,26 & B# 2763/ Pg# 64,65						

Dissolution Parameters:
Apparatus : **USP Apparatus II (Paddle)**
Medium : **0.05M Phosphate Buffer, pH 6.8 ,900mL**
Temperature(°C) :**37±0.5**
RPM :**50**

Prepared By: VM 07-14-11 **Checked By:** Divya Tandon 07/15/11 **Approved By:** LG 07/15/11

Table 13. F2 Metric, 80 mg Strength vs. other Strengths

F2 metric, biostudy strengths compared to other strength(s) (10 – 75 minutes, n=7)			
Biostudy Strength	**Other Strength**	**F2 metric for Test**	**F2 metric for RLD**
80 mg (b) (4) API for Test and	10 mg (b) (4) API	58.46	60.84
80 mg Lipitor® for Reference	20 mg API	62.23	77.82
	40 mg API	73.28	89.16
80 mg Ranbaxy Process-I	10 mg Ranbaxy Process-I	70.81	---
	20 mg Ranbaxy Process-I	72.76	---
	40 mg Ranbaxy Process-I	75.31	---
80 mg Ranbaxy Process-II	10 mg Ranbaxy Process-II	65.62	---
	20 mg Ranbaxy Process-II	78.44	---
	40 mg Ranbaxy Process-II	71.35	---

Table 14. F2 Metric for Test (Biostudy Batch, (b) (4) API), 80 mg Strength vs. Other Test Strengths and Test Products

F2 metric, biostudy strength compared to other Products (10 – 75 minutes, n=7)			
Biostudy Strength	**Other Strength**	**F2 metric for Test**	**F2 metric for RLD**
80 mg (b) (4) API	10 mg Ranbaxy Process-I	57.56	---
	20 mg Ranbaxy Process-I	51.71	---
	40 mg Ranbaxy Process-I	70.49	---
	80 mg Ranbaxy Process-I	60.46	---
80 mg (b) (4) API	10 mg Ranbaxy Process-II	70.49	---
	20 mg Ranbaxy Process-II	81.35	---
	40 mg Ranbaxy Process-II	68.62	---
	80 mg Ranbaxy Process-II	91.73	---

Table 15. F2 Metric for Reference (Biostudy Batch, Lipitor®) 80 mg Strength vs. Other Test Strengths and Test Products

F2 metric, biostudy strength compared to other Products (10 – 75 minutes, n=7)			
Biostudy Strength	**Other Strength**	**F2 metric for Test**	**F2 metric for RLD**
80 mg Lipitor®	10 mg (b) (4) API	63.37	---
	20 mg API	70.70	---
	40 mg API	66.09	---
	80 mg API I	82.84	---
80 mg Lipitor®	10 mg Ranbaxy Process-I	61.09	---
	20 mg Ranbaxy Process-I	56.10	---
	40 mg Ranbaxy Process-I	83.84	---
	80 mg Ranbaxy Process-I	67.79	---
80 mg Lipitor®	10 mg Ranbaxy Process-II	78.44	---
	20 mg Ranbaxy Process-II	69.80	---
	40 mg Ranbaxy Process-II	61.05	---
	80 mg Ranbaxy Process-II	76.32	---

4.2.Copied from CMC Review on Stability

Refer: DARRTS, ANDA 076477, CMC Review, Section 29, Stability, page 69. LI, HAITAO 06/14/2011 N/A 06/14/2011 REV-QUALITY-03 (General Review) Original-1

(See the Chemist's Conclusion at the bottom of the page)

Stability protocol for bulk core tablets under CRT condition is:

Attributes Recorded (b) (4)	Initial	3	6
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x

Stability protocol for bulk coated tablets under CRT condition is:

Attributes Recorded (b) (4)	Initial	3	6
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x
	x	x	x

The firm proposed 24 months expiry date for the DP. The expiry date is appropriate base on stability data provided.
Post Approval Stability Commitments

BIOEQUIVALENCE DEFICIENCY

ANDA:	076477
APPLICANT:	Ranbaxy Laboratories Ltd.
DRUG PRODUCT:	Atorvastatin Calcium Tablet 10, 20 , 40 and 80 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

The dissolution testing data as submitted in the current amendment for the test lots Nos. RI530902, RI540901, RI550901 and RI560901 (all with (b) (4) Active Pharmaceutical Ingredient (API)), using the modified dissolution method with a slower paddle speed of 50 rpm, are **incomplete**. The dissolution testing for these lots was conducted between June and July 2011, and these lots were manufactured in May 2009. Therefore, these lots were more than 24 months old at the time of testing. Unless you provide adequate additional stability data to support any expiry period beyond 24 months, these lots are considered expired and unacceptable for the testing at this time. In addition, we note that there was a discrepancy in the expiration dates reported by you for the test lots with (b) (4) API between the current amendment and previous submissions: The expiration date for each of (b) (4) API test products, 10, 20, 40 and 80 mg, Lot Nos. RI530902, RI540901, RI550901 and RI560901, was reported to be 4/2012 in the 07/18/2011 submission, whereas in the previous submission, dated 11/12/2010, the expiration date for each of these lots was correctly reported as 4/2011.

For the above reason, please repeat the dissolution testing on ***unexpired*** test batches of Atorvastatin Calcium Tablets (with (b) (4) API), 10, 20, 40 and 80 mg, using the following modified FDA method:

Medium: 0.05M Phosphate Buffer, pH 6.8 at 37^0C
Volume: 900 mL
USP Apparatus: II (Paddle) at 50 rpm

[NOTE: The method should use conventional USP II Vessels, and not (b) (4) Vessels.]

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.3. Outcome Page

ANDA: 076477

5. COMPLETED ASSIGNMENT FOR 076477 ID: 14611

Reviewer: Shrivastava, Surendra **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Atorvastatin Calcium Tablets

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal		
14611	7/18/2011	Other	Study Amendment	1	1	Edit	Delete
				Bean Total:	1		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURENDRA P SHRIVASTAVA
08/04/2011

YIH CHAIN HUANG
08/04/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
08/08/2011

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	076477					
Drug Product Name	Atorvastatin Calcium Tablets					
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg					
Applicant Name	Ranbaxy Laboratories Ltd., India					
Address	Plot # GP-5, Sector 18, HSIDC, Old Delhi, Gurgaon Road, Gurgaon, 122015, Hariyana, India					
Applicant's Point of Contact	Scott D. Tomsky, US Agent, 600 College Road East, Ranbaxy Inc., Princeton, NJ 08540					
Contact's Telephone Number	609-720-5609					
Contact's Fax Number	609-514-9797					
Original Submission Date(s)	August 19, 2002 December 9, 2009 November 12, 2010 (additional API – Ranbaxy Process 1 and Process 2)					
Submission Date(s) of Amendment(s) Under Review	July 18, 2011 (Additional Dissolution Data for all Strengths) **August 26, 2011**					
Reviewer	S. P. Shrivastava, Ph.D.					
Study Number (s)	**R09-1032**	**R09-1033**	**BE-248-ATOR-2009**	**BE-249-ATOR-2009**	**365-ATORV-09**	**3023-ATORV-08**
Study Type (s)	Fasting	Fed	Fasting	Fed	Fasting	Fed
Strength (s)	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg
Clinical Site	**Cetero Research**		**Clinical Services Fortis Clinical Research Ltd.**		**Ranbaxy Labs. Ltd.**	
Clinical Site Address	4801 Amber Valley Pkwy. Fargo, ND 58104		Ltd., Sunflag Hospital & Research Centre Sector-16A, Faridabad 121 002, Haryana, India		Majeedia Hospital, Hamdard Nagar New Delhi India	
Analytical Site	(b) (4)				**Ranbaxy Labs. Ltd**	
Analytical Site Address					Plot No. GP-5, Sector 18, HSIDC, Gurgaon, Haryana, India	
Dissolution Testing Site	Ranbaxy Laboratory Ltd.					
OSI Inspection Status	No OSI inspections of pivotal study sites, Cetero Research (Clinical) or (b) (4) (Analytical) is pending or necessary **For Cause OSI Inspection of Dissolution Testing Site, Ohm Labs., Inc., North Brunswick, NJ, is pending**					
Overall Review Result	**INADEQUATE** (pending acknowledgment of the dissolution method and specification, and OSI For Cause dissolution inspection)					
Waiver Request Result	**ADEQUATE :** 10, 20 and 40 mg					
OSI Report Result	**Clinical: ADEQUATE.** **Analytical: ADEQUATE** (Details covered in 12/9/2009 submission review) **Dissolution: Pending**					
Bioequivalence Study Tracking/Supporting	**Study/Test Type**		**Strength**		**Review Result**	

Document #			
Supporting Document #57, 58, 71	**Dissolution**	80 mg	**INADEQUATE**
	Dissolution	40 mg	**INADEQUATE**
	Dissolution	20 mg	**INADEQUATE**
	Dissolution	10 mg	**INADEQUATE**
Supporting Document # 57	**Fasting (Pivotal) - using** (b) (4) **API**	80 mg	**ADEQUATE**
	Fed (Pivotal) – using (b) (4) **API**	80 mg	**ADEQUATE**
	Pilot Fasting (BE-248-ATOR-2009)	80 mg	**INADEQUATE**
	Pilot Fed (BE-249-ATOR-2009)	80 mg	**INADEQUATE**
	Pilot Fasting (365-ATORV-09)	80 mg	**INADEQUATE**
	Pilot Fasting (3023-ATORV-08)	80 mg	**INADEQUATE**
	Permeability Study	**N/A**	**N/A**
	Solubility Study	**N/A**	**N/A**

1. EXECUTIVE SUMMARY

This application references Atorvastatin Calcium Tablets, 10, 20, 40 and 80 mg [Lipitor®, Pfizer, NDA 020702, Approved 10, 20 mg, 40 mg-12/17/1996; 80 mg-4/7/2000 (RLD)]. The firm had previously conducted acceptable single-dose fasting and fed studies on 80 mg tablets, and dissolution testing results on all strengths [see JEChaney, V:\FIRMSNZ\RANBAXY\LTRS&REV\76477N0802.doc., V:\FIRMSNZ\RANBAXY\LTRS&REV\76477A0503.doc], HTNguyen, V:\firmsnz\ranbaxy\ltrs&rev\76477a0906.doc, DARRTS, 076477, SHRIVASTAVA, SURENDRA P 09/27/2007 N/A 09/27/2007 REV-BIOEQ-01(General Review) Original-1, SHRIVASTAVA, SURENDRA P 06/19/2008 N/A 06/19/2008 REV-BIOEQ-01(General Review) Original-1].

In the current review document, the three different issues are addressed: (1). Finalization of the dissolution method and specification for the test products. (2). Clarification concerning the DBI recommendation of granting waivers to the test products manufactured using the alternate API sources, Ranbaxy Process-I and Ranbaxy Process-II, based on comparative dissolution data of the test products manufactured using (b) (4) API, Ranbaxy Process-I and Process-II APIs. (3). Requesting an inspection of the dissolution testing conduct and data.

1. Finalization of the Dissolution Method and Specification:

In the 12/09/2009 amendment, the firm made CMC pre-approval changes (polymorphic form, component and composition, manufacturing process and manufacturing site). The firm did not provide specific reason for the proposed changes. It is probably due to the regulatory issues related to the original manufacturing site (Ranbaxy Lab, Paonta Sahib's API). In support of the CMC changes the firm submitted additional single-dose fasting and fed studies on 80 mg strength and requested waivers of BE studies for 10, 20 and 40 mg tablets. The fasting and fed studies were found acceptable [see DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1]. The test product in these additional BE studies used the API from (b) (4) (crystalline form). However, in a subsequent amendment dated 11/12/2010, the firm proposed an additional source of API (Ranbaxy Labs.,

DMF 24139) for Atorvastatin Calcium, USP (crystalline), manufactured by two different processes. In support of these changes, the firm provided comparative dissolution data for Test (Ranbaxy's APIs by Process-I and Process-II) and Reference (b) (4) API) products using the FDA-recommended dissolution method (900 mL of 0.05 M Phosphate buffer at pH 6.8 and Paddle at 75 rpm). The dissolution testing data appeared to be insufficiently discriminatory and, therefore, the firm was requested to repeat the testing using a modified version of the FDA recommended method (Paddle speed of 50 rpm instead of 75 rpm). Additionally, a discriminatory method was explored for detecting any differences in the test products manufactured with three different APIs (b) (4), Ranbaxy Process-I and Ranbaxy Process-II)[1].

In 07/18/2011 amendment, the firm provided additional dissolution data on (b) (4) API and Ranbaxy Process-I and Process-II API products using the modified FDA method (Paddle speed of 50 rpm). The dissolution testing on Ranbaxy Process-I and Process-II API products were found acceptable. However, (b) (4) API products were tested on expired lots. Therefore, the firm was requested to repeat the dissolution testing on unexpired lots of Atorvastatin Calcium Tablets (b) (4) API), 10, 20, 40 and 80 mg, using the modified FDA method.[2]

In this amendment, the firm has provided explanation and additional stability data to justify the validity of the dissolution testing results submitted earlier. Although the firm is proposing 24-month Expiration Date, the firm has provided additional stability data for >26 months (5/2009 to 8/2011). The Chemistry Division finds the additional stability data acceptable. Therefore, the dissolution testing results for (b) (4) API products are accepted at this time. The deficiency response is considered satisfactory.

When considering all dissolution data submitted (using 75 rpm in the previous submission and using 50 rpm in the current amendment), the dissolution data generated using the modified FDA method with a slower Paddle speed of 50 rpm (for more discriminating power) did not show any significant difference in dissolution profiles of the test products manufactured with (b) (4) API, Ranbaxy Process I and Ranbaxy Process II APIs. Therefore, the OGD recommends that the original FDA method (Paddles at 75 rpm) and specification should be used for the test products to be consistent with the dissolution and specifications recommended for most of other ANDAs of the same drug product (Please see attachment for the office's recommendation, Sections 4.6, 4.7 and 4.8). No other ANDAs have more than one API for their products.

For the original FDA method, the firm provided adequate dissolution data obtained for ***unexpired*** test lots manufactured using any of the three mentioned APIs. Also, based on these dissolution data, the originally recommended specification remains the same. Therefore, the DBE acknowledges that the firm will conduct its dissolution testing for its products using the following FDA-recommended method and specification:

[1] DARRTS, ANDA 076477, SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1; SHRIVASTAVA, SURENDRA P 05/12/2011 N/A 05/12/2011 REV-BIOEQ-01(General Review) Original-1

[2] DARRTS, ANDA 076477, 07/18/2011, SHRIVASTAVA, SURENDRA P 08/08/2011 N/A 08/08/2011 REV-BIOEQ-01(General Review) Original-1

Medium:	0.05M Phosphate Buffer, pH 6.8 at 37^0C
Volume:	900 mL
USP Apparatus:	II (Paddle) at 75 rpm
Specification:	NLT (b) (4) (Q) in 15 minutes

2. Clarification of Reasons for the DBI Recommendation of Granting Waivers to the Test Product Manufactured with Ranbaxy Process-I and Process-II APIs:

As it was not clearly stated in the bioequivalence review of the amendment dated 11/12/ 2010, in addition to the changes in the APIs of the test product, the firm proposed additional minor manufacturing changes at the same time. These changes were due to the alternate APIs used. Those additional changes were as follows:

i) Manufacturing process

The following minor changes have been proposed in the manufacturing process:

(b) (4)

3. Other editorial changes have also been made in the batch records.

Per the investigative report submitted, upon replacing the Ranbaxy Process-I API, the dissolution profiles of the test products containing the alternate API changed and slowed down drastically. The firm conducted an investigation and found out that (b) (4) The chemistry division evaluated the API and API-related manufacturing changes in the review [DARRTS, ANDA 076477, 11/12/2010, LI, HAITAO 06/14/2011 N/A 06/14/2011 REV-QUALITY-03(General Review) Original-1], and concluded that *"The data generated on the drug product test batches manufactured incorporating the new source API and with proposed manufacturing changes confirm that the changes do not*

have any adverse effect on the quality of the drug product." [see Chemistry Assessment, Section 25, Manufacturing and Processing, page 51, DARRTS, ANDA 076477, 11/12/2010, LI, HAITAO 06/14/2011 N/A 06/14/2011 REV-QUALITY-03(General Review) Original-1].

In addition, per the request of the OMPQ on September 28, 2011, the DBI obtained confirmation from the chemistry reviewer that the above-mentioned manufacturing changes were considered minor, and therefore, do not necessitate a recommendation for an in vivo bioequivalence study comparing the new-API test products with that of the (b) (4) -API test product, which underwent acceptable bioequivalence testing (See Appendix, Section 4.9).

Based on the above information, and the comparable dissolution data between the test products of different APIs, the DBI considers it is adequate for granting the waivers of an additional in vivo bioequivalence study (provided that the dissolution testing data can be authenticated in the inspection requested below).

3. Requesting for OSI Inspection of Dissolution Testing: The Ranbaxy products have a long history of dissolution testing, and have gone through number of pre-approval changes over the years (see Appendix Section 4.7). In the latest amendments, the firm introduced the new test lots manufactured using the new Ranbaxy Process-I and Process II APIs, and requested waiver of in vivo bioequivalence testing based on the BE studies of the lot with (b) (4) API. Additionally, the firm is planning to manufacture commercial batches using the Ranbaxy-Process II API as the primary source. Therefore, it is important to make certain that the dissolution testing for these new test lots was conducted appropriately, and the latest dissolution data can be authenticated. Based on these reasons, the DBI recommends that an OSI inspection be requested immediately for dissolution testing conducted for the biostudy test lot as well as exhibit lots manufactured using the (b) (4) API (comparing them against the RLD product), and for the test lots manufactured using the Ranbaxy Process-I and Ranbaxy Process-II APIs (comparing them against the RLD product), based on both the previously FDA-recommended method as well as the modified method with a slower paddle speed.

The application is **inadequate** pending the results of OSI inspection on the dissolution testing site.

2. TABLE OF CONTENTS

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1 [See DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

3. SUBMISSION SUMMARY

3.1.Drug Product Information

[See DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

3.2.PK/PD Information

[See DARRTS, ANDA 076477, Submission date 12/09/2009; SHRIVASTAVA, SURENDRA P 05/04/2011 N/A 05/04/2011 REV-BIOEQ-01(General Review) Original-1].

3.3. Contents of Submission

Response to information request – Deficiency response.

3.4. In Vitro Dissolution

Location of DBE Dissolution Review	See Appendix, Section 4.1, Stability Data (current review)
Source of Method (USP, FDA or Firm)	**FDA**
Medium	0.05 M Phosphate buffer, pH 6.8 @ 37°C
Volume (mL)	900 mL
USP Apparatus type	II (Paddle)
Rotation (rpm)	75 rpm
Firm's specification	Not provided
DBE-recommended specification	NLT (b) (4) (Q) is dissolved in 15 minutes
If a modified-release tablet, was testing done on 1/2 tablets?	N/A
F2 metric calculated?	Yes
If no, reason why F2 not calculated	N/A
Is method acceptable?	No (see comment)
If not then why?	See Deficiency Comment

3.5. Deficiencies, Firm's Response and Conclusion

DEFICIENCY-1: *The dissolution testing data as submitted in the current amendment for the test lots Nos. RI530902, RI540901, RI550901 and RI560901 (all with* (b) (4) *Active Pharmaceutical Ingredient (API)), using the modified dissolution method with a slower paddle speed of 50 rpm, are* ***incomplete****. The dissolution testing for these lots was conducted between June and July 2011, and these lots were manufactured in May 2009. Therefore, these lots were more than 24 months old at the time of testing. Unless you provide adequate additional stability data to support any expiry period beyond 24 months, these lots are considered expired and unacceptable for the testing at this time. In addition, we note that there was a discrepancy in the expiration dates reported by you for the test lots with* (b) (4) *API between the current amendment and previous submissions: The expiration date for each of* (b) (4) *API test products, 10, 20, 40 and 80 mg, Lot Nos. RI530902, RI540901, RI550901 and RI560901, was reported to be 4/2012 in the*

07/18/2011 submission, whereas in the previous submission, dated 11/12/2010, the expiration date for each of these lots was correctly reported as 4/2011.

*For the above reason, please repeat the dissolution testing on **unexpired** test batches of Atorvastatin Calcium Tablets (with (b) (4) API), 10, 20, 40 and 80 mg, using the following modified FDA method:*

Medium:	*0.05M Phosphate Buffer, pH 6.8 at 37^{0}C*
Volume:	*900 mL*
USP Apparatus:	*II (Paddle) at 50 rpm*

[NOTE: The method should use conventional USP II Vessels, and not (b) (4) Vessels.]

Additionally, during a telephone conversation between Scott Tomsky of Ranbaxy and Nam Chun of OGD on August 24, 2011, the Agency requested for the following:

- **Exact dates of manufacturing for each of the exhibit batches.**
- **Exact dates of analysis for the 24 month stability testing.**
- **Exact dates for testing of dissolution data submitted in the July 18, 2011 amendment.**
- **Clarification on which API will be used for commercial manufacturing**

Firm's Response: The firm has provided the following response:

In addition, as per the stability protocol, the stability studies at controlled room temperature conditions are continued until 36 months. Based on the Agency's comments, the 26 months controlled room temperature (CRT) stability samples of the (b) (4) API drug product batches have been tested as per the stability specifications. In addition, the dissolution profile of the 26 months CRT stability samples, using the FDA recommended parameters, has also been generated. The reports are provided in **Attachment 1.** The results for all the tests parameters comply with the requirement. This additional stability data supports the expiry beyond 24 months and therefore the dissolution profile data generated on these batches (performed after 24 months of manufacturing) can be considered acceptable.

Please note, even though the 26 months controlled room temperature data generated on the (b) (4) API drug product batches support expiry beyond 24 months, Ranbaxy is proposing only 24 months as the expiry date for the commercial batches at this time. Any increase in the expiration dating will be based on the real time data generated on at least three commercial batches.

Regarding the discrepancy in the expiration dating noted in the Agency's comment, we acknowledge that there is an error in the expiration date of the (b) (4) API drug product batches in the dissolution profile report submitted in the July 18, 2011 amendment. We apologize for the oversight. The corrected reports are provided in **Attachment 4.**

Please note, at present time, other than the exhibit batches, no further batches have been taken with the (b) (4) API. As noted in the July 27, 2011 CMC amendment, at this time, Ranbaxy's Process II API is proposed as the primary source of API for commercial manufacturing. Ranbaxy's Process I API and (b) (4) API are proposed as secondary sources of API.

The manufacturing dates, dissolution testing dates and stability data are provided in Appendix, Sections 4.1- 4.4.

Summary: Originally, the DBE considered recommending the modified FDA method with a slower paddle speed for the current ANDA. For this modified method, the dissolution data were generated for the test product with the (b) (4) API when the lots of this test product had already expired. Therefore, the DBE requested the firm for additional stability data to support the expired lots. Based on the manufacturing and dissolution testing dates for (b) (4) API products and on 2-year expiration date, the firm has conducted dissolution beyond expiration dates (48-65 days, see Appendix below). Although the firm is proposing 24-month Expiration Date, the firm has provided additional stability data for >26 months (5/2009 to 8/2011). The Chemistry Division finds the additional stability data acceptable (see Appendix, Section 4.5). Therefore, the dissolution testing results for (b) (4) API products are accepted at this time. The deficiency response is considered satisfactory.

However, since the dissolution data generated using the modified FDA method with a slower paddle speed of 50 rpm (for more discriminating power) did not show any significant difference in dissolution profiles of the test products manufactured with (b) (4) API, Ranbaxy Process I and Ranbaxy Process II APIs, the OGD recommends that the original FDA method and specification should be used for the test products to be consistent with the dissolution and specifications recommended for other ANDAs of the same drug product (Please see attachment for the office's recommendation). No other ANDAs have more than one API for their products.

For the original FDA method, the firm provided adequate dissolution data obtained for ***unexpired*** test lots manufactured using any of the three mentioned APIs. Also, based on these dissolution data, the originally recommended specification remains the same. Therefore, the DBE acknowledges that the firm will conduct its dissolution testing for its products using the following FDA-recommended method and specification:

Medium: 0.05M Phosphate Buffer, pH 6.8 at 37^0C
Volume: 900 mL
USP Apparatus: II (Paddle) at 75 rpm
Specification: NLT (b) (4) (Q) in 15 minutes

The deficiency response is **satisfactory**.

3.6. Deficiency Comments

Per the current amendment, the firm is planning to manufacture commercial batches using the Ranbaxy Process II API as the primary source, instead of the (b) (4) API from which the biostudy test lot was manufactured. Therefore, the validity of these production batches, with respect to bioequivalence evaluation, is mainly hinged on the dissolution data for biostudy test lot with (b) (4) API.

Additionally, the Ranbaxy products have a long history of dissolution testing, and have gone through number of pre-approval changes over the years (see Appendix Section 4.7). In the latest amendments, the firm introduced the new test lots manufactured using the new Ranbaxy Process-I and Process II APIs, and requested waiver of in vivo bioequivalence testing based on the BE studies of the lot with (b) (4) API. Additionally, the firm is planning to

manufacture commercial batches using the Ranbaxy-Process II API as the primary source. Therefore, it is important, to make certain that the dissolution testing for these new lots was conducted appropriately, and the latest dissolution data can be authenticated.

Based on the above reasons, the DBE recommends that an OSI inspection be requested immediately for dissolution testing conducted for the biostudy test lot as well as exhibit lots manufactured using the (b) (4) API (comparing them against the RLD product), and for the test lots manufactured using the Ranbaxy Process-I and Ranbaxy Process-II APIs (comparing them against the RLD product), using both the previously FDA-recommended method as well as the modified FDA method with a slower paddle speed.

3.7. Recommendations

1. The dissolution testing conducted by Ranbaxy Laboratories Ltd. on its Atorvastatin Calcium, 10, 20, 40 and 80 mg Tablets, manufactured with (b) (4) and Ranbaxy's APIs (Process-1 and Process-2), comparing them with Pfizer, Lipitor® (Atorvastatin Calcium), 10, 20, 40 and 80 mg Tablets, respectively, is **incomplete** due to deficiencies cited above.

2. The Division of Bioequivalence has previously **accepted** the fasting BE study (R09-1032) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #R1560901 (with (b) (4) API) comparing it to Pfizer, Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V.

3. The Division of Bioequivalence has previously **accepted** the fed BE study (R09-1033) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #R1560901 (with (b) (4) API) comparing it to Pfizer, Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V.

4. The Division of Bioequivalence has previously acknowledged the pilot fasting BE study (BE-248-ATOR-2009) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #B204130 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA), and Canada Lipitor®, 80 mg, Lot # B0378088 (Pfizer, Canada).

5. The Division of Bioequivalence has previously acknowledged the pilot fed BE study (BE-249-ATOR-2009) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #B204130 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA).

6. The Division of Bioequivalence has previously acknowledged the pilot fasting BE study (365-_ATORV_09) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #ANK (3926)071A comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #04558V (Pfizer, USA), and Belgium Lipitor®, 80 mg, Lot # 0904118B (Pfizer, Belgium).

7. The Division of Bioequivalence has previously acknowledged the pilot fasting BE study (3023-_ATORV_08) conducted by Ranbaxy on its Atorvastatin Calcium, 80 mg Tablets, Lot #ANK (3926)049 comparing it to US Lipitor® (Atorvastatin Calcium) Tablets, 80 mg, Lot #22537V (Pfizer, USA).

8. The DBE acknowledges that the firm will conduct its dissolution testing for its products using the following FDA-recommended method and specification:

Medium:	0.05M Phosphate Buffer, pH 6.8 at 37^0C
Volume:	900 mL
USP Apparatus:	II (Paddle) at 75 rpm
Specification:	NLT (b) (4) (Q) in 15 minutes

9. The formulations for the 10, 20 and 40 mg strengths ((b) (4) API) were found (b) (4) to the 80 mg strength of the test product ((b) (4) API), which underwent bioequivalence testing. The waivers of in vivo bioequivalence study requirements for 10, 20 and 40 mg strength Tablets of the test product ((b) (4) API) are granted.

3.8. Comments for Other OGD Disciplines

Discipline	Comment
PM	**Please request a For Cause OSI inspection for the dissolution testing.**

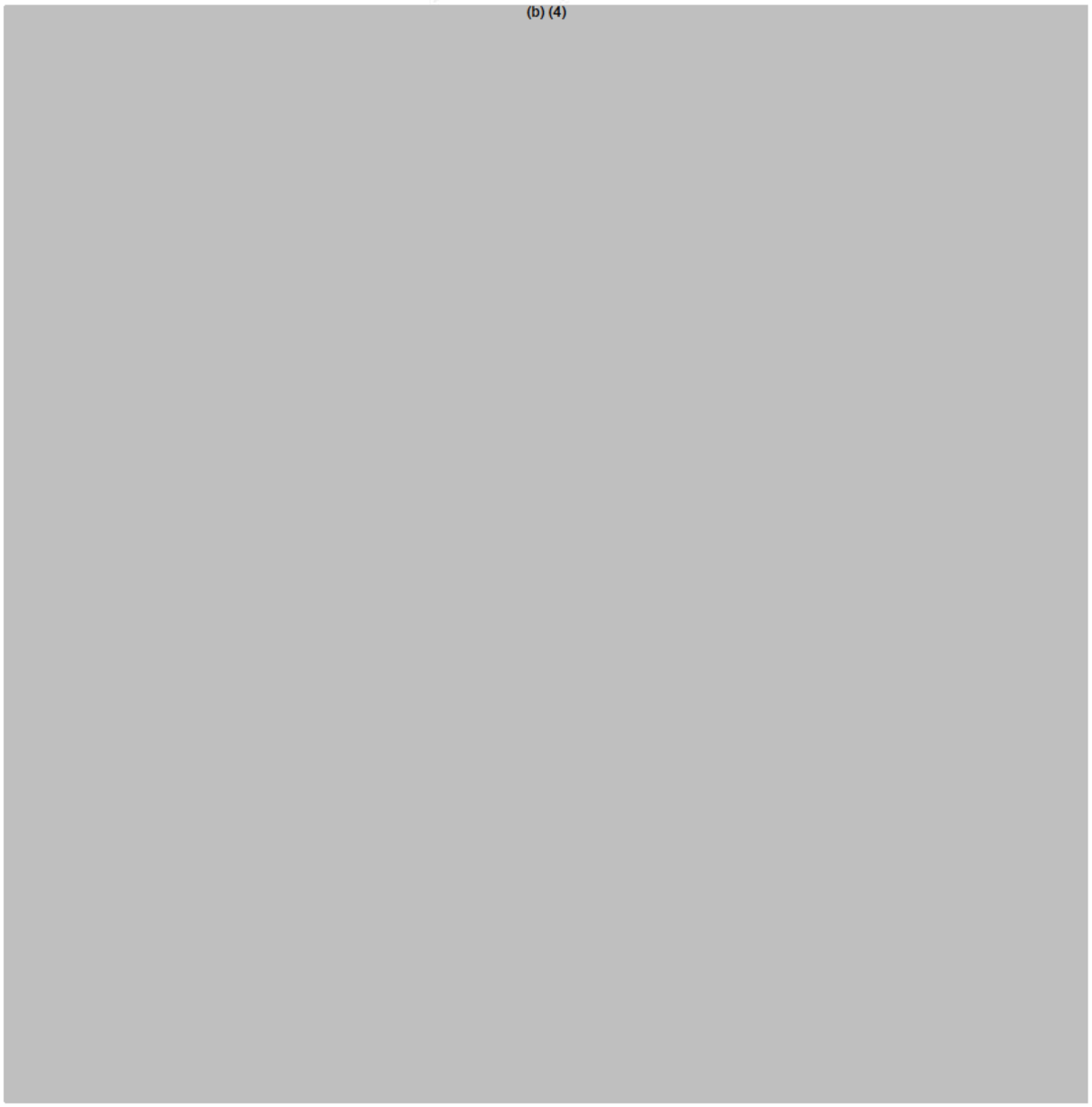
4. APPENDIX

4.1.Stability Data

ohm LABORATORIES, INC.

ANALYTICAL REPORT
(SHELF LIFE)

(b) (4)



4.2. Manufacturing Dates for Exhibit Batches

Batch No.	Strength	API Source	Exact date of the exhibit batches
RI530901	(b) (4)	(b) (4)	05/01/2009
RI530902	10 mg		05/11/2009
RI540901	20 mg		05/12/2009
RI550901	40 mg		05/08/2009
RI560901	80 mg		05/12/2009
RI531001	(b) (4)	Ranbaxy (Process I)	02/04/2010
RI531002	10 mg		02/12/2010
RI541001	20 mg		02/12/2010
RI551001	40 mg		02/12/2010
RI561001	80 mg		02/16/2010
RI531003	(b) (4)	Ranbaxy (Process II)	03/02/2010
RI531004	10 mg		03/11/2010
RI541002	20 mg		03/11/2010
RI551002	40 mg		03/12/2010
RI561002	80 mg		03/12/2010

4.3.Dissolution Testing Dates (Amendment, Dated 07/18/2011)

Batch numbers	Strength (mg)	Date of analysis completed (1-6 units) and (7-12 units)
Atorvastatin Calcium Tablets (b) (4) API)		
RI530902	10	06/28/2011 & 07/01/2011
RI540901	20	07/06/2011 & 07/07/2011
RI550901	40	07/08/2011 & 07/12/2011
RI560901	80	06/28/2011 & 07/12/2011
Atorvastatin Calcium Tablets (Ranbaxy Process I API)		
RI531002	10	06/30/2011 & 06/302011
RI541001	20	07/06/2011 & 07/07/2011
RI551001	40	07/08/2011 & 07/12/2011
RI561001	80	07/12/2011 & 07/13/2011
Atorvastatin Calcium Tablets (Ranbaxy Process II API)		
RI531004	10	07/05/2011 & 07/05/2011
RI541002	20	07/06/2011 & 07/07/2011
RI551002	40	07/08/2011 & 07/12/2011
RI561002	80	07/12/2011 & 07/13/2011

4.4. Stability Testing Dates

Batch No.	Strength	Pack size	Exact date of 24 month stability testing				
			Description	Dissolution	Assay	Degradation	(b) (4)
RI530902	10 mg	90's bottle	06/23/2011	06/21/2011	06/24/2011	06/25/2011	06/22/2011
RI530902	10 mg	500's bottle	06/23/2011	06/21/2011	06/24/2011	06/25/2011	06/22/2011
RI540901	20 mg	90's bottle	06/23/2011	06/22/2011	06/24/2011	06/25/2011	06/22/2011
RI540901	20 mg	500's bottle	06/23/2011	06/22/2011	06/24/2011	06/25/2011	06/22/2011
RI550901	40 mg	90's bottle	06/23/2011	06/22/2011	06/24/2011	06/25/2011	06/22/2011
RI550901	40 mg	500's bottle	06/23/2011	06/22/2011	06/24/2011	06/25/2011	06/22/2011
RI560901	80 mg	90's bottle	06/23/2011	06/21/2011	06/24/2011	06/25/2011	06/22/2011
RI560901	80 mg	500's bottle	06/23/2011	06/21/2011	06/24/2011	06/25/2011	06/22/2011

Note: Samples were placed on stability: 06/17/2009
Actual expiry date for the batches: 04/2011
Samples due for 24 months testing: 06/17/2011
Date analysis completed as per stability specifications: 06/25/2011

4.5. Chemist's Evaluation of Stability Data for (b) (4) API Products

From: Li, Haitao
Sent: Wednesday, September 07, 2011 12:35 PM
To: Shrivastava, Surendra P
Cc: Gill, Devinder; Sayeed, Vilayat A; Huang, Yih Chain; Nguyen, Hoainhon T; Nagavelli, Laxma
Subject: RE: ANDA 076477 Atorvastatin: Consult Request for the Review of Additional Stability Study by Chemistry

Surendra,

All the stability data (up to 26 months) submitted in the Amendment dated 8/26/2011 for Ranbaxy's Atorvastatin Calcium Tablets, 10, 20, 40 and 80 mg, manufactured with (b) (4) API in 500 ct Bottles are acceptable.

Thanks! Haitao

From: Shrivastava, Surendra P
Sent: Tuesday, September 06, 2011 12:51 PM
To: Li, Haitao
Cc: Sears, Leigh Ann; Gill, Devinder; Sayeed, Vilayat A; Huang, Yih Chain; Nguyen, Hoainhon T
Subject: ANDA 076477 Atorvastatin: Consult Request for the Review of Additional Stability Study by Chemistry

Hello Haitao,

I understand you are the Chemistry Reviewer for this ANDA. Therefore, I am sending this consult to you.

With respect to the above ANDA, we need to know, based on the additional stability study data provided by the firm (dated 8/26/2011), as to how long Ranbaxy's Atorvastatin Calcium Tablets, 10, 20, 40 and 80 mg, manufactured with (b) (4) API (see the batch numbers below), may be considered stable for a valid dissolution/BE study.

A brief background is provided below and in the attached Draft Bio-review.

In 07/18/2011 amendment, the firm provided additional dissolution data on (b) (4) API and Ranbaxy Process-I and Process-II API products. The dissolution testing on Ranbaxy Process-I and Process-II API products were found acceptable. However, (b) (4) API products were tested on expired lots [see DARRTS, ANDA 076477, 07/18/2011, SHRIVASTAVA, SURENDRA P 08/08/2011 N/A 08/08/2011 REVBIOEQ-01(General Review) Original-1]. Therefore, the firm was requested to repeat the dissolution testing on unexpired lots of Atorvastatin Calcium Tablets ((b) (4) API), 10, 20, 40 and 80 mg, using the modified FDA method as follows:

Medium: 0.05M Phosphate Buffer, pH 6.8 at 37^0C
Volume: 900 mL
USP Apparatus: II (Paddle) at 50 rpm

In 8/26/2011 amendment, the firm has provided explanation and additional stability data to justify the validity of the dissolution testing results submitted earlier. Although the firm is proposing 24-month Expiration Date, additional stability data for >26 months (5/2009 to 8/2011) provided should be sufficient to validate the dissolution testing results. However, the data need to be evaluated by you or the assigned Chemistry Reviewer.

Please note that, this ANDA is being EXPEDITED. Thank you. Surendra

Manufacturing Dates for Exhibit Batches << OLE Object: Picture (Metafile) >> Draft-only Bio-Review

<< File: 076477A0811.doc >>

4.6. Dissolution Method and Specification Accepted for other Atorvastatin Calcium Tablets

ANDA	Firm	Dissolution Method	Specification
091650	Reddys Labs.	FDA Method*	NLT (b) (4) (Q) in 15 min.
(b) (4)			
091226	Matrix Labs. Ltd.	FDA Method*	NLT (b) (4) (Q) in 15 min.
078773	Teva Pharms, USA	FDA Method*	NLT (b) (4) (Q) in 15 min.
077575	Sandoz Inc.	FDA Method*	NLT (b) (4) (Q) in 15 min.
090548	Apotex Inc.	FDA Method*	NLT (b) (4) (Q) in 15 min.
091624	Kudco Ireland Ltd.	Firm's Method**	NLT (b) (4) (Q) in 30min.

* 900 mL 0.05 M Phosphate buffer, pH 6.8, Paddle at 75 rpm
** 900 mL 0.05 M Phosphate buffer at pH 6.8 with 0.3% Tween® 80, Paddle at 75 rpm

4.7. E-Mails between DBE and OC, and History of Dissolution Testing for ANDA 076477

From: Nguyen, Hoainhon T
Sent: Wednesday, September 14, 2011 9:55 AM
To: Huang, Yih Chain; Shrivastava, Surendra P
Cc: Nguyen, Hoainhon T; Conner, Dale P; Chun, Nam
Subject: Requesting OSI Inspection of Dissolution Testing Site(s) and Data for Ranbaxy's Atorvastatin Products

YC and Surendra,
I had previously cc'ed you in the attached email. I am resending it just in case you could not locate the previous email.

Based on the following reasons:
(1) The history of dissolution data (as well as other data not discussed in the email below) submitted for ANDA 76477 as discussed in the email below;
(2) The fact that, based on the latest amendment dated August 26, 2011, the firm stated that it is planning to manufacture commercial batches using the Ranbaxy-Process II API as the primary source, instead of the (b) (4) API from which the biostudy test lot was manufactured, and therefore, the validity of these production batches, with respect to bioequivalence evaluation, is mainly hinged on the dissolution data comparing the biostudy test lot with (b) (4) API and the lots manufactured from the Ranbaxy Process-I API and Ranbaxy Process-II API: It is important to make certain that the dissolution testing for these lots was conducted appropriately and the lastest dissolution data can be authenticated;
(3) Since the Agency rarely conducts inspection on dissolution testing sites and data, the DBE is currently considering initiating such inspection requests on a regular basis in the near future to assure the quality and validity of dissolution data submitted in ANDAs;

We recommend that an OSI inspection be requested immediately for dissolution testing conducted for the biostudy test lot as well as exhibit lots manufactured using the (b) (4) API (comparing them against the RLD product), and the test lots manufactured using the Ranbaxy Process-I and Ranbaxy Process-II APIs (comparing them against the RLD product), using both the previously FDA-recommended method as well as the currently revised and recommended method.

Please revise the latest draft review to include the OSI inspection request.

Thanks, Hoai

From: Nguyen, Hoainhon T
Sent: Monday, April 11, 2011 9:08 AM
To: Takahashi, Karen
Cc: Nagavelli, Laxma; Conner, Dale P; Nguyen, Hoainhon T; Nerurkar, Shriniwas G; Huang, Yih Chain; Shrivastava, Surendra P
Subject: Questions Concerning Dissolution Data of Ranbaxy's Atorvastatin from the FDA Compliance Officer

Karen,

I believe that your question that we discussed on the phone on March 31, 2011 was about the dissolution data the firm submitted on August 10, 2007 and were reviewed by DBE in the attached review:

76477_BE_2007.pd
f (62 KB)

You would like to know why the dissolution data for the 80 mg test Lot No. (b) (4) (submitted in 2007) were so much different from those of the 80 mg biostudy Lot No. 1200558 (submitted in the 2002 original submission) when both lots were tested using the same FDA-recommended dissolution method (75 rpm USP II (paddle) in 900 mL of pH 6.8 phosphate buffer). You also raised the question of the authenticity of the dissolution data of the biostudy Lot No. 1200558 and whether the firm had submitted adequate bioequivalence study/dissolution data at filing.

Following our discussion, I have looked up the ANDA 76477 submission and review history in order to get a better understanding of the ANDA's regulatory developments and the sequence of bioequivalence review events. Here are what I found:

1. **Original Bioequivalence Submission of August 19, 2002 and Bioequivalence Amendment of March 4, 2003 (Long-term Stability Data Amendment):** The DBE reviewed the fasting and fed BE studies comparing the biostudy test Lot No. 1200558 with the RLD product Lot No.00371V, as well as comparative dissolution data for the biostudy test and reference lots, and exhibit lots of all strengths of the test products (vs corresponding strengths of the RLD product) and found the BE studies, dissolution testing and waiver requests acceptable. The DBE recommended the FDA dissolution method (75 rpm USP II (paddle) in 900 mL of pH 6.8 phosphate buffer), and a specification of NLT (b) (4) Q) in 15 minutes (The BE review was completed in 2003).

2. **Bioequivalence Amendment of September 13, 2006:** (b) (4)

3. **Bioequivalence Amendment of August 10, 2007:** In (b) (4)

(b) (4)

[redacted]

[redacted]

4. Bioequivalence Amendment of January 25, 2008: (b) (4)

[redacted]

5. CMC/Labeling Amendment of February 14, 2008: During my search on the ANDA submission history, I came across a subsequent CMC/Labeling amendment the firm submitted on 2/14/2008 to outline proposed changes in API manufacturing process (at the original Paonta Sahib, India), minor formulation changes among other manufacturing and labeling changes. This amendment included dissolution data of the reformulated test product comparing with the ***original*** dissolution data of the bio lot (80 mg) as well as other exhibit lots of other strengths. It is noted that in this amendment, ***original conventional USP vessels (and not*** (b) (4) ***vessels) and the FDA dissolution method (with the originally recommended spec of NLT*** (b) (4) ***Q) in 15 minutes) were used in the dissolution testing and in support of the amendment. It is also important to note that the dissolution data provided for all strengths of the reformulated test product were more comparable to those of the biostudy Lot No. 1200558, than those of the "laboratory scale" submitted a month earlier (i.e., in the Bio amendment dated 1/25/2008 mentioned above).***

However, the amendment was never assigned in DARRTS as a Bioequivalence amendment since it was marked with CMC/Labeling amendment. Also, no Bioequivalence, Chemistry or Labeling review was done for this amendment, due to the AIP hold on the ANDA during this time period.

6. Bioequivalence Amendment of December 9, 2009 (and CMC Amendment of December 4, 2009): The firm submitted a Bioequivalence Amendment which contained new BE studies to support newly reformulated test product, using new manufacturing site, Ohm (US) and (b) (4) API (crystalline instead of the original amorphous API). New dissolution data submitted for the newly reformulated product were also based on **the original FDA method and spec with the conventional USP *vessels***. The amendment is currently reviewed. It is noted that the dissolution data submitted for the reformulated test product manufactured at Ohm, USA, were ***comparable with the data of the biostudy Lot* No. *1200558***. We also note that the firm submitted the CMC data and information for the new biostudy Lot No RI560901 in the CMC amendment submitted on 12/4/2009 for review.

7. **CMC Amendment of November 12, 2010:** The firm submitted another CMC amendment to add two alternate APIs manufactured from Ranbaxy's Punjab site using the API manufacturing Process I and Process II, respectively. To support the proposed alternate APIs, the firm provided the dissolution data for the test product lots manufactured using the two additional APIs. Again, the dissolution testing was done using ***the originally recommended FDA dissolution method, spec and conventional USP vessels, and the dissolution data of these proposed products were comparable to those of the original biostudy Lot No 1200558.*** The amendment is being currently reviewed by the DBE in addition to the 12/9/2009 amendment above. We note that the CMC data and information for the proposed test products manufactured using two alternate APIs from Punjab India were also submitted to the Division of Chemistry for review.

In summary, the 2002 dissolution data for the original biostudy test Lot No. 1200558 (used in the original BE studies and manufactured at Paonta Sahib, India) were comparable to: (i) the Feb 2008 dissolution data submitted for reformulated test product (still manufactured at Paonta Sahib, India, the 80 mg test Lot No. 1743352), (ii) the 2009 dissolution data of the reformulated biostudy test Lot No. RI560901 (used in the most recent BE studies and manufactured at Ohm, USA, with (b) (4) API), and (iii) the 2010 dissolution data of the reformulated test product manufactured using two alternate Ranbaxy's Punjab APIs. All of these dissolution data were generated using the original FDA-recommended dissolution method (75 rpm USP II (paddle) in 900 mL of pH 6.8 phosphate buffer), and appeared to meet the original FDA-recommended specification of NLT (b) (4) Q) in 15 minutes. All of these dissolution data were submitted with CMC data and information of the tested lots. (b) (4) To the best of my knowledge, the CMC data and information have not been either submitted and/or reviewed by the Division of Chemistry to confirm whether Lot No. (b) (4) was manufactured under identical conditions as the original biostudy Lot No. 1200558.

With respect to your concern for the authenticity of the dissolution data of the original biostudy test Lot No. 1200558, or any of the subsequent dissolution data of the test product, only an inspection by the Agency of the dissolution testing site(s) could help determine that. It is my understanding that the Agency generally lacks resources for frequent inspection of dissolution testing sites, and only conducts such inspections if there is a reason for the inspection.

Please let me know if you have additional questions, or would like to discuss your concerns further.

Thanks, Hoai

Hoainhon Nguyen Caramenico Acting Deputy Director
Division of Bioequivalence I Office of Generic Drugs
CDER/FDA
Telephone: 240-276-8804

Email: hoainhon.caramenico@fda.hhs.gov

From: Takahashi, Karen
Sent: Friday, April 08, 2011 2:01 PM
To: Nagavelli, Laxma; Nguyen, Hoainhon T
Subject: RE: ANDA 76-477 atorvastatin Ranbaxy

Laxma or Hoai,

I know that there is a lot going on right now, but I think we need to understand why these numbers may be so much different. A couple chemists from my office have suggested particle size or hardness, and of course there could be differences in the (b) (4) vessel vs. USP methods. Could you check the application to see if any of these variable changed between the 2002 and 2007 data?

Eda Howard has the application in her office. Thanks,

Karen

From: Nagavelli, Laxma
Sent: Wednesday, April 06, 2011 5:00 PM
To: Takahashi, Karen
Subject: RE: ANDA 76-477 atorvastatin Ranbaxy

Karen,

Per our earlier discussion, the dissolution data in question and it's verification/assessment is part of the DBE evaluation.

Thanks, Laxma

From: Takahashi, Karen
Sent: Friday, April 01, 2011 10:28 AM
To: Nagavelli, Laxma
Subject: RE: ANDA 76-477 atorvastatin Ranbaxy

Laxma,

I was talking to Haoi in DBEI about the dissolution data that was the subject of a deficiency letter from DBEI (dated October 3, 2006 for ANDA 76-477). Haoi suggested I contact you about the data to gain your perspective. Do you have time to discuss this today? I think it would not take longer than 15 minutes.

Thanks,

Karen Takahashi
Compliance Officer
International Compliance Branch

FDA/CDER/OC/DMPQ
10903 New Hampshire Avenue
White Oak, Bldg. 51, Rm. 4244
Silver Spring, MD 20993
Phone: 301.796.3191
Fax: 301.847.8741
Email: karen.takahashi@fda.hhs.gov

From: Nguyen, Hoainhon T
Sent: Thursday, March 31, 2011 2:20 PM
To: Takahashi, Karen
Cc: Nguyen, Hoainhon T; Sanchez, Aida L
Subject: RE: ANDA 76-477 atorvastatin Ranbaxy

Hello Karen,
I left a phone message with you today in response to your request to discuss a deficiency letter from our group (Division of Bioequivalence I (DBEI)) to Ranbaxy for ANDA 76477 in 2006. Please call me at the number listed below, or email me.
Thanks,
Hoai

Hoainhon Nguyen Caramenico
Acting Deputy Director Division of
Bioequivalence I Office of Generic Drugs
CDER/FDA
Telephone: 240-276-8804
Email: hoainhon.caramenico@fda.hhs.gov

From: Sanchez, Aida L
Sent: Thursday, March 31, 2011 1:49 PM
To: Nerurkar, Shriniwas G; Nguyen, Hoainhon T
Cc: Ramson, Teresa; Solana-Sodeinde, Diana A; Chun, Nam **Subject:** FW: ANDA 76-477 atorvastatin Ranbaxy

Who would like to call this Compliance Officer about this ANDA? It was reviewed by Surendra and secondary by Vijay.

Lizzie

From: Sigler, Aaron
Sent: Thursday, March 31, 2011 12:26 PM
To: Sanchez, Aida L
Subject: FW: ANDA 76-477 atorvastatin Ranbaxy

Hey Lizzie,

I'm forwarding this to you since it's DBE 1's. I'm not sure what the issue is exactly.

Aaron

From: Takahashi, Karen
Sent: Thursday, March 31, 2011 12:08 PM
To: Sigler, Aaron
Subject: ANDA 76-477 atorvastatin Ranbaxy

Dr Sigler,

I just left you a voicemail message asking to talk to you or one of your staff about the dissolution data that was the subject of a deficiency letter from your group (dated October 3, 2006 for ANDA 76-477). Please contact me today at (b) (6) as I am working at home or tomorrow at my office 301.796.3191. As I mentioned in my voicemail, I am with CDER's office of compliance and have been asked by my management to look at this application. I will be running out briefly for lunch.

Thanks,

Karen Takahashi Compliance Officer

International Compliance Branch
FDA/CDER/OC/DMPQ
10903 New Hampshire Avenue White Oak, Bldg. 51,
Rm. 4244 Silver Spring, MD 20993
Phone: 301.796.3191
Fax: 301.847.8741
Email: karen.takahashi@fda.hhs.gov

4.8. Email Recommending the use of the Original FDA Dissolution Method for the Current ANDA:

From: Yu, Lawrence
Sent: Wednesday, September 21, 2011 6:24 PM
To: Nguyen, Hoainhon T
Subject: FW: ANDA A76477 dissolution

Hoai,

Per our conversation, I have reviewed the dissolution data submitted by Ranbaxy for ANDA 76477.

In my opinion, the much slower dissolution at 50 rpm than 75 rpm is likely due to the coning effect, not so much the characterization of the product.

Therefore, I would recommend that Ranbaxy use the FDA-recommended dissolution method (900 mL of 0.05 M phosphate buffer at pH 6.8 and Paddle of 75 rpm).

Thank you for your consideration.

Lawrence

From: Nagavelli, Laxma
Sent: Tuesday, September 20, 2011 4:35 PM
To: Yu, Lawrence
Subject: RE: ANDA A76477 dissolution

Lawrence,

Yes, they do have the following specification for PSD.

Particle size† (By Malvern Mastersizer)	(b) (4)

Let me know if you need any other info.

Thanks,
Laxma

From: Yu, Lawrence
Sent: Tuesday, September 20, 2011 3:38 PM
To: Nagavelli, Laxma
Subject: ANDA A76477 dissolution

Laxma,

I wonder if we have a particle size specification for this Ranbaxy ANDA A76477.

Thanks,

Lawrence

4.9. Chemistry Consult Pertaining to Process Changes for the Manufacture of Drug Products with Ranbaxy Process-1 API

From: Sayeed, Vilayat A
Sent: Monday, October 03, 2011 1:10 PM
To: Nguyen, Hoainhon T; Yu, Lawrence; Chun, Nam
Cc: Nagavelli, Laxma; Schwartz, Paul; Gill, Devinder; Li, Haitao; Shrivastava, Surendra P; Huang, Yih Chain; West, Robert L; Webber, Keith; Shrivastava, Surendra P; Huang, Yih Chain
Subject: RE: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

A change in the API source is allowed in the ANDA, if the additional source of API used in the ANDA meets the following conditions: Adequate DMF, manufacture a drug product batch (strength used to support bio-study) using the new API source, provide stability data and a comparative dissolution profile and Ranbaxy has met all of these conditions using API source from process 1 and 2.

In the submission dated 11/12/2010, they have included all the data on the drug product manufactured using Ranbaxy API sourced from both the process 1 or 2 and these batches meet the establish specifications and were found acceptable by CMC and Bio.

Although a (b) (4) is needed in the manufacturing of the drug product made with Ranbaxy API sourced from process 1 only, this step was not considered as a major change as it does not change the (b) (4) of the API (with in the method variability). Thus having a (b) (4) step was found to be acceptable by the team.

Based on the raw material understanding (QbD) and the manufacturing controls provided to CMC, in our opinion there will be no impact on the performance (dissolution) of the product made by API sourced from process 1 or 2 (Ranbaxy) and (b) (4). Based on what I have seen in DARRTS both CMC and Bio are on the same page.

Please ask Doug to contact me if additional clarification is needed on this topic. I hope this email obviates the need for an internal meeting.

Vilayat

Vilayat A. Sayeed, Ph.D.
Director, Division of Chemistry III
FDA/CDER/OPS/OGD
7500 Standish Place
MPN II Rockville, MD 20855
Office (240) 276-8486, fax (240) 276-8474
Vilayat.Sayeed@FDA.HHS.GOV

From: Nguyen, Hoainhon T
Sent: Thursday, September 29, 2011 6:15 PM
To: Yu, Lawrence
Cc: Nguyen, Hoainhon T; Nagavelli, Laxma; Schwartz, Paul; Gill, Devinder; Sayeed, Vilayat A; Li, Haitao; Shrivastava, Surendra P; Huang, Yih Chain
Subject: FW: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Hi Lawrence,

I talked with Doug Campbell yesterday and today, and he conveyed that it is important that our reviews show that DBE and the Division of Chemistry are on the same page regarding the API changes and the manufacturing changes associated with the API changes (following the bioequivalence studies for the test product with (b) (4) API), namely, the firm added a (b) (4) step at (b) (4) present only in the Ranbaxy Process I and II APIs and not in (b) (4) With this step incorporated, and few other minor parameter limit changes, the firm was able to reproduce test batches (with Ranbaxy's APIs) within the original specifications, including dissolution data. The DBE interpreted, as usual, that for such changes, if they were not considered major to the chemistry reviewer, they don't necessitate a need for us to require a bioequivalence study, as long as the dissolution data showed no difference between pre-change and post-change products. However, the OMPQ is concerned that it is not clear to others outside both divisions, when reading both BE and chemistry reviews, that there was an agreement between two divisions that these changes were minor and should be waived of in vivo bioequivalence testing.

To address Doug's concern, we have sent an email (below) to the chemistry review team to request a confirmation of such agreement in assessment of the changes.

We have not received a response from the chemistry division, and we are anxious to clarify this issue for the OMPQ and Doug as soon as possible. Could you please provide us with assistance and advice on this matter. If necessary, we could set up a meeting between our division and chemistry to discuss about the OMPQ's concern.

Thanks,

Hoai

From: Shrivastava, Surendra P
Sent: Thursday, September 29, 2011 2:51 PM
To: Li, Haitao
Cc: Gill, Devinder; Sayeed, Vilayat A; Huang, Yih Chain; Nguyen, Hoainhon T
Subject: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Hello Haitao,

The DBE is requesting the chemistry review confirmation for the following:

In 11/12/2010 submission, Ranbaxy has requested to include additional APIs for its products, Ranbaxy Process-1 and Ranbaxy Process-2. Additionally, they have made some other minor changes (see attachment) in manufacturing process as the result of (b) (4) of the Ranbaxy Process-I and Process-II APIs. We understand that you have reviewed these changes and the data associated with the changes as submitted in the November 12, 2010 amendment, and have concluded that *"these changes do not have any adverse effect on the quality of the drug product*" in your review of this amendment. We would like to confirm with you that, from the chemistry point of view, you agree with the DBE assessment that these manufacturing changes were considered minor and equivalent to SUPAC Level 1 or Level 2 changes and should not necessitate the need for an in vivo bioequivalence study, and dissolution data are sufficient for supporting such change. We would like to close our BE review with this confirmation if possible. Please note there is also a pending OMPQ inspection of the dissolution testing at this time.

Thanks very much in advance for your response.

Surendra

<< OLE Object: Picture (Device Independent Bitmap) >>

PLEASE HOLD THE LETTER UNTIL THE PENDING FOR CAUSE OSI INSPECTION FOR DISSOLUTION TESTING IS COMPLETE AND ADEQUATE.

BIOEQUIVALENCE COMMENTS TO BE COMMUNICATED TO THE APPLICANT

ANDA:	076477
APPLICANT:	Ranbaxy Laboratories Ltd.
DRUG PRODUCT:	Atorvastatin Calcium Tables 10, 20 , 40 and 80 mg

The Division of Bioequivalence I (DBI) has completed its review of your submission(s) acknowledged on the cover sheet and has no further questions at this time.

The DB I acknowledges that you will conduct dissolution testing for your test product using the following FDA-recommended dissolution method and specification for your Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, manufactured with (b) (4) Ranbaxy Process-1 and Ranbaxy Process-2 active pharmaceutical ingredients (APIs):

Medium: 0.05M Phosphate Buffer, pH 6.8 at 37 ^{OC}
Volume: 900 mL
USP Apparatus: II (Paddle) at 75 rpm
Specification: NLT (b) (4) (Q) is dissolved in 15 minutes

[NOTE: The method should use conventional USP II Vessels, and not (b) (4) Vessels.]

Please note that the bioequivalence comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence I
Office of Generic Drugs
Center for Drug Evaluation and Research

4.10. Outcome Page

ANDA: 076477

5. COMPLETED ASSIGNMENT FOR 076477 ID: 14951

Reviewer: Shrivastava, Surendra **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description: Atorvastatin Calcium Tablets

Productivity:

ID	Letter Date	Productivity Category	Sub Category	Productivity	Subtotal		
14951	8/26/2011	Other	Study Amendment	1	1	Edit	Delete
				Bean Total:	1		

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SURENDRA P SHRIVASTAVA
10/05/2011

YIH CHAIN HUANG
10/05/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
10/05/2011

DIVISION OF BIOEQUIVALENCE
ACCEPTABLE DSI INSPECTION REPORT REVIEW

ANDA No.	076477
Drug Product Name	Atorvastatin Calcium Tablets
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg
Applicant Name	Ranbaxy Laboratories Ltd., India
Original Submission Date(s)	August 19, 2002 December 9, 2009 November 12, 2010 (additional API – Ranbaxy Process 1 and Process 2)
Date of Report	October 18, 2011
Reviewer	Nam Chun, Pharm.D.
Dissolution Testing Site	Ohm Laboratories, Inc.
Dissolution Testing Site Address	1385 Livingston Avenue, North Brunswick, New Jersey 08902
OUTCOME DECISION	**ADEQUATE**

EXECUTIVE SUMMARY

The Office of Manufacturing and Product Quality (OMPQ) inspection report of the dissolution site, Ohm Laboratories, Inc., was received by the Division of Bioequivalence and found acceptable. The site inspection was requested for ANDA **076477**. Given the acceptable inspection of the site, the bioequivalence section of the application is now acceptable

COMMENTS:

The original inspection request for the dissolution site was submitted to the Office of Scientific Investigation (OSI) on September 22, 2011 by Hoainhon N. Caramenico. Since then, the inspection request has been reassigned to OMPQ and the inspection report was received via email on October 25, 2011. See **attachments 1 and 2**.

DEFICIENCY COMMENTS:

None

RECOMMENDATIONS:

The Office of Manufacturing and Product Quality (OMPQ) inspection report of the dissolution site, Ohm Laboratories, Inc., was received by the Division of Bioequivalence on **October 25, 2011** and found acceptable.

From a bioequivalence point of view, the firm has met the requirements for in-vivo bioequivalence and in-vitro dissolution testing. The bioequivalence section of the application is acceptable.

ATTACHMENT 1

[redacted]

Date Assigned: 09/23/2011 **Inspection Start Date:** 09/28/2011 **Inspection End Date:** 10/03/2011

Firm Name & Address: Ohm Laboratories Inc , 14 Terminal Rd New Brunswick, NJ 08901-3616 US

Firm Mailing Address: 14 Terminal Rd, New Brunswick, NJ 08901-3616 United States

FEI: 3004132058 **JD/TA:** 33 **County:** MIDDLESEX **Est Size:** 10,000,000 - 24,999,999

Phone: (732)514-4400 **District:** NWJ-DO **Profiled:** Yes

Conveyance Type: **% Interstate:** 100 **Inspectional Responsibility:** Field

Endorsement

The inspection of this generic pharmaceutical manufacturer of tablets and capsules was initiated as per request from the New Jersey Pre-approval Manager, FACTS Assignment 7315655, Operation ID 5721265 to provide pre-approval coverage to ANDA 76-477, Atorvastatin Calcium Tablets. The inspection was conducted in accordance to CP 7346.832, Pre-approval Inspections.

The previous inspection of 11/2-10/2010 provided pre-approval coverage to ANDA 76-786 for Donepezil Hydrochloride Tablets, 5 mg and 10 mg and coverage to an NDA Field Alert Report for Simvastatin Tablets, USP (10, 20, 40, 80 mg) and was classified VAI. Form FDA 483 was issued for not expanding an investigation to other batches of Simvastatin Tablets after a failure investigation determined that the excipient used in the process was mislabeled by the supplier.

The current inspection was limited to pre-approval coverage of ANDA 76-477, Atorvastatin Calcium Tablets, 10mg, 20mg 40mg and 80mg. A discussion with management was held concerning controls to prevent operators from inadvertently carrying visible powder on the floors of the (b) (4) area into the common corridor with their shoes. On 10/3/2011, an approval recommendation for ANDA 76-477 was forwarded to the New Jersey Pre-approval Manager.

No form FDA 483, Inspectional Observations was issued, no samples were collected and no refusals were encountered.

EU: This EI is classified NAI. NWJ-IBr recommends approval for ANDa 76-477. Reinspect per workplan.

Distribution:
M/Att/Exh: CST/Files (EF)
EES + TAS: HFR-CE350 (DIB)
Ees+cc: HFD-322 (C. Cruz)
Ees: HFR-CE 3565 (Grp 6 Drug Monitor)
cc: HFR-CE350 (PAI- D'Orazio)
MD 145: HFR-CE350 (Gp 2)

Endorsement Location:

Inspector Name	Date & Time of Signature	Supervisor Name	Date & Time of Signature
Douglas C Kovacs	10/14/2011 08:42 AM ET	Lisa Harlan	10/14/2011 08:54 AM ET

RECEIVED
OCT 18 2011
BY: IBR

TO: FILE
BY: 10/18/2011

[redacted]

FEI: 3004132058 **Inspection Start Date:** 09/28/2011 **Inspection End Date:** 10/03/2011

Firm Name & Address: Ohm Laboratories Inc , 14 Terminal Rd New Brunswick, NJ 08901-3616 US

Inspection Basis: Surveillance

Inspected Processes & District Decisions

PAC	Establishment Type	Products/ Process	MQSA	Reschedule Insp Date	Re-Inspection Priority	Inspection Conclusions
52832	Manufacturer	61 J C A		09/2013	Surveillance	No Action Indicated (NAI)

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
Y	10/03/2011	No Action Indicated (NAI)	Harlan, Lisa	NWJ-GRP-02

Remarks:

Final Decision?	District Decision Date	District Decision Type	District Decision Made By	Org Name
	10/03/2011	No Action Indicated (NAI)	Kovacs, Douglas C	NWJ-GRP-02

Remarks:

Inspection Result

EIR Location
TurboEIR

Trips Num

Inspection Summary
see hardcopy EIR

IB Suggested Actions

Action	Remarks

Referrals

Org Name	Mail Code	Remarks

Refusals

Inspection Refusals: No refusal

Samples Collected

Sample Number

Recall Numbers

Recall Number

Related Complaints

Consumer Complaint Number

FDA 483 Responses

483 Issued?: **483 Location:**

Response Type	Response Mode	Response Date	Response Summary

ADMINISTRATIVE DATA

Inspected firm:	Ohm Laboratories Inc
Location:	14 Terminal Rd New Brunswick, NJ 08901-3616
Phone:	732-514-4400
FAX:	
Mailing address:	14 Terminal Rd New Brunswick, NJ 08901-3616
Dates of inspection:	9/28/2011, 9/29/2011, 9/30/2011, 10/3/2011
Days in the facility:	4
Participants:	Douglas C. Kovacs, Investigator Jose M. Cayuela, Investigator

Investigator Kovacs was present on all inspectional days.
Investigator Cayuela was present on 9/28, 29 and 10/3/2011.

On 9/28/2011, Jose M. Cayuela, Investigator and I showed our credentials, issued form FDA 482, Notice of Inspection to Robert Patton, Vice President and General Manager, the site's most responsible person and explained the purpose of the inspection.

Post-inspectional correspondence should be addressed to:
Robert Patton, Vice President and General Manager
Ohm Laboratories Inc.
14 Terminal Road
New Brunswick, New Jersey 08901

HISTORY

Written by D. Kovacs

Ohm Laboratories Inc. is a wholly owned subsidiary of Ranbaxy Laboratories Limited, Gurgaon, India and is a manufacturer of tablets and capsules. Ranbaxy's US Headquarters are located at 600 College Road, Princeton, New Jersey. Ohm Laboratories has another manufacturing facility at 1385 Livingston Avenue, North Brunswick, New Jersey and a warehouse at 22 Vandyke Avenue, New Brunswick, New Jersey. There have not been any significant changes to personnel or operations since the previous inspection. Robert Patton, Vice President/General Manager is the site's most responsible person. The firm's site master file is attached as **Exhibit 1,** which includes organizational charts (pp 10-13). Manufacturing operations occur (b) (4) and the QC Laboratory operates under one shift. Operations with the exception of manufacturing are also conducted (b) (4). The building is approximately (b) (4) square meters and contains administrative offices, testing laboratories, manufacturing and packaging areas, quality assurance/product development, technical services, and quality engineering departments. There are approximately (b) (4) people employed at this site.

- (b) (6) **Associate Director Warehouse** oversees warehousing operations at all of Ohm's facilities and reports to Robert Patton, Vice President and General Manager.
- (b) (6), **Manager Technical Services** is responsible for prevalidation and process validation activities, equipment qualification, preparing and/or approving batch records, process optimization and troubleshooting, and deviation investigations.

Additional people that participated in the inspection include:

- Scott Tomsky, Vice President Regulatory Affairs
- (b) (6), Associate Director Regulatory Affairs
- (b) (6), Associate Director Production
- (b) (6), Senior Manager, QC Finished Product Testing
- (b) (6), Senior Manager, Method Development and Validation/R&D Support
- (b) (6), Warehouse Manager
- (b) (6), QC Stability Manager
- (b) (6), QC Group Leader
- (b) (6), Senior Chemist, QC

MANUFACTURING/DESIGN OPERATIONS

Written by D. Kovacs

We provided pre-approval inspectional coverage to ANDA 76-477, Atorvastatin Calcium tablets, 10mg, 20mg, 40mg and 80mg. (b) (4) The manufacturing steps include (b) (4). Tablets are subsequently compressed and film coated. Packaging is conducted under a humidity controlled area at Ohm's facilities at Terminal Road, New Brunswick and Livingston Avenue, North Brunswick, New Jersey. The product is packaged into 90 and 500 count bottles.

The firm has two suppliers of the API, Atorvastatin Calcium; (b) (4) and Ranbaxy. With regard to Ranbaxy API, two different processes, referred to as Process I and Process II can be used to manufacture the API. According to Pruthvipathy Katikaneni, Ph.D., Associate Vice President Product Development and Technical Services, the difference in Process I and II is the (b) (4) used during the manufacturing steps and that Ranbaxy's Process II material is the primary source for manufacturing the finished product. Flow diagrams of the finished product manufacturing process using the different sources of API are included as **Exhibit 2.** The process is the same for each of the sources with the exception of a (b) (4) step of the API when using Ranbaxy's Process I API. Dr. Katikaneni stated that this step is done to (b) (4) the API, but not to change the particle size.

Exhibit batches were manufactured with each of the API sources; (b) (4) Ranbaxy Process I and Ranbaxy Process II. The following table summarizes the exhibit batches:

Strength	Lot number	Batch size	API Source
10mg	RI530902	(b) (4)	(b) (4)

80mg	2284259	(b) (4)
80mg	2284262	(b) (4)
80mg	2284265	(b) (4)

At the time of the inspection, the firm had completed the process validation batches for all strengths. My review of the process validation batches included batch records, deviations and OOS investigations, and the process validation protocols and final reports. Summaries of the process validation studies are included as **Exhibits 9-12.** During the manufacturing of the 10mg batches, one batch, 2262711 was rejected during processing, due to the lid of the (b) (4) was not securely fastened and resulted in a loss of blend that spilled out of the blender onto the floor. Post-validation batches have also been manufactured and are listed in **Exhibit 17.** I reviewed deviations and OOS investigations related to these batches, cleaning validation studies, and we also observed manufacturing operations of Atorvastatin Calcium tablets. We discussed the following item with the firm's management concerning controls to prevent raw materials from entering the common corridor:

On 9/28/2011, we noticed during our walkthrough of the manufacturing area, room (b) (4) had visible powder on the floor. Atorvastatin Calcium, lot 2320415 was being processed in this room. This room is used for (b) (4). We asked Mr. Patton how the operators in this area keep their shoes clean to prevent powder from being brought into the common corridor. Mr. Patton indicated that the rooms are kept under negative pressure to the corridor, but they did not have a written procedure for addressing our concern. We did not observe any powder residues in the corridors; however, we discussed that this could become an opportunity for cross contamination if not controlled.

Laboratory review

The following section was written by Investigator Jose Cayuela regarding laboratory data for Atorvastatin Calcium tablets:

1) On 09/28/2011, I reviewed the current Atorvastatin Calcium Tablets Standard Test Method FT 005849, revision 1.0, which is used to evaluate, test and release this product. My review found that this Standard Test Method is a comprehensive written instruction for the analysis of all dosage forms. It includes the test requirements and procedure for the dissolution of the tablets using (b) (4) which compare in instrument parameters with the validation lots. I did not observe deficiencies with this document. Refer to **Exhibit 13.**

2) I reviewed SOP 3115, titled: Operation, Calibration and Maintenance of (b) (4) Apparatus model (b) (4). I found this procedure comprehensive for its intended purpose applicable for Atorvastatin Calcium Tablets.

3) On 09/29/2011, I reviewed the Atorvastatin method transfer data for the dissolution test from (b) (4) to Ranbaxy Research laboratory India to Ohm Labs in USA. Research report No. RR-

indicating that the equipment is qualified for its intended use, and I did not observe any deficiencies.

11) The evaluation of the calibration data for the (b) (4) used to determine the dissolution of the validation Atorvastatin Calcium 20 mg tabs lot 2280820 covering the validation time period from March 2011 to September 2011 indicated that it met all calibration requirements and acceptance criteria.

COMPLAINTS

Written by D. Kovacs

Medical and quality related complaints are received at the firm's headquarters in Princeton, New Jersey. The quality related complaints are then forwarded to the manufacturing facility for follow-up. Since this inspection was limited to pre-approval coverage of Atorvastatin Calcium tablets, I did not provide coverage to the complaint handling system.

OBJECTIONABLE CONDITIONS AND MANAGEMENT'S RESPONSE

We did not observe any significant deficiencies during the inspection and we did not issue form FDA 483, Inspectional Observations.

REFUSALS

We did not encounter any refusals during the inspection.

GENERAL DISCUSSION WITH MANAGEMENT

Written by D. Kovacs

On 10/3/2011, we held a closeout meeting with the firm's management, which included Robert Patton, Vice President and General Manager; Manjeet Bindra, Vice President, Quality Assurance and Quality Control; Pruthvipathy Katikaneni, Ph.D., Associate Vice President Product Development and Technical Services; Prasad Uppalapati, Senior Director, Manufacturing; Dan Martins, Director of Quality Control; (b) (6), Associate Director QA; (b) (6) Associate Director Product Development; Lincoln Burgher, Associate Director Warehouse; (b) (6) Associate Director Quality Compliance/Training and (b) (6) Manager Technical Services. We discussed the following verbal observation, which Mr. Bindra indicated that corrective actions would be implemented to address our concern.

On 9/28/2011, we noticed during our walkthrough of the manufacturing area, room (b) (4) had visible powder on the floor. Atorvastatin Calcium, lot 2320415 was being processed in this room. This room is used for (b) (4). We asked Mr. Patton how the operators in this area keep their shoes clean to prevent powder from being brought into the common corridor. Mr. Patton indicated that the rooms are kept under negative pressure to the corridor, but they did not have a written procedure for addressing our concern. We did not observe any powder residues in the corridors; however, we discussed that this could become an opportunity for cross contamination if not controlled.

Douglas C. Kovacs, Investigator

Jose M. Cayuela, Investigator

ATTACHMENT 2

From: Nguyen, Hoainhon T
Sent: Tuesday, October 25, 2011 10:42 AM
To: Chun, Nam
Subject: Fw: INSPECTION STATUS RE: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Esther,
Are you Surendra's PM? If so, please take a look at the inspection document attached and let me know if you can close out ANDA 76477.
Thanks,
Hoai

Ohm EIR 2011 (Atorvastatin PAI).pc

From: Campbell, Douglas (CDER)
Sent: Tuesday, October 25, 2011 09:21 AM
To: Nguyen, Hoainhon T
Subject: RE: INSPECTION STATUS RE: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Hoai,

I trust all is well.

Here is the EIR. Let me know if you have any questions.

Best,
Doug

Douglas A. Campbell
Senior Policy Advisor
International Compliance Branch
Office of Manufacturing and Product Quality
FDA- Center for Drug Evaluation and Research
(301) 796-3201
douglas.campbell@fda.hhs.gov

<<Ohm EIR 2011 (Atorvastatin PAI).pdf>>

From: Nguyen, Hoainhon T
Sent: Friday, October 21, 2011 5:41 PM
To: Campbell, Douglas (CDER)
Cc: Nguyen, Hoainhon T
Subject: RE: INSPECTION STATUS RE: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Thank you.

From: Campbell, Douglas (CDER)
Sent: Friday, October 21, 2011 5:36 PM
To: Nguyen, Hoainhon T
Subject: RE: INSPECTION STATUS RE: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Hoai,

Let me look into it. I will get back to you asap.

Thanks,
Doug

From: Nguyen, Hoainhon T
Sent: Friday, October 21, 2011 5:18 PM
To: Campbell, Douglas (CDER)
Cc: Nguyen, Hoainhon T
Subject: INSPECTION STATUS RE: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Hi Doug,
Bob just informed us that the inspection by OMPQ at Ohm Laboratories for dissolution testing of ANDA 076477 Ranbaxy's Atorvastatin has been completed. Yet we could not access the inspection report since it is not submitted in DARRTS. Could you please forward to our division a copy of the inspection report so that we can finalize the bioequivalence review of this ANDA?

Thanks,
Hoai

From: Campbell, Douglas (CDER)
Sent: Monday, October 03, 2011 3:25 PM
To: Nguyen, Hoainhon T
Subject: RE: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Thanks for this input, and thanks for your assistance with this question.
Best,
Doug

From: Nguyen, Hoainhon T
Sent: Monday, October 03, 2011 1:28 PM
To: Campbell, Douglas (CDER)
Cc: Nguyen, Hoainhon T
Subject: FW: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Hi Doug,
Please see the emails below for the confirmation from the Chemistry review team concerning the API changes and the minor manufacturing changes associated with API changes as outlined by Ranbaxy in the 11/12/2010 amendment. The latest bioequivalence review will incorporate the chemistry confirmation to further support the Division of Bioequivalence I's recommendation for granting waivers to the test products manufactured using Ranbaxy Process-I and Ranbaxy Process-II APIs, and thus, clarifying the question raised by the OMPQ recently.

Please let us or the Chemistry review division know if you or OMPQ have any additional questions and/or concerns.
Thanks,
Hoai

From: Nguyen, Hoainhon T
Sent: Monday, October 03, 2011 1:18 PM
To: Sayeed, Vilayat A; Yu, Lawrence; Chun, Nam
Cc: Nagavelli, Laxma; Schwartz, Paul; Gill, Devinder; Li, Haitao; Shrivastava, Surendra P; Huang, Yih Chain; West, Robert L; Webber, Keith; Shrivastava, Surendra P; Huang, Yih Chain; Conner, Dale P

Subject: RE: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Great. Thanks very much, Vilayat, for your confirmation. Based on your response, we will not need to meet to discuss further. At this time, please disregard our meeting request.

We will include your confirmation in our latest BE review and inform Doug of the confirmation also. We hope with that, we can tentatively conclude our BE review, pending only the results of the inspection by the OMPQ for the dissolution testing.

Hoai

From: Sayeed, Vilayat A
Sent: Monday, October 03, 2011 1:10 PM
To: Nguyen, Hoainhon T; Yu, Lawrence; Chun, Nam
Cc: Nagavelli, Laxma; Schwartz, Paul; Gill, Devinder; Li, Haitao; Shrivastava, Surendra P; Huang, Yih Chain; West, Robert L; Webber, Keith; Shrivastava, Surendra P; Huang, Yih Chain

Subject: RE: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

A change in the API source is allowed in the ANDA, if the additional source of API used in the ANDA meets the following conditions: Adequate DMF, manufacture a drug product batch (strength used to support bio-study) using the new API source, provide stability data

and a comparative dissolution profile and Ranbaxy has met all of these conditions using API source from process 1 and 2.

In the submission dated 11/12/2010, they have included all the data on the drug product manufactured using Ranbaxy API sourced from both the process 1 or 2 and these batches meet the establish specifications and were found acceptable by CMC and Bio.

Although a (b) (4) is needed in the manufacturing of the drug product made with Ranbaxy API sourced from process 1 only, this step was not considered as a major change as it does not change the (b) (4) of the API (with in the method variability). Thus having a (b) (4) step was found to be acceptable by the team.

Based on the raw material understanding (QbD) and the manufacturing controls provided to CMC, in our opinion there will be no impact on the performance (dissolution) of the product made by API sourced from process 1 or 2 (Ranbaxy) and (b) (4). Based on what I have seen in DARRTS both CMC and Bio are on the same page.

Please ask Doug to contact me if additional clarification is needed on this topic. I hope this email obviates the need for an internal meeting.

Vilayat

Vilayat A. Sayeed, Ph.D.
Director, Division of Chemistry III
FDA/CDER/OPS/OGD
7500 Standish Place
MPN II Rockville, MD 20855
Office (240) 276-8486, fax (240) 276-8474
Vilayat.Sayeed@FDA.HHS.GOV

This communication is consistent with 21CFR10.85(k) and constitutes an informal communication that represents our best judgment at this time but does not constitute an advisory opinion, does not necessarily represent the formal position of the FDA, and does not bind or otherwise obligate or commit the agency to the views expressed.

From: Nguyen, Hoainhon T
Sent: Thursday, September 29, 2011 6:15 PM
To: Yu, Lawrence
Cc: Nguyen, Hoainhon T; Nagavelli, Laxma; Schwartz, Paul; Gill, Devinder; Sayeed, Vilayat A; Li, Haitao; Shrivastava, Surendra P; Huang, Yih Chain

Subject: FW: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Hi Lawrence,
I talked with Doug Campbell yesterday and today, and he conveyed that it is important that our reviews show that DBE and the Division of Chemistry are on the same page regarding the API changes and the manufacturing changes associated with the API changes (following the bioequivalence studies for the test product with (b) (4) API), namely, the firm added a (b) (4) present only in the Ranbaxy Process I and II APIs and not in (b) (4) With this step incorporated, and few other minor parameter limit changes, the firm was able to reproduce test batches (with Ranbaxy's APIs) within the original specifications, including dissolution data. The DBE interpreted, as usual, that for such changes, if they were not considered major to the chemistry reviewer, they don't necessitate a need for us to require a bioequivalence study, as long as the dissolution data showed no difference between pre-change and post-change products. However, the OMPQ is concerned that it is not clear to others outside both divisions, when reading both BE and chemistry reviews, that there was an agreement between two divisions that these changes were minor and should be waived of in vivo bioequivalence testing.

To address Doug's concern, we have sent an email (below) to the chemistry review team to request a confirmation of such agreement in assessment of the changes.

We have not received a response from the chemistry division, and we are anxious to clarify this issue for the OMPQ and Doug as soon as possible. Could you please provide us with assistance and advice on this matter. If necessary, we could set up a meeting between our division and chemistry to discuss about the OMPQ's concern.

Thanks,
Hoai

From: Shrivastava, Surendra P
Sent: Thursday, September 29, 2011 2:51 PM
To: Li, Haitao
Cc: Gill, Devinder; Sayeed, Vilayat A; Huang, Yih Chain; Nguyen, Hoainhon T
Subject: ANDA 076477 Atorvastatin: Consult Request for the Assessment of Manufacturing Change

Hello Haitao,

The DBE is requesting the chemistry review confirmation for the following:

In 11/12/2010 submission, Ranbaxy has requested to include additional APIs for its products, Ranbaxy Process-1 and Ranbaxy Process-2. Additionally, they have made some other minor changes (see attachment) in manufacturing process as the result of the (b) (4) level of the Ranbaxy Process-I and Process-II APIs. We understand that you have reviewed these changes and the data associated with the changes as

submitted in the November 12, 2010 amendment, and have concluded that *"these changes do not have any adverse effect on the quality of the drug product*" in your review of this amendment. We would like to confirm with you that, from the chemistry point of view, you agree with the DBE assessment that these manufacturing changes were considered minor and equivalent to SUPAC Level 1 or Level 2 changes and should not necessitate the need for an in vivo bioequivalence study, and dissolution data are sufficient for supporting such change. We would like to close our BE review with this confirmation if possible. Please note there is also a pending OMPQ inspection of the dissolution testing at this time.

Thanks very much in advance for your response.

Surendra

<< OLE Object: Picture (Device Independent Bitmap) >>

I. Completed Assignment for 076477 ID: 15295

Reviewer: Chun, Nam **Date Completed:**
Verifier: , **Date Verified:**
Division: Division of Bioequivalence
Description:

Productivity:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Productivity*	*Subtotal*
15295	10/18/2011	Other	DSI Inspection Report PMs	1	1
				Bean Total:	1

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/s/

NAM J CHUN
10/25/2011

AIDA L SANCHEZ
10/25/2011

DIVISION OF BIOEQUIVALENCE REVIEW - ADDENDUM

ANDA No.	076477					
Drug Product Name	Atorvastatin Calcium Tablets					
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg					
Applicant Name	Ranbaxy Laboratories Ltd., India					
Address	Plot # GP-5, Sector 18, HSIDC, Old Delhi, Gurgaon Road, Gurgaon, 122015, Haryana, India					
Applicant's Point of Contact	Scott D. Tomsky, US Agent, 600 College Road East, Ranbaxy Inc., Princeton, NJ 08540					
Contact's Telephone Number	609-720-5609					
Contact's Fax Number	609-514-9797					
Original Submission Date(s)	August 19, 2002 December 9, 2009 November 12, 2010 (additional API – Ranbaxy Process 1 and Process 2)					
Submission Date(s) of Amendment(s) Under Review	July 18, 2011 (Additional Dissolution Data for all Strengths) **August 26, 2011**					
Reviewer	S.P.Srivastava, Ph.D.					
Study Number (s)	**R09-1032**	**R09-1033**	**BE-248-ATOR-2009**	**BE-249-ATOR-2009**	**365-ATORV-09**	**3023-ATORV-08**
Study Type (s)	Fasting	Fed	Fasting	Fed	Fasting	Fed
Strength (s)	80 mg	80 mg	80 mg	80 mg	80 mg	80 mg
Clinical Site	**Cetero Research**		**Clinical Services** **Fortis Clinical Research Ltd.**		**Ranbaxy Labs. Ltd.**	
Clinical Site Address	4801 Amber Valley Pkwy. Fargo, ND 58104		Ltd., Sunflag Hospital & Research Centre Sector-16A, Faridabad 121 002, Haryana, India		Majeedia Hospital, Hamdard Nagar New Delhi India	
Analytical Site	(b) (4)				**Ranbaxy Labs. Ltd**	
Analytical Site Address					Plot No. GP-5, Sector 18, HSIDC, Gurgaon, Haryana, India	
Dissolution Testing Site	Ranbaxy Laboratory Ltd.					
OSI Inspection Status	No OSI inspections of pivotal study sites, Cetero Research (Clinical) or (b) (4) (Analytical) is pending or necessary **For Cause OSI Inspection of Dissolution Testing Site, Ohm Labs., Inc., North Brunswick, NJ, is pending**					
Overall Review Result	**INADEQUATE** (pending acknowledgment of the dissolution method and specification, and OSI For Cause dissolution inspection)					
Waiver Request Result	**ADEQUATE :** 10, 20 and 40 mg					
OSI Report Result	**Clinical: ADEQUATE.** **Analytical: ADEQUATE** (Details covered in 12/9/2009 submission review) **Dissolution: ADEQUATE**					

Bioequivalence Study Tracking/Supporting Document #	Study/Test Type	Strength	Review Result
Supporting Document #57, 58, 71	**Dissolution**	80 mg	**ADEQUATE**
	Dissolution	40 mg	**ADEQUATE**
	Dissolution	20 mg	**ADEQUATE**
	Dissolution	10 mg	**ADEQUATE**
Supporting Document # 57	**Fasting (Pivotal) - using** (b) (4) **API**	80 mg	**ADEQUATE**
	Fed (Pivotal) – using (b) (4) **API**	80 mg	**ADEQUATE**
	Pilot Fasting (BE-248-ATOR-2009)	80 mg	**For Information Only**
	Pilot Fed (BE-249-ATOR-2009)	80 mg	**For Information Only**
	Pilot Fasting (365-ATORV-09)	80 mg	**For Information Only**
	Pilot Fasting (3023-ATORV-08)	80 mg	**For Information Only**

1. EXECUTIVE SUMMARY

This review addendum is to clarify the bioequivalence recommendations in the review of ANDA 76477 regarding:

1. Failed pilot studies found for the test product (with (b) (4) API)
2. Dissolution data used to support the change in APIs of the test product

Failed Pilot Studies: Although the test formulations used in the four pilot studies, Nos. BE-248-ATOR-2009 (n=13), BE-249-ATOR-2009 (n=11), 365_ATOR_09 (n=17) and 3023_ATOV_08 (n=12), were identical to those used in the acceptable pivotal bioequivalence (BE) fasting and fed studies, these pilot studies failed to demonstrate bioequivalence. This can easily be explained by the lack of statistical study power in the pilot studies. Atorvastatin is known to be a highly variable drug, especially for Cmax parameter. For this reason, the current draft guidance for the drug product, the applicants are recommended to consider using a reference-scaled average bioequivalence approach for this drug product, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm082580.pdf.

In addition, the high variability of Cmax was evident in both the acceptable pivotal fasting and fed bioequivalence (BE) studies, where 80 subjects were recruited and 76 completed each study, and where the RMSE values (reflecting intra-subject variability) for lnCmax were 0.2928 and 0.3726, respectively (By definition, a highly variable drug has a RMSE value = >0.3000). Pilot studies are not expected to meet BE confidence interval criteria; however, sometimes they do pass the BE criteria. The pilot studies with small sample sizes were usually conducted to estimate the variability of the PK parameters which was used for determining appropriate sample sizes of pivotal studies. In addition, pilot studies such as these were conducted also to determine the lot-to-lot variability of the RLD product.

For the above reasons, the fact that these pilot studies failed to demonstrate bioequivalence is not at all of a concern. On the contrary, it showed that the study design and the test and RLD products were well studied prior to the pivotal BE studies being performed.

Dissolution Data for API Changes: As per the Agency's current recommendations stated in the Guidance for Industry: Alternate Source of the Active Pharmaceutical Ingredient in Pending ANDAs (issued December 2000), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072853.pdf: *"An ANDA applicant can propose an alternate source for the API if the applicant can assure the Agency that the specifications and test data are essentially the same as those of the API originally used in the bioequivalence or test batch.* ***Generally, a new in vivo bioequivalence study will not be needed using the alternate source.*** *However, applicants should provide comparative dissolution data depending on the dosage form of the proposed product.*

To substitute an alternative source for the API, the following circumstances should exist:

1. The original API source is not being withdrawn due to deficiencies specifically relating to that API, such as:

- *Lack of adequate controls*
- *Evidence of adulteration*
- *Evidence of falsification of data in the application or identified in the preapproval Inspection*

If any of these situations apply, a new acceptable bioequivalence (test) batch, an in vivo bioequivalence study (if dictated by the dosage form), and comparative dissolution data for all strengths (based on the dosage form) will be needed to support the alternate source of the API (21 CFR 314.50(d)(1)(i) and (ii)).

2. The previous bioequivalence (test) batches and bioequivalence studies were acceptable except for the CGMP issues that were specific to the original API.

3. The specifications of the alternate source API are essentially the same as the original source API."

Based on the above recommendations, a change in API normally does not require a new *in vivo* bioequivalence study, but instead only comparative dissolution data. Only when dissolution data for the product with a new API are found inadequate to support the API change, (e.g., the API change appears to affect the dissolution profiles of the test product significantly and causes a concern for a possible change in *in vivo* performance), will an additional *in vivo* bioequivalence study be considered to support the API change.

The above criteria for permitting a change in supplier without the submission of a new in vivo bioequivalence study were present in Ranbaxy's amendment to add the Toansa API site, so it was appropriate to review the amendment to add this API site based on dissolution data.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HOAINHON N CARAMENICO
11/21/2011

DALE P CONNER
11/21/2011

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076477Orig1s000

PHARMACOLOGY/TOXICOLOGY REVIEW

Signed off on 10/11/06

2.6 PHARMACOLOGY/TOXICOLOGY REVIEW

2.6.1 INTRODUCTION AND DRUG HISTORY

ANDA number: NDA 76-477
Date of submission: 3/9/2006 (4 volumes). In the current submission sponsor (or DMF holder's Ranbaxy Laboratories, India) is responding to FDA deficiency dated 2/7/2005.

Review Number: 1

Drug Names: Atorvastatin Calcium (Lipitor), 10, 20, 40, 80 mg.

Consult #: 20006-0060 for atorvastatin calcium tablets.

Consult from: Lisa Kwok. Request date: 7/19/06

Generic drug name: Atorvastatin calcium tablets from Ranbaxy Laboratories Ltd, Guragaon, India. The reference listed drug is Lipitor tablets from Pfizer. This is an abbreviated NDA (ANDA).

Drug class: Statins (generic atorvastatin). Cholesterol lowering drug.
Category: Lipid altering, hypolipidemic. Indication: To lower cholesterol.

Type of document: DMF # 16098 for atorvastatin, frorm Ranbaxy laboratories, India.

Subject of Consult: A consult is requested by OGD. The Ranbaxy laboratories, India was notified that their DMF # 16098 was found deficient. They were asked to qualify all known impurities according to ICH Q3A(R). The DMF holder responded to OGD deficiencies on 3/9/06.

In the current consult, OGD has requested a pharmacology/toxicity review of the impurities present in the generic substance. No chemistry consult is requested.

Reviewer name: Indra Antonipillai, Ph.D. Pharmacology Reviewer.
Division: Division of Metabolic and Endocrinology products.

Review completion date: 10/2/2006

Introduction and drug history: This submission indicates a marketing plan for atorvastatin as a generic drug. Presently it is marketed in USA with a physician's prescription as Lipitor for oral administration, to reduce both normal and elevated LDL-cholesterol.

Sponsor was requested to qualify all known impurities *according to ICH Q3A as stated below:*

a. Please tighten the limits for (b) (4) and total impurities.

b. Please qualify all known impurities according to ICH Q3A (R) You may use the impurities profiles of the reference listed drug (RLD) to help you qualify the impurities present in your drug substance. Please be advised that mere comparison of HIPLC retention times of peaks does not provide proof of the identities of the impurities.

c. Please clarify "any other known impurity". Alternatively, you may delete this specification.

The Ranbaxy Laboratories, Ltd., India in response has submitted following studies:

1. A 13-week oral toxicity study in rats with a 4-week drug free recovery period with and without impurities in the drug product
2. Ames assay with atorvastatin amorphous
3. Chromosomal aberration assay with atorvastatin amorphous

The sponsor states that due to the process difference between the active pharmaceutical ingredient (API) in the RLD and Ranbaxy's API, the impurity profile of the reference listed drug (RLD) product cannot be used to support the impurity levels in our API. Therefore, all the impurities including specified unidentified impurities observed above the qualification threshold (0.15%) have been qualified by conducting comparative toxicity studies on Atorvastatin calcium (with and without the impurities) in accordance with the ICH Guidelines for Impurities ICH Q3A (R).

They further state that specified impurity (b) (4) at RRT ~(b) (4)) is found to be an (b) (4) as this impurity is formed from (b) (4) impurity during (b) (4) . Further, (b) (4) impurity may (b) (4) to (b) (4) impurity. As (b) (4) , (b) (4) and specified impurity ((b) (4)) at RRT (b) (4) are interrelated, these impurities are reported together under the heading "Other (b) (4) " wherein Specified impurity ((b) (4) at RRT ~(b) (4)) is reported as part of Total other (b) (4) .

(b) (4)

The complete reaction is summarized below:

(b) (4)

Based on the available data, limits for (b) (4) have been tightened in Atorvastatin calcium (Amorphous) specifications.

Additionally, as per the Agency's recommendation, the other known impurities of Atorvastatin Calcium (Amorphous) (b) (4) have been included by name in the API specification. Accordingly, limit for "Any other known impurity" has been deleted from API specification.

Thus the levels of all the known impurities observed in the toxicity batches along with the proposed limits of impurities are provided on the following page:

Atorvastatin Calcium (Amorphous) API

Related substances (%w/w)	Toxicity Batches		Existing Limits (% w/w)	Proposed Limits (% w/w)
	Without Impurities	Spiked with Impurities		
	(b) (4)			
		(b) (4)		
Any unknown impurity			(b) (4)	
Total impurities				

* ND=Not detectable

Sum of (b) (4)

Toxicity studies

As indicated earlier, sponsor has conducted a study to compare the toxicological profile of two batches of Atorvastatin calcium (test article) viz., Batch No.: (b) (4) and (b) (4) in order to qualify the impurities present in the latter batch, determine target organs of toxicity and a no-observed-adverse-effect-level (NOAEL) and to assess the reversibility of any observed effects following a 4-week recovery period.

In this study, both batches of Atorvastatin calcium were administered as suspension in 0.5% methylcellulose daily by oral gavage to rats (1 5/sexlcontrol and high dose groups; 10/sex/low and mid dose groups) of both sexes at dose levels of 10, 30 and 125 mg/kg bodyweight /day and dose volume of 10 ml/kg/day for a period of 13 consecutive weeks. A control group was treated similarly with vehicle, 0.5 % methylcellulose in water. Satellite animals (3/sex/control group; 1 8/sexltreated groups) were administered the vehicle or test article for 13 weeks and bled on Day 0 and 84 for toxicokinetic analysis. The following parameters were evaluated: viability, clinical observations, functional observation battery parameters, ophthalmology, body weights, feed consumption, clinical pathology, organ weights, macroscopic observations and microscopic Pathology. These studies are summarized below:

In the comparative 13-week repeated dose oral toxicity study in Wistar rats (0, 10, 30, 125 mg/kg/day), the incidence and/or severity of the findings following the oral administration of Atorvastatin calcium amorphous [Batch No.: (b) (4)] were in general similar to the ones observed with Atorvastatin calcium crystalline [Batch No.: (b) (4)]. Under the conditions of the study, based on the histopathological findings, the no-observed-adverse-effect level was not determined. This is because toxicity was noted at all doses with both batches of atorvastatin mainly in the liver at all doses in both sexes (hepatocellular hypertrophy, biliary/oval cell hyperplasia, increased number of mitotic figures, hepatocellular fatty change and basophilic/eosinophilic foci hepatocellular alteration). The toxicity was also noted in the stomach (at a HD of 100 mg/kg/day in the forestomach, epithelial hyperplasia/hyperkeratosis, mixed inflammatory cell infiltrate with or without edema) and in mesenteric lymph nodes (at 10-30 mg/kg/day, increased paracortical size). Following 1-month recovery period, liver (hepatocellular hypertrophy, biliary/oval cell hyperplasia and areas of hepatocellular fatty changes) showed partial recovery with both the test articles. The changes in stomach and mesenteric lymph node were comparable between the recovery groups.

The dose range used in this study was intended to explore the comparative toxicity of the two forms of Atorvastatin calcium. The chosen doses produced the expected effects known to be the effects produced by atorvastatin calcium in rats, and were therefore appropriate for a study intended to determine if the impurity profile of the amorphous form caused additional toxicity.

Note that the systemic AUC exposure is higher with the amorphous form (approximately by 1.3-4.8 times) than with the crystalline form at a HD of 125 mg/kg/day on both days 0 and 84 (see Table 7.1 below). $AUC_{0\text{-}24h}$ values on day 84 with the crystalline form were 8.7/4.0 ug.h/ml in males/females respectively. These with the amorphous form were 11.7/19.5 ug.h/ml respectively. There were some subtle differences in toxicity of two compounds, for example the relative and absolute kidney weights were significantly increased by 19% in females at 125 mg/kg/day with the amorphous form, not seen with the crystalline form at this dose, however no associated histopathology findings were observed. Overall, toxicity in general appeared to be similar with both forms.

Table 7.1-1 Dose Proportional Factors for Atorvastatin in Male and Female Rats

Day	Batch	Group	Dose (mg/kg/day)	Gender	*Theoretical Increases in Exposure (fold)*	*Observed Increases in Exposure (fold)*		
						$AUC_{0\text{-}24h}$	$AUC_{0\text{-}Infinity}$	C_{max}
0	1	2	10	Male	1.00	1.00	1.00	1.00
				Female	1.00	1.00	1.00	1.00
		3	30	Male	3.00	3.59	3.35	4.75
				Female	3.00	5.43	4.52	9.19
		4	125	Male	12.50	56.33	51.94	59.95
				Female	12.50	115.20	95.03	150.00
	2	5	10	Male	1.00	1.00	1.00	1.00
				Female	1.00	1.00	1.00	1.00
		6	30	Male	3.00	3.94	4.01	5.51
				Female	3.00	8.30	8.45	21.98
		7	125	Male	12.50	178.34	185.86	131.65
				Female	12.50	165.29	169.70	143.80
84	1	2	10	Male	1.00	1.00	1.00	1.00
				Female	1.00	1.00	1.00	1.00
		3	30	Male	3.00	2.68	2.74	3.60
				Female	3.00	5.39	5.44	8.04
		4	125	Male	12.50	66.54	68.65	37.44
				Female	12.50	35.95	36.70	37.64
	2	5	10	Male	1.00	1.00	1.00	1.00
				Female	1.00	1.00	1.00	1.00
		6	30	Male	3.00	11.18	11.25	21.57
				Female	3.00	13.44	13.50	17.06
		7	125	Male	12.50	122.26	124.20	103.80
				Female	12.50	203.13	209.00	122.73

Batch 1 = (b) (4) or crystalline Atorvastatin Calcium without impurities
Batch 2 = (b) (4) or amorphous Atorvastatin Calcium with impurities

These studies conclude that the impurities present in Atorvastatin calcium amorphous, batch No.: (b) (4) did not produce any additional toxicity. The doses of the impurities in rats were approximately 36 to 167 times higher than the maximum possible consumption of the impurities in clinical situation (Appendix IV). After considering allometric extrapolation, the doses of the impurities in rats were approximately 5 to 26 times higher than the maximum possible consumption of the impurities in clinical situation (see Table below). Hence, the impurities present in atorvastatin calcium amorphous [Batch No.: (b) (4) can be considered as qualified

Appendix IV: Extrapolation of level of impurities in Atorvastatin calcium amorphous at highest dose used in toxicity study and its consumption at therapeutic dose in human

Impurities in Atorvastatin Calcium amorphous [Batch No.: (b) (4)	Level in spiked API used in tox. study (%)	Proposed Tablet Shelf Life Limits (%)	Dose in rats (mg/kg)	Maximum Possible Consumption in Clinical Situation According to Proposed tablet Shelf Life Limits (mg/kg)	Ratio of Dose in Rat and Maximum Possible Consumption in Clinical Situation According to Proposed tablet Shelf Life Limits	Ratio of extrapolated dose** in Rat and Maximum Possible Consumption in Clinical Situation According to Proposed tablet Shelf Life Limit*
(b) (4)						

*The maximum recommended dose of Atorvastatin Calcium is 1.33 mg/kg/day according to the SPC
** The factor used for extrapolation is 0.16 to convert the dose from Rat to Human[9]

Genotoxicity studies

Atorvastatin calcium amorphous [Batch No.: [(b) (4) was found to be non-mutagenic and non-clastogenic in Salmonella-Escherichia coli/mammalian-microsome reverse mutation assay (at doses up to 5000 ug/plate) and chromosomal aberrations in cultured human peripheral blood lymphocytes assay (at doses up to 202 ug/ml) assays without and with exogenous metabolic activation system.

Safety evaluation:

In the comparative 13-week repeated dose oral toxicity study in Wistar rats (0, 10, 30, 125 mg/kg/day), the incidence and/or severity of the findings following the oral administration of atorvastatin calcium amorphous [Batch No.: (b) (4)] containing spiked impurities were in general similar to the ones observed with atorvastatin calcium crystalline [Batch No.: (b) (4) . Thus, no new or additional toxicity was observed in the presence of impurities.

Thus, sponsor in the current submission has shown that in a 13 week toxicity study with the crystalline form of the drug (vs with the amorphous form of the drug, which has higher levels of all impurities than the crystalline form), no additional or new toxicity was noted. Note that the sponsor did not include a marketed atorvastatin arm for comparison in this 13-week toxicity study in rats. However, the pure atorvastatin batch appeared to be a representative of material intended for commercial release.

In a 13 week oral toxicity study in rats with the marketed atorvastatin (at doses of 10, 30, 100 mg/kg/day, NDA 20-702), the target organ of toxicity was again shown to be mainly the liver (atrophy, atypia, fatty change, hyperplasia, single cell necrosis and infiltration of mononuclear cells, findings in both sexes at all doses), and at a HD toxicity was noted in the epididymis (aplasia, aspermia in males) and lungs (infiltrate, foamy macrophages in females). The AUC exposures were higher with the crystalline form than with the amorphous form at all doses. The $AUC_{0\text{-}24h}$ values with the crystalline form were 0.74, 2.6, 21/ 0.33, 0.79, 12 ug.h/ml in males/females at 10, 30, 100 mg/kg/day respectively. These with the amorphous form were 0.42, 1.2, 13/ 0.37, 0.64, 9.5 ug.h/ml in males/females respectively. Thus at 100 mg/kg/day the AUC exposures with the crystalline form in the currently marketed atorvastatin ranged between 12-21 ug.h/ml and with amorphous between 10-13 ug.h/ml (vs in the current study at 125 mg/kg/day with the crystalline form were between 4-9 ug.h/ml and with amorphous form between 12-20 ug.h/ml). Thus exposures appeared to be different in the original (conducted in 1995) vs the current application (study conducted in 2005). However, it is possible that original pre-clinical studies conducted with atorvastatin (NDA 20-702) may have had some formulation changes over time.

From the pharmacology/toxicity point of view, the sponsor has qualified the impurities in their API.

Internal Recommendations:

Sponsor by providing a 3-month comparative toxicity study in rats with their pure atorvastatin batch (crystalline form) vs the amorphous form (with spiked impurities), as well as by conducting two geno-toxicity studies with the amorphous form, has qualified the impurities in atorvastatin calcium and these are acceptable.

Thus from the pharmacology/toxicity point of view, the proposed levels of different impurities are qualified based on toxicity studies.

Signatures (optional):

Reviewer Signature _____

Supervisor Signature_____
Concurrence Yes ___ No ___

cc: IND Arch
HFD-510
HFD-510/davisbruno/Antonipillai/Johnson/cunnigham.v/Kwok Lisa/Ripper, L
File name: ANDA76477-OGD consult (atorvastatin consult)

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/s/

Robert Iser
2/19/2008 03:00:58 PM
CHEMIST

Consult was not placed into DFS, as it was completed prior to DFS coming on-line. The review was submitted in support of ANDA 76477 and DMF 16088.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 076477Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

VAL 2/14/03 P.Z.P
Δ P III to P IV
4,681,893

January 8, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS and FAX

Revision to Patent Certification

NEW CORRESP
NC

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002. Reference is also made to the Patent Amendment dated December 9, 2002.

Included with this letter is the following information:

A revised Patent Certification and Exclusivity Statement letter to reflect Ranbaxy's decision to change from a Paragraph III Certification to a Paragraph IV Certification for US Patent No. 4,681,893, which expires March 24, 2010.

Ranbaxy certifies that in the opinion and to the best of its knowledge, no valid or enforceable claim of said patent will be infringed after May 30, 2006, by the manufacture, use or sale of Ranbaxy's Atorvastatin Calcium Tablets for which this abbreviated new drug application is submitted.

Due to the fact we are changing certification for the '893 patent, Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Office of Generic Drugs.

RECEIVED

JAN 0 9 2003

OGD / CDER

If you have any questions or comments regarding this supplement, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

August 19, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

505 (j)(2)(A) OK
11-OCT-2002
Gregory S. Davis

Reference: **Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg**
Abbreviated New Drug Application

Dear Sir/Madam:

Ranbaxy Laboratories Limited herewith submits an abbreviated new drug application (ANDA) for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

This ANDA refers to the listed drug, Lipitor® (Atorvastatin Calcium) Tablets, 10 mg, 20 mg, 40 mg and 80 mg. The holder of the approved application for Lipitor® Tablets is Pfizer as listed in the 2002 Approved Drug Products with Therapeutic Equivalence Evaluations, 22nd Edition.

Ranbaxy Laboratories Limited herewith certifies that with reference to US Patent Nos. 5,686,104; 5,969,156 and 6,126,971 the applicant certifies that in the opinion and to the best of its knowledge, no valid or enforceable claim of said patents will be infringed by the manufacture, use or sale of Ranbaxy's Atorvastatin Calcium Tablets for which this abbreviated new drug application is submitted.

Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

Further, with reference to US Patent Nos. 4,681,893 and 5,273,995 the applicant certifies that in the opinion and to the best of its knowledge, the last expiring of said patents will expire on June 28, 2011.

The drug product manufacturer is Ranbaxy Laboratories Limited. Atorvastatin Calcium Tablets 10 mg, 20 mg, 40 mg and 80 mg will be manufactured at Ranbaxy Laboratories Limited's FDA registered and inspected Paonta Sahib, India facility in accordance with 21 CFR 210 and 211.

The drug product will also be packaged in bottles and bulk packs at Ranbaxy laboratories Limited, Paonta Sahib, India facility.

The manufacturer of the Atorvastatin Calcium drug substance used to produce the ANDA batches of drug product is Ranbaxy Laboratories Limited, Toansa, India. The Drug Master File was submitted on August 19, 2002. The information on DMF numbers will be submitted for this ANDA when assigned by the Agency. A sample of the bulk raw material and is available and will be provided to the Agency upon request.

The required bio-availability/bio-equivalence studies were conducted on Atorvastatin Calcium Tablets, 80 mg and Lipitor® Tablets, 80 mg at Department of Clinical Pharmacology and Pharmacokinetics, Ranbaxy Research Laboratories, Plot No. 20, Sector 18, Udyog Vihar Industrial Area, Gurgaon 122001, Haryana, India. The studies indicate that Atorvastatin Calcium Tablets, 80 mg are bio-equivalent to Lipitor® Tablets, 80 mg. The in-vitro dissolution profiles for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg are comparable to the in-vitro dissolution profiles of Lipitor® Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Therefore, a waiver of in-vivo bio-availability/bio-equivalence study requirements for Atorvastatin Calcium Tablets, 10 mg, 20 mg and 40 mg is requested.

Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg are stable and a two year expiration dating is requested. The two year expiration dating for these products is supported by one, two and three months accelerated stability data (40°C/75% relative humidity).

The dosage form, route of administration, indications and usage, dosage and route of administration, active ingredient, potency and labeling (except DESCRIPTION and HOW SUPPLIED sections) for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg are the same as those for Lipitor® Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

This ANDA is submitted in seventeen volumes:

Volume I:	Section I through Section V.
Volume II: through Volume XIII:	Section VI.
Volume XIV: 14	Section VII through Section XI
Volume XV:	Section XII through Section XIV
Volume XVI:	Section XV
Volume XVII: 17	Section XVI through Section XXII Stability

Ranbaxy Laboratories Limited commits to resolve any issues identified in the method validation process after approval.

Please contact the undersigned at (609)720-5666 if you have any questions regarding this submission.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs.

Sincerely,

Abha Pant

Abha Pant
US Agent for Ranbaxy Laboratories Limited.

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

October 9, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS and FAX

ADDITIONAL INFORMATION

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002. Reference is also made to the telephone contact of October 9, 2002 between Ranbaxy and the Agency.

Included with this letter is the following information as requested in the telephone contact:

1. A revised Patent Certification and Exclusivity Statement letter to reflect each specific exclusivity for the reference listed drug. See attached revised pages 0011 and 0011-A.
2. Revised accelerated stability data tables to correct the typographical error regarding the storage conditions (from 25°C ± 2°C/60%±5% RH to 40°C ± 2°C/75% ± 5% RH) . See attached, Revised pages.
3. Clarification regarding the financial certification (3454) and financial disclosure (3455) forms included in the application.

Regarding the 3454 and 3455 forms, Ranbaxy requests that the Agency disregard the 3454 forms (pages 0396 – 0399 and pages 3934 – 3937). These forms were accidentally and mistakenly included in the final application. The 3455 forms submitted on pages 0117 and 0131 are the correct financial disclosure forms.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Office of Generic Drugs.

If you have any questions or comments regarding this supplement, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

E Thomas NT 10/22

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

NEW CORRESP

NC

October 10, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS and FAX

ADDITIONAL INFORMATION

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002. Reference is also made to the telephone contact of October 10, 2002 between Ranbaxy and the Agency.

Included with this letter is the following information as requested in the telephone contact:

A revised Patent Certification and Exclusivity Statement letter to reflect the expiration of each of the Patents which Ranbaxy is claiming Paragraph III Certification. See attached revised pages 0011 and 0011-A.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Office of Generic Drugs.

If you have any questions or comments regarding this supplement, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

RECEIVED
OCT 11 2002
OGD / CDER

ANDA 76-477

OCT 11 2002

Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Abha Pant
600 College Road East
Princeton, NJ 08540

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated October 9, 2002 and your correspondences dated October 9 and 10, 2002.

NAME OF DRUG: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

DATE OF APPLICATION: August 19, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 19, 2002

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day

period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,

Gregory S. Davis for

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: ANDA 76-477
DUP/Jacket
Division File
Field Copy
HFD-610/R.West
HFD-610/P.Rickman
HFD-92
HFD-615/M.Bennett
HFD-600/

Endorsement: HFD-615/GDavis, Chief, RSB 11-OCT-2002 date
HFD-615/BFritsch, CSO 10/10/02 date
Word File
V:/FIRMSNZ/Ranbaxy/ltrs&rev/76477.ack
FT/
ANDA Acknowledgment Letter!

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA# 76-477 **FIRM NAME** RANBAXY LABORATORIES LTD

RELATED APPLICATION(S) _____ **FIRST GENERIC? YES**

DRUG NAME: ATORVASTATIN CALCIUM
DOSAGE FORM: TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG

Electronic Submission: NA E-mail notification sent: NA Comments: NA

Random Assignment Queue: Random 2 Chem Team Leader: Smela, Mike PM: Chen, Peter

Labeling Reviewer: Payne, Angela Micro Review: NA PD study (Med Ofcr): NA

Letter Date AUGUST 19, 2002	**Received Date** August 19, 2002
Comments EC 4 YES **On Cards YES** **ALTERING AGENTS**	**Therapeutic Code 3021600 LIPID**
Methods Validation Package (3 copies) (Required for Non-USP drugs) YES	
Archival, and Review copies Field Copy Certification (Original Signature) YES	
Cover Letter YES	
Table of Contents YES	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) RX YES, 80 mg is RLD	☒
Sec. II	**Basis for Submission** **NDA: 20-702** RLD: LIPITOR Firm: PFIZER ANDA suitability petition required? If yes, consult needed for pediatric study requirement.	☒

Sec. III	**Patent Certification** 1. Paragraph: IV 2. Expiration of Patent: JANUARY 8, 2017 3. SEPT. 24, 2009 U-161 4. MARCH 24, 2010 PED - U-161 5. DECEMBER 28, 2010 U-162 6. JUNE 28, 2011 U-162 7. NOVEMBER 11, 2014 U-213 8. MAY 11, 2015 U-213 9. JULY 8, 2016 10. Jan 8, 2017 11. JAN 19, 2013 12. JULY 19-2013 PED 13. A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement YES DEC 2, 2002, APRIL 22, 2005, JUNE 2, 2003 - CHECK EXCLUSIVY STATEMENT** **Exc. Statement. - doesn't list exclusivities, says exclusivity will expire on 4/22/05. Firm revised 10/09/02.**	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ok 2. Active ingredients ok 3. Route of administration ok 4. Dosage Form ok 5. Strength ok	☒
Sec. V	**Labeling** 1. 4 copies of draft (each strength and container) or 12 copies of FPL ok 2. 1 RLD label and 1 RLD container label ok 3. 1 side by side labeling comparison with all differences annotated and explained ok (b) (4)	☒

Sec. VI	**Bioavailability/Bioequivalence** 1. Financial certification (Form FDA 3454) and Disclosure stmt (Form 3455) (for BE studies only!) YES, Both a 3454 and 3455 were submitted. Asked firm to clarify. Clarification provided 10/09/02. 2. In Vivo Study Protocol(s): YES 3. In Vivo Study(ies): FED AND FAST 80 MG 4. Computer Disk Submitted: YES 5. Request for Waiver of In Vivo Study(ies): YES 10 MG, 20 MG, 40 MG 6. In Vitro Dissolution Data: YES 7. Formulation Data Same? (Comparison of all Strengths) (Opthalmics, Otics, Externals, Parenterals) YES 8. Paragraph IV bio study acceptable for filing YES 9. Lot numbers of products used in Bio-study 1200558 for 80 mg 10 mg 1201336 20 mg 1201334 40 mg 1201328 10.DSI inspection request needed? NA ☐ 1st Generic ☐ 1st study for site ☐ Other **E-mail notification to Bio PMs sent**	☒
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ok 2. Inactive ingredients as appropriate YES	☒
Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers Yes b. Type II DMF authorization letters or synthesis ok, DMF 16098 c. COA(s) specifications and test results from drug substance mfgr(s) ok d. Applicant certificate of analysis ok e. Testing specifications and data from drug product manufacturer(s) ok f. Spectra and chromatograms for reference standards and test samples ok g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified ok b. Testing specifications (including identification and characterization) ok c. Suppliers' COA (specifications and test results) ok d. Applicant certificate of analysis ok	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ok 2. CGMP Certification ok 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address NA, none used 2. Functions NA 3. CGMP Certification/GLP NA 4. CFN numbers	☒

Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including MicrobiologicalValidation, if Appropriate) ok 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified ok 10 mg - (b) (4) 20 mg - 40 mg - 80 mg - 3.If sterile product: Aseptic fill / Terminal sterilization NA 4.Filter validation (if aseptic fill) NA 5. Reprocessing Statement Yes	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ok 10 mg - lot 1201336 (b) (4) 20 mg - lot 1201334 40 mg - lot 1201328 80 mg - lot 1200558 2. In-process Controls a. Sampling plans and test procedures ok b. Specifications and data ok	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ok 2. Components Specification and Test Data (Type III DMF References) ok 3. Packaging Configuration and Sizes ok 4. Container/Closure Testing ok 5. Source of supply and suppliers address ok	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Sampling Plans and Test Procedures ok 2. Testing Specifications and Data ok 3. Certificate of Analysis for Finished Dosage Form ok 10 mg - lot 1201336 20 mg - lot 1201334 40 mg - lot 1201328 80 mg - lot 1200558	☒

Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ok 2. Post Approval Commitments ok 3. Expiration Dating Period 2 yr 4. Stability Data Submitted YES a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch Conditions on the accelerated stability data are 25 C/60% RH - Spoke with firm, the sheets contain typographical errors. Corrected accelerated stability data sheets sent. (10/9/02) 10 mg - (b) (4) 20 mg - 40 mg - 80 mg -	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ok 2. Finished Dosage Form ok 3. Same lot numbers yes 10 mg - lot 1201336 Drug substance - 1197242, 1199895, 1199898 20 mg - lot 1201334 40 mg - lot 1201328 80 mg - lot 1200558	☒
Sec. XVII	**Environmental Impact Analysis Statement** orig sig.	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) yes 2. Debarment Certification (original signature) YES 3. List of Convictions statement (original signature) yes	☒

Reviewing CSO/CST **Beth Fabian-Fritsch** **Date** **10/09/02**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 11-OCT-2002
Duplicate copy sent to bio: (Hold if RF and send when acceptable) Duplicate copy to **HFD-** for consult: Type:	

ADDITIONAL COMMENTS REGARDING THE ANDA:

10/09/02 - Spoke with Abha Pant and Scott Tomsky. They will fax the information to me and follow up with hard copy.

I asked for a revised exclusvity statement that acknowledges all of the exclusivities that exist for atorvastatin.
I also need clarification for the financial disclosure. Forms 3454 and 3455 were submitted for both studies.
Lastly, the accelerated stability data sheets list the conditions as 25 degrees Celsius and 60 % relative humidity.
I asked if this was a typographical error. It was confirmed. I asked the firm to revise the data sheets with the correct conditions. This will lead to less confusion with the reviewing chemist.

10/10/02 left message for Abha Pant.
I need the patent certification to be revised. The p III certification should contain the expiration dates of the patents.

OGD Form Revised 11/30/2001
MSWord Template revised: 8/7/2002

10/10/02: rec'd fax addressing the p III patent certification

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

UAE Oct-18-2002 P.M.P

October 17, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

Amendment

NEW CORRESP
NC

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Please find the attached following letter:

- Letter of authorization (letter of access) which permits the Food and Drug Administration to reference the Type II DMF for Atorvastatin Calcium (Amorphous) (16098) manufactured by Ranbaxy Laboratories Limited which is referenced in the ANDA for Atorvastatin Calcium Tablets filed by Ranbaxy Laboratories Limited.

The letter of authorization was included in the original ANDA, however, at that time a DMF number had not been assigned. Ranbaxy Laboratories has now received a DMF number (16098) for their Atorvastatin Calcium (Amorphous) DMF. Accordingly, the revised LOA is enclosed for your review.

Field Copy : We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this submission has been provided to the Office of Generic Drugs, International Operations Group.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited.

RECEIVED
OCT 1 8 2002
OGD / CDER

RANBAXY
LABORATORIES LIMITED

SECTOR-18, UDYOG VIHAR INDUSTRIAL AREA, GURGAON-122001
PHONE: (91-1246) 342001-10, Fax: (91-1246) 342017, 342036

December 9, 2002

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT
NEW CORRESP
NC

Reference: **ANDA 76-477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Notification to Patent Holders

Dear Sir/Madam:

Reference is made to our pending Abbreviated New Drug Application 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Ranbaxy Laboratories Limited has complied with the requirements under 21 CFR 314.95 (a) with respect to providing a notice to each owner of said patents or their representatives and to the holder of the approved drug application for the listed drug, and with the requirements under 21 CFR 314.95 (c) with respect to the content of the notice.

We are amending this application to certify that Ranbaxy Laboratories Limited has notified the appropriate holder via U. S. certified mail on November 4, 2002. The certified letter was delivered to Pfizer Inc. on November 6, 2002. Attached are copies of the certified receipt and the notice by Ranbaxy to the listed drug holder, Pfizer Inc.

If you have any questions or comments regarding this submission, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Regulatory Affairs Associate (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
DEC 10 2002
OGD / CDER

MINOR AMENDMENT

ANDA 76-477

FEB 5 2003

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

TO: APPLICANT: Ranbaxy Pharmaceuticals Inc.
U.S. Agent for Ranbaxy Laboratories Limited
ATTN: Abha Pant

TEL: 609-720-5666

FAX: 609-720-1155

FROM: Wanda Pamphile

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 19, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (3 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120, which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry comments included. Please include in your response.

2/5/03

FEB 5 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **76-477** APPLICANT: **Ranbaxy Laboratories Limited**

DRUG PRODUCT: **Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.**

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. The Drug Master File No. 16098 was found deficient. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

2. Regarding the drug substance specifications, we have the following comments:

(b) (4)

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10

11

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. The bioequivalence portion of your submission is under review. Deficiencies, if any, will be communicated to you under separate cover. Please be advised that the acceptance of the dissolution method and specifications are contingent upon their acceptance by the DBE. You may be required to submit additional accelerated stability data using the method and specifications recommended by DBE.

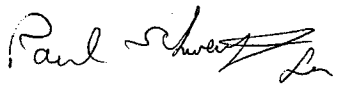
2. We will issue a method validation request to an FDA laboratory, when all testing issues are resolved.

3. The firms referenced in your application must be in compliance with cGMP at the time of approval.

4. Please provide any available drug product room temperature stability data.

5. Please obtain a copy of the revised COA from the DMF holder and revise the drug substance specifications accordingly (See comment 2 under Section A above).

Sincerely yours,



Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

RANBAXY
PHARMACEUTICALS INC.

February 10, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT

NEW CORRESP
NC

Reference: **ANDA 76-477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Notification to Patent Holders

Dear Sir/Madam:

Reference is made to our pending Abbreviated New Drug Application 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to our letter dated January 8, 2003 in which we revised our patent certification on the '893 patent.

Ranbaxy Laboratories Limited has complied with the requirements under 21 CFR 314.95 (a) with respect to providing a notice to each owner of said patents or their representatives and to the holder of the approved drug application for the listed drug, and with the requirements under 21 CFR 314.95 (c) with respect to the content of the notice.

We are amending this application to certify that Ranbaxy Laboratories Limited has notified the appropriate holder via U. S. certified mail on January 23, 2003. The certified letter was delivered to Pfizer Inc. on January 27, 2003. Attached are copies of the certified receipt and the notice by Ranbaxy to the listed drug holder, Pfizer Inc.

If you have any questions or comments regarding this submission, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
FEB 11 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX:** (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

'L NEW CORRESP

NC Patent Revision 2/27/03
Δ PIII to PIV
for '995

February 18, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS and FAX

Revision to Patent Certification

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002. Reference is also made to the Revised Patent Certification dated January 8, 2003.

Included with this letter is the following information:

A revised Patent Certification and Exclusivity Statement letter to reflect Ranbaxy's decision to change from a Paragraph III Certification to a Paragraph IV Certification for US Patent No.5,273,995, which expires June 28, 2011. By this letter Ranbaxy is also changing its certification with respect to US Patent 4,681,893 as to the date included in the cover letter of January 8, 2003.

Ranbaxy certifies that in the opinion and to the best of its knowledge, no valid or enforceable claim of US Patent Nos. 4,681,893 and 5,273,995 will be infringed by the manufacture, use or sale of Ranbaxy's Atorvastatin Calcium Tablets for which this abbreviated new drug application is submitted.

Due to the fact we are changing certification for the '995 patent, Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Office of Generic Drugs.

RECEIVED
FEB 2 0 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX:** (609) 720-1155

If you have any questions or comments regarding this supplement, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
Official US Agent for Ranbaxy Laboratories Limited

RANBAXY
PHARMACEUTICALS INC.

EW CORRESP

NC 3/14/03 P.17.P Sued on 893

February 28, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT
Notice of Civil Action

Reference: **ANDA 76-477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to our pending Abbreviated New Drug Application 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

The holder of the approved drug application for the listed drug, Pfizer Inc. was notified of Ranbaxy's ANDA 76-447 filing of Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg via certified mail.

We are including a copy of the Civil Action, filed on behalf of Pfizer Inc. to the U.S District Court of Delaware on February 21, 2003.

If you have any questions or comments regarding this submission, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAR 0 3 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

March 4, 2003

ORIG AMENDMENT
N/AB

UPS and Fax

BIO TELEPHONE AMENDMENT

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

Reference: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg
ANDA – 76-477

Dear Mr. Sigler,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg submitted to the Agency on August 19, 2002.

Reference is also made to the Telephone Bioequivalence deficiency comments received February 14, 2003.

The deficiency questions and responses are addressed and detailed on the following page.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this response has been provided to the Food and Drug Administration, International Operation Group as this product is manufactured in India.

Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott D. Tomsky (for)

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAR 0 5 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

9 Thomas NDA I 9/8/03

RANBAXY
PHARMACEUTICALS INC.

. NEW CORRESP
NC

March 6, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT

Reference: **ANDA 76-477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Notification to Patent Holders

Dear Sir/Madam:

Reference is made to our pending Abbreviated New Drug Application 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to our letter dated February 18, 2003 in which we revised our patent certification on the '995 and '893 patents.

Ranbaxy Laboratories Limited has complied with the requirements under 21 CFR 314.95 (a) with respect to providing a notice to each owner of said patents or their representatives and to the holder of the approved drug application for the listed drug, and with the requirements under 21 CFR 314.95 (c) with respect to the content of the notice.

We are amending this application to certify that Ranbaxy Laboratories Limited has notified the appropriate holder via U. S. certified mail on February 28, 2003. The certified letter was delivered to Pfizer Inc. on March 3, 2003. Attached are copies of the certified receipt and the notice by Ranbaxy to the listed drug holder, Pfizer Inc.

If you have any questions or comments regarding this submission, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAR 1 0 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

L NEW CORRESP

March 7, 2003

NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT

Reference: **ANDA 76-477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Notification to Patent Holders

Dear Sir/Madam:

Reference is made to our pending Abbreviated New Drug Application 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to our Patent Amendment letter dated February 10, 2003 in which included information regarding the notification to Patent Holders for the '893 Patent certification.

Please note that Ranbaxy initially sent this notification to the Patent holder dated January 10, 2003. We are enclosing the notification and certified receipt which was sent on January 10, 2003 and delivered to Pfizer on January 15, 2003. This notification incorrectly referred to the form of the drug product as capsules rather than tablets. The notification was revised to correctly identify the dosage form as tablets, and the Patent Amendment sent to the Agency dated February 10, 2003 included the revised letter which was sent to Pfizer dated January 23, 2003 and the return receipt was dated January 27, 2003.

In addition, we are attaching a summary to highlight the various patent amendments for this ANDA.

If you have any questions or comments regarding this submission, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAR 1 0 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX:** (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

March 11, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT

NC

Reference: **ANDA 76-477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Notification to Patent Holders

Dear Sir/Madam:

Reference is made to our pending Abbreviated New Drug Application 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to our letter dated March 6, 2003 in which we informed the Agency that we notified the patent holder (Feb. 28th) and received the stamped certified receipt for our patent certifications on the '995 and '893 patents.

It has just come to our attention that the notices sent to Pfizer on February 28, 2003 for the '893 and '995 patents were sent separately rather than under one certified receipt. In the Patent Amendment letter sent to the Agency dated March 6, 2003 we had included a stamped certified receipt (date delivered 3/3/03); this receipt was for the notice sent to Pfizer for the '893 patent. We hereby are including the other stamped certified receipt which is for the notice sent to Pfizer on the '995 Patent.

We are amending this application to certify that Ranbaxy Laboratories Limited has notified the appropriate holder via U. S. certified mail on February 28, 2003. The certified letter was delivered to Pfizer Inc. on March 6, 2003. Attached are copies of the certified receipt and the notice by Ranbaxy to the listed drug holder, Pfizer Inc.

In addition, we are updating the summary of the various patent amendments for this ANDA that was sent to the Agency in the letter dated March 7, 2003.

If you have any questions or comments regarding this submission, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAR 12 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

E Thomas NDA 4/4/03

RANBAXY
PHARMACEUTICALS INC.

March 19, 2003

NEW CORRESP

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT

NEW CORRESP
NC

Reference: **ANDA 76-477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Amendment – No Response from Patent Holder to Notification of filing ANDA 76-477 with Paragraph IV cert on the '104, '156 and '971 patents

Dear Sir/Madam:

We are submitting an amendment to Ranbaxy Laboratories Limited's pending ANDA # 76-477, for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg, in accordance with 21 CFR 314.95.

Ranbaxy Laboratories Ltd. has complied with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patents or their representatives and to the holder of the approved drug application for the listed drug, and with the requirements under 21 CFR 314.95(c) with respect to the content of the notice. We notified the appropriate holders on November 4, 2002 regarding our ANDA with Paragraph IV certification for the '104, '156, and '971 patents. The stamped certified receipt was returned to Ranbaxy stating that Pfizer received the notification November 6, 2002. Reference is made to our Patent Amendment sent to the Agency dated December 6, 2002.

Ranbaxy hereby would like to inform the Agency that Pfizer did not file suit against Ranbaxy Laboratories Ltd. regarding the submission of ANDA 76-409, with Paragraph IV certification on the '104, '156, and '971 patents.

Ranbaxy has sent additional paragraph IV certifications to Pfizer (for the '893 and '995 patents) after the original paragraph IV certification. In regard to these patents, as of today, Pfizer has filed suit against Ranbaxy for the '893 patent at this time, please note the 45 day period has not expired for the '995 patent. As soon as any action on the '995 patent becomes available Ranbaxy will notify the Agency at such time.

If you have any questions or comments regarding this submission, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

RECEIVED
MAR 2 1 2003
OGD / CDER

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT

N1 MM

April 11, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and Fax

MINOR AMENDMENT RESPONSE

Reference: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg
ANDA – 76-477

Dear Mr. Sigler,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg submitted to the Agency on August 19, 2002.

Reference is also made to the Minor deficiency comments received February 5, 2003.

The deficiency questions and responses are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this response has been provided to the Food and Drug Administration, International Operation Group as this product is manufactured in India.

Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
APR 15 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

April 17, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

PATENT AMENDMENT

NEW COMPLSP
NC

Reference: **ANDA 76-477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Notice of Civil Action on the '893 and '995 Patents

Dear Sir/Madam:

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets, 10mg, 20mg, 40mg and 80mg. Reference is also made to our Patent Amendment, Notice of Civil Action sent to the FDA dated February 28, 2003. The letter dated February 28, 2003 was notice for Civil Action filed in reference to the '893 patent, and Ranbaxy's Notice to the Patent Holder dated January 10, 2003.

The holder of the approved drug application for the listed drug, Pfizer Inc. was notified of Ranbaxy's new Paragraph IV certification on the '893 and '995 patents in a letter dated February 28, 2003 via certified mail. This was summarized in Ranbaxy's Patent Amendment sent to the Agency dated March 6, 2003.

We are including a copy of the Civil Action, filed on behalf of Pfizer Inc. to the U.S District Court of Delaware on April 11, 2003 in regard to the '893 and '995 patents.

Please note, reference is made to Ranbaxy's Patent Amendment dated March 19, 2003 in which we notified the Agency that Ranbaxy was not sued in respect to the original Patent Certification on the '104, '156 and '971 patents sent to Pfizer on November 4, 2002 and received delivered to Pfizer on November 6, 2002. Therefore, Ranbaxy would like to clarify that Pfizer has not filed civil action on the '104, '156 and '971 patents, but only on the '893 and '995 patents.

If you have any questions or comments regarding this submission, please call me at 609-720-5609 or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Scott D. Tomsky
Manager Regulatory Affairs (for)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
APR 18 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

MINOR AMENDMENT

ANDA 76-477

MAY 21 2003

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Ranbaxy Pharmaceuticals, Inc. TEL: 609-720-5666
U.S. Agent for: Ranbaxy Pharmaceuticals Limited

ATTN: Abha Pant FAX: 609-514-9797

FROM: Wanda Pamphile PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 19, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40mg, and 80 mg.

Reference is also made to your amendment(s) dated: April 11, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120, which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry comments included. Please include in your response.

WR 5/21/03

MAY 21 2003

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **76-477** APPLICANT: **Ranbaxy Laboratories Limited**

DRUG PRODUCT: **Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.**

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File No. 16098 was found deficient. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

2. Regarding the drug substance specifications, we have the following comments:

   a. Please tighten the related substances limit for individual known and specified impurities based on the current information provided by the drug substance manufacturer.

   b. Please tighten the limit (lower end) for assay based on the current information provided by the drug substance manufacturer.

3. Please provide assurance that the (b) (4) will have uniformity of mixing in the routine commercial batches of the drug product.

4. We acknowledge your response concerning the assay limits for Lovastatin Tablets and Simvastatin Tablets in the current USP monographs. However, we are unable to accept your assay limit of (b) (4) % of the labeled claim for Atorvastatin Calcium Tablets at this time. Please tighten the assay limits.

5. Please revise the limits for dissolution based on the DBE recommendations dated May 5, 2003 and submit the revised specifications for drug product release and stability.

6. Since you have been informed of the dissolution specification for product release and stability by the Division of Bioequivalence on May 5, 2003, please provide dissolution study data at the 15 minutes time point using the third month stability samples of the bio batch in all container/closure configurations that had been stored under the accelerated conditions. Alternatively, if during the accelerated study of the bio batch, you have recorded the dissolution data at the 15 minutes time points, you may submit them to support your 24 months expiration dating period. Please be advised that if you choose to submit additional stability data generated on the room temperature samples, you need to provide full term room temperature stability data in order to support the 24 months expiry.

7. We are unable to accept your limit for the related substances for the drug product release and stability at this time. Please tighten the limits for related substances for product release and stability.

8. (b) (4)

1.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Please provide a commitment to work with us to expeditiously resolve any deficiencies from the Methods Validation study if the ANDA is approved prior to its completion.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

RANBAXY
PHARMACEUTICALS INC.

May 29, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and Fax

ORIG AMENDMENT
N/AB

BIOEQUIVALENCY RESPONSE

Reference: **Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg**
ANDA – 76-477

Dear Mr. Sigler,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg submitted to the Agency on August 19, 2002.

Reference is also made to the Bioequivalency deficiency comments received May 5, 2003.

The deficiency questions and responses are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this response has been provided to the Food and Drug Administration, International Operation Group as this product is manufactured in India.

Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

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MAY 3 0 2003
OGD / CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

LAW OFFICES

CONNOLLY BOVE LODGE & HUTZ LLP
1220 MARKET STREET
P.O. BOX 2207
WILMINGTON, DELAWARE 19899

TELEPHONE (302) 658-9141
FACSIMILE (302) 656-9072

www.cblhlaw.com

WASHINGTON OFFICE
SUITE 800
1990 M STREET NW
WASHINGTON, DC 20036-3425
TELEPHONE: (202) 331-7111
FACSIMILE: (202) 293-6229

June 11, 2003

NEW CORRESP

NC

BY CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
HFD-600
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 76-477
Notice of Filing Legal Action for Patent Infringement

Dear Sir or Madam:

We represent Pfizer Inc, Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company, LLC and Warner-Lambert Export, Ltd. (collectively "Pfizer") who have brought suit against Ranbaxy Laboratories Limited, and Ranbaxy Pharmaceuticals Inc. for infringement and inducing infringement of US Patent No. 4,681,893 by the submission of the above-referenced ANDA.

Pursuant to 21 CFR § 314.107(f)(2), Pfizer provides notification as follows:

(i) The ANDA number is 76-477;

RECEIVED
JUN 18 2003
OGD / CDER

(ii) The name of the abbreviated new drug applicant is Ranbaxy Laboratories Limited;

(iii) The notice from Ranbaxy Pharmaceuticals Inc. to Pfizer about the ANDA filing provided an established name for the ANDA drug product as atorvastatin, in the form of tablets, which contain the equivalent of 10 mg, 20 mg, 40 mg and 80 mg of atorvastatin as the active ingredient.

(iv) We certify that the above-referenced patent infringement suit was filed under Civil Action No. 03-375 JJF in the United States District Court for the District of Delaware on April 11, 2003. A copy of the complaint is enclosed.

Pfizer received notice dated February 28, 2003, pursuant to § 505(j)(2)(B) of the Food, Drug and Cosmetic Act (the "Act") of submission of the above-referenced ANDA. Accordingly, pursuant to § 505(j)(4)(B)(iii) of the Act, approval of the above-referenced ANDA may not be made effective until the expiration of the 30-month period beginning from Pfizer's receipt of such notice, i.e., until August 28, 2005, or such shorter or longer period as the court may order pursuant to said section of the Act.

Respectfully submitted,

Jeffrey B. Bove

JBB\jjh
Enclosures

cc: Janet Woodcock, Director (w/ enclosures)
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-001, Room 6027
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

Jane Axelrad (w/ enclosures)
Associate Director for Policy
Center for Drug Evaluation and Research
Food and Drug Administration
HFD-005, Room 6027
Woodmont Office Complex 2
1451 Rockville Pike
Rockville, MD 20852

RANBAXY
PHARMACEUTICALS INC.

August 14, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and Fax

MINOR AMENDMENT RESPONSE

ORIG AMENDMENT
N/AM

RECEIVED
AUG 15 2003
OGD/CDER

Reference: **Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg**
ANDA – 76-477

Dear Sir/Madam,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg submitted to the Agency on August 19, 2002.

Reference is also made to the Minor deficiency comments received May 21, 2003.

The deficiency questions and responses are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this response has been provided to the Food and Drug Administration, International Operation Group as this product is manufactured in India.

Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NAI
Beth Fehn
9/11/03
Not listed in Orange Book
NEW CORRESP
NC

August 19, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS and FAX

Revision to Patent Certification

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002.

At this time we are submitting a patent certification amendment. We recently became aware of a new patent (U.S. 6,605,729) for the reference listed drug Lipitor®. Please find attached the patent certification for this ANDA, as amended.

Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Office of Generic Drugs.

If you have any questions regarding this amendment, please contact me at (609) 720-5609 or, Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
AUG 19 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NEW CORRESP
NC

NCE
B. Sitz
9/11/03
Not yet listed in Orange Book

August 20, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS and FAX

Revision to Patent Certification

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002.

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If you have any questions regarding this amendment, please contact me at (609) 720-5609 or, Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
AUG 20 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

August 21, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

~~NEW EXPRESS~~ NC **Revision to Patent Certification**

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

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Abha Pant
US Agent for Ranbaxy Laboratories Limited

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OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

Nat
B. Fritsen
9/11/03
Not yet listed
in orangebook

NEW CORRESP
NC

August 22, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

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Sincerely,

Scott Tomsky (for)

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
AUG 2 2 2003

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NEW CORRESP
NC Nal
B. Filar
9/11/03
Not yet listed
in orange
Book

August 23, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

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Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

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AUG 2 5 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NCA
B. Fitton
9/11/03
Patent not yet
listed in Orange Book

August 25, 2003

NEW CHARGE
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

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Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
AUG 25 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NA1
B. Fritsen
9/11/03
Patent not yet listed in Orange Book

August 26, 2003

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

RE: ANDA 76-477
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Sincerely,

RECEIVED
AUG 2 6 2003
OGD/CDER

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

NA1
B. Autar
9/11/03
Patent not yet listed in Orange Book

RANBAXY
PHARMACEUTICALS INC.

August 27, 2003

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

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Sincerely,

Scott D. Tomsky (/s)

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
AUG 27 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

August 28, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP

UPS

Revision to Patent Certification

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Sincerely,

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Abha Pant
US Agent for Ranbaxy Laboratories Limited

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AUG 28 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

Nat B. Pitsen 9/4/03 Patent not yet listed in Orange Book

August 29, 2003

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

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Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
AUG 29 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

September 2, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS NEW CORRESP
NC
Revision to Patent Certification

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Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
SEP 0 2 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

September 3, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS NEW CORRESP

Revision to Patent Certification

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Abha Pant
US Agent for Ranbaxy Laboratories Limited

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SEP 0 3 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 FAX: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

September 4, 2003

NEW CORRESP
NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

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Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
SEP 0 4 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

September 5, 2003

NEW CORRESP

NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

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Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

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SEP 0 5 2003
OGD, CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

September 8, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

NEW CORRESP
NC

UPS

Revision to Patent Certification

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Scott D. Tomsky (for)

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
SEP 0 8 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NEW CORRESP

NC

September 9, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

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Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
SEP 09 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

September 10, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

NEW CORRESP
NC

RE: ANDA 76-477
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Sincerely,

Scott D. Tomsky (for)

RECEIVED
SEP 10 2003
OGD/CDER/FDA

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NEW CORRESP
NC

September 11, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

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RECEIVED
SEP 11 2003

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

September 12, 2003

NEW CORRESP

NC

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002.

At this time we are submitting a patent certification amendment. We recently became aware of a new patent (U.S. 6,605,729) for the reference listed drug Lipitor®. Please find attached the patent certification for this ANDA, as amended.

Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Office of Generic Drugs.

If you have any questions regarding this amendment, please contact me at (609) 720-5609 or, Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky (for)

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

SEP 12 2003

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NEW CORRESP
NC

September 15, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002.

At this time we are submitting a patent certification amendment. We recently became aware of a new patent (U.S. 6,605,729) for the reference listed drug Lipitor®. Please find attached the patent certification for this ANDA, as amended.

Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Office of Generic Drugs.

If you have any questions regarding this amendment, please contact me at (609) 720-5609 or, Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
SEP 15 2003

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NEW CORRESP
NC

September 16, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002.

At this time we are submitting a patent certification amendment. We recently became aware of a new patent (U.S. 6,605,729) for the reference listed drug Lipitor®. Please find attached the patent certification for this ANDA, as amended.

Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Office of Generic Drugs.

If you have any questions regarding this amendment, please contact me at (609) 720-5609 or, Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

SEP 1 6 2003

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY
PHARMACEUTICALS INC.

NEW CORRESP
NC

September 17, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Revision to Patent Certification

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002.

At this time we are submitting a patent certification amendment. We recently became aware of a new patent (U.S. 6,605,729) for the reference listed drug Lipitor®. Please find attached the patent certification for this ANDA, as amended.

Ranbaxy Laboratories Limited will comply with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of said patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94(d)(5) of this additional information has been provided to the Office of Generic Drugs.

If you have any questions regarding this amendment, please contact me at (609) 720-5609 or, Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
SEP 17 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

NAI withdraw -729 Aparna Bhan 10/29/03

RANBAXY
PHARMACEUTICALS INC.

October 22, 2003

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS & FAX

Revised Patent Amendment

NEW CORRESP
NC

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to the above pending ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted August 19, 2002. Reference is also made to our Patent Amendment, Revision to Patent Certification submitted September 17, 2003.

At this time Ranbaxy is withdrawing the patent amendment which included certification for US Patent 6,605,729. This patent although issued by the USPTO has not been listed in the Orange Book. Please find attached the revised patent certification attached with this letter.

If you have any questions regarding this amendment, please contact me at (609) 720-5609 or, Abha Pant at (609) 720-5666.

Sincerely,

Scott D. Tomsky (for)
Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
OCT 23 2003
OGD/CDER

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

MINOR AMENDMENT

ANDA 76-477

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

NOV - 5 2003

APPLICANT: Ranbaxy Pharmaceuticals, Inc.
U.S. Agent for Ranbaxy Laoratories Limited
ATTN: Abha Pant

TEL: 609-720-5666

FAX: 609-514-9797

FROM: Wanda Pamphile

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 19, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment(s) dated: August 14, 2003.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (2 pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry comments included. Please include in response.

WDP 11/5/03

NOV - 5 2008

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **76-477** APPLICANT: **Ranbaxy Laboratories Limited**

DRUG PRODUCT: **Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.**

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (DMF) No. 16098 was found deficient. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

2. Regarding the drug substance specifications, we have the following comments:

   a. Please tighten the related substances limit for total impurities based on the current specifications for release provided by the drug substance manufacturer.

   b. Please tighten the limit (lower end) for assay based on the current specifications for release provided by the drug substance manufacturer.

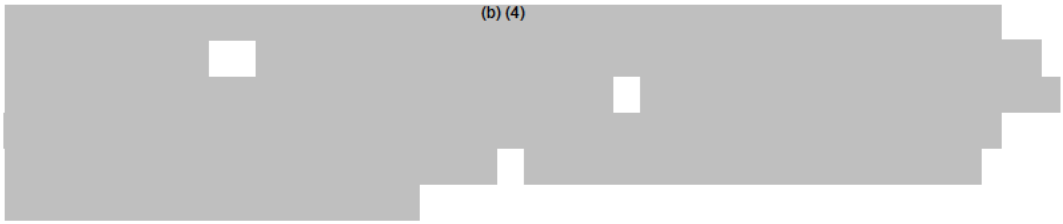
3. We are unable to accept your limit for the related substances for the drug product release and stability at this time. Please tighten the limits for related substances for product release and stability. Alternatively, you may provide the related substances profiles for each strength of the reference listed drug (RLD) at or close to the expiry for justification of the proposed limits. We recommend that you obtain RLD samples from two lots for each strength.

4. Your insert labeling contains the following description: *Atorvastatin Calcium Tablets are a white to off-white crystalline powder that is insoluble in aqueous solution of pH 4 and below.* The word "Tablets" should be deleted. Also, the active ingredient you

used in your ANDA batch was amorphous powder, not crystalline powder. Please clarify.

5. You do not use the trihydrate form of the active ingredient. Yet, the structural formula, molecular formula, and molecular weight in your insert labeling indicate the trihydrate form. Please clarify.

6. (b) (4)



7. Your proposed dissolution specification is not acceptable. Please revise your specification per current DBE requirements for release and stability.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Please provide any additional stability data that may be available.

Sincerely yours,

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

RANBAXY
PHARMACEUTICALS INC.

ORIG AMENDMENT

January 28, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

N/A

LABELING AMENDMENT

Reference: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg
ANDA – 76-477

Dear Sir/Madam,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg submitted to the Agency on August 19, 2002.

Reference is also made to the Minor deficiency comments dated November 5, 2003, specifically question 4:

> *Your insert labeling contains the following description: Atorvastatin Calcium Tablets are a white to off-white crystalline powder that is insoluble in aqueous solution of pH 4 and below. The word "Tablets" should be deleted. Also, the active ingredient you used in your ANDA batch was amorphous powder, not crystalline powder. Please clarify.*

We note and acknowledge the Agency's comments regarding these observations and we have revised the insert labeling to capture these revisions. In addition, the RLD has updated their insert, August 2003 (included in **Attachment 1**). We have updated the insert labeling and it is included in **Attachment 2**. In addition, we have provided a side-by-side comparison against the previously submitted labeling in **Attachment 3**.

Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
JAN 3 0 2004
OGD/OBE

600 COLLEGE ROAD EAST • PRINCETON, NEW JERSEY 08540
PHONE: (609) 720-9200 **FAX**: (609) 720-1155

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

March 2, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

LABELING AMENDMENT

DRUG ADMINISTRATION
N/AF

Reference: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg
ANDA – 76-477

Dear Sir/Madam,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg submitted to the Agency on August 19, 2002. Reference is also made to Minor deficiency comments dated November 5, 2003 and Ranbaxy's response to this deficiency dated January 28, 2004 which contained revised Package Insert labeling.

At this time we wish to revise 3 pages pertaining the package insert labeling submitted on January 28, 2004. We intended to include the solubility information for the amorphous form of Atorvastatin Calcium, which is the form used in our drug product. However, in error we did not include this information in the January 28, 2004 submission. Therefore, we are hereby submitting the revised Package Insert pages, (Revised pages 25, which is the revised final printed PI and pages 30 and 31which are from the side-by-side comparison. These pages now contain the solubility information on the amorphous form of Atorvastatin Calcium.

Please find enclosed in **Attachment 1** our revised insert (page 25). In addition, we have provided the two revised pages (30 and 31) for the side-by-side comparison against the previously submitted package insert labeling in **Attachment 2**.

Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAR - 3 2004
OGD/CDER

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

ORIG AMENDMENT

March 16, 2004

N/AM

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and Fax

MINOR AMENDMENT RESPONSE

Reference: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg
ANDA – 76-477

Dear Sir/Madam,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg submitted to the Agency on August 19, 2002.

Reference is also made to the Minor deficiency comments received November 6, 2003.

The deficiency questions and responses are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this response has been provided to the Food and Drug Administration, International Operation Group as this product is manufactured in India.

Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott D. Tomsky (for)

Scott D. Tomsky
Manager, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
MAR 17 2004
OGD/CDER

MINOR AMENDMENT

ANDA 76-477

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

MAY 27 2004

APPLICANT: Ranbaxy Pharmaceuticals, Inc.
U.S. Agent for: Ranbaxy Laboratories Limited

TEL: 609-720-5666

FAX: 609-514-9797

ATTN: Abha Pant

PROJECT MANAGER: (301) 827-5763

FROM: Wanda Pamphile

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 19, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment(s) dated: March 16, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__1__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:
Chemistry comments included. Please include in response.

WF 5/27/04

MAY 27 2004

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: **76-477** APPLICANT: **Ranbaxy Laboratories Limited**

DRUG PRODUCT: **Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.**

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (DMF) No. 16098 was found deficient. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

2. Please tighten the limits of the following related substance, for drug substance specifications: (b) (4) These limits have been widened from the previous limits. Please submit the revised raw material specifications sheets.

3. We are unable to accept your limit for related substances for the drug product release and stability at this time. Please tighten the limits for related substances for product release and stability. Alternatively, you may provide the related substances profiles for each strength of the reference listed drug (RLD) at or close to the expiry for justification of the proposed limits. We recommend that you obtain RLD samples from two lots for each strength.

4. Your proposed dissolution specification is not acceptable. Please revise your specification per current DBE requirements for release and stability.

B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response:

Please provide any additional stability data that may be available.

Sincerely yours,

Shrujhon Jani for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

ORIG AMENDMENT

N/AM

August 16, 2004

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS and Fax

MINOR AMENDMENT RESPONSE

Reference: **Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg**
ANDA – 76-477

Dear Sir/Madam,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg submitted to the Agency on August 19, 2002.

Reference is also made to the Minor deficiency comments received May 27, 2004.

The deficiency questions and responses are addressed and detailed on the following pages.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this response has been provided to the Food and Drug Administration, International Operation Group as this product is manufactured in India.

Please contact me at 609-720-5362, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

(for)

Scott McGuinness
Regulatory Affairs Associate (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
AUG 17 2004
OGD/CDER

MINOR AMENDMENT

ANDA 76-477

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

FEB 07 2005

APPLICANT: Ranbaxy Pharmaceuticals, Inc.
U.S. Agent for: Ranbaxy Laboratories Ltd.
ATTN: Abha Panp

TEL: 609-720-5666

FAX: 609-514-9797

FROM: Benjamin Danso

PROJECT MANAGER: 301-827-5848

Dear Madam:

This facsimile is in reference to your abbreviated new drug application dated August 19, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment dated August 16, 2004.

The application is deficient and, therefore, Not Approvable under Section 505 of the Act for the reasons provided in the attachments (__2__ pages). This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

The file on this application is now closed. You are required to take an action described under 21 CFR 314.120 which will either amend or withdraw the application. Your amendment should respond to all of the deficiencies listed. Facsimiles or partial replies will not be considered for review, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. The designation as a MINOR AMENDMENT should appear prominently in your cover letter. You have been/will be notified in a separate communication from our Division of Bioequivalence of any deficiencies identified during our review of your bioequivalence data. If you have substantial disagreement with our reasons for not approving this application, you may request an opportunity for a hearing.

SPECIAL INSTRUCTIONS:

2/4/05

FEB 07 2005

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-477 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Drug Master File (DMF) No. 16098 was found deficient. The DMF holder has been notified. Please do not respond to this letter until you have been informed by the DMF holder that all deficiencies have been addressed.

2. Regarding the related substances specifications for the drug substance, we have the following comments:

   a. Please tighten the limits for (b) (4) and total impurities.

   b. Please qualify all known impurities according to ICH Q3A (R). You may use the impurities profiles of the reference listed drug (RLD) to help you qualify the impurities present in your drug substance. Please be advised that mere comparison of HPLC retention times of peaks does not provide proof of the identities of the impurities.

   c. Please clarify "any other known impurity". Alternatively, you may delete this specification.

3. Regarding the proposed limits for related substances for the drug product release and stability, we have the following comments:

   a. Please qualify all known impurities according to ICH Q3B (R). You may use the impurities profiles of the reference listed drugs (RLD) to help you qualify the impurities present in your drug product. Please be advised that mere comparison of HPLC retention times of peaks does not provide proof of the identities of the impurities.

   b. In spite of your 24 month CRT stability studies data, we are unable to accept the total related substances limits for the drug product release and stability. Please tighten the total impurities specifications based on the results of your analysis of the RLD at or near expiry.

c. Please clarify "any other known impurity". Alternatively, you may delete this specification.

4. Your proposed dissolution specification is not acceptable. Please be advised that in the deficiency letter issued by the Division of Bioequivalence on November 18, 2003, you were informed of the following:

"Your request to increase the time at which NLT (b)(4) % (Q) of the labeled amount of atorvastatin calcium is dissolved from 15 minutes to (b)(4) minutes is denied.

Please continue to use the following dissolution testing in your stability and quality control programs:

The dissolution testing should be conducted in 900 ml of 0.05M phosphate buffer, pH 6.8 using USP apparatus 2 (paddle) at 75 rpm.

We recommend the following dissolution specification:

NLT (b)(4) % (Q) of the labeled amount of atorvastatin calcium is dissolved in 15 minutes.

Please discuss with the Division of Bioequivalence on your proposed specification.

Sincerely yours,

for

Rashmikant M. Patel, Ph.D.
Director
Division of Chemistry I
Office of Generic Drugs
Center for Drug Evaluation and Research

CONNOLLY BOVE LODGE & HUTZ LLP
ATTORNEYS AT LAW

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P.O. Box 2207
Wilmington DE 19899
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FAX (302) 658 5614

1990 M Street, NW, Suite 800
Washington DC 20036
TEL (202) 331 7111
FAX (202) 293 6229

WEB www.cblh.com

N/xP.

Jeffrey B. Bove
Partner
TEL (302) 888-6242
FAX (302) 656-9072
EMAIL jbove@cblh.com
REPLY TO Wilmington Office

January 13, 2006

BY CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Office of Generic Drugs
Center of Drug Evaluation and Research
Food and Drug Administration
HFD-600
5600 Fishers Lane
Rockville, MD 20857

Re: ANDA 76-477 – Ranbaxy Laboratories Limited
Notice of Entry of Judgment for Patent Infringement

Dear Sir or Madam:

We represent Pfizer Inc, Pfizer Ireland Pharmaceuticals, Warner-Lambert Company, Warner-Lambert Company, LLC and Warner-Lambert Export, Ltd. (collectively "Pfizer"). Pfizer brought suit against Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Inc. (collectively "Ranbaxy") for infringement of US Patent Nos. 4,681,893 and 5,273,995 by the submission of the above-referenced ANDA. On January 3, 2006, Final Judgment of Infringement of both patents was entered against Ranbaxy by the United States District Court for the District of Delaware in case number 03-209-JJF (consolidated). A copy of the Final Judgment Order is attached for your reference.

Pursuant to 21 CFR § 314.107(b)(3)(iii), Pfizer provides notification as follows:

(i) The ANDA number is 76-477;
(ii) The name of the abbreviated new drug applicant is Ranbaxy Laboratories Limited;

(iii) Judgment was entered in favor of Pfizer and against Ranbaxy on Pfizer's claims that Ranbaxy has infringed claims 1-4, and 8-9 of United States Patent No. 4,681,893 (the "'893 Patent") and claim 6 of United States Patent No. 5,273,995 (the "'995 Patent").

(iv) Judgment was further entered in favor of Pfizer and against Ranbaxy on all counterclaims alleging noninfringement, invalidity, or unenforceability of the '893 Patent or its patent term extension and on all counterclaims alleging noninfringement, invalidity, or unenforceability of the '995 Patent.

(v) The Court further ordered pursuant to 35 U.S.C. § 271 (e) (4) (A), that the effective date of any approval of Ranbaxy's Abbreviated New Drug Application No. 76-477 shall be a date which is not earlier than the date of expiration of the '995 Patent (December 28, 2010, with attached six months of pediatric exclusivity ending on June 28, 2011, to which FDA has previously ruled that Pfizer is entitled).

(vi) Alternatively, the Court ordered pursuant to 35 U.S.C. § 271 (e) (4) (A), that the effective date of any approval of Ranbaxy's Abbreviated New Drug Application No. 76-477 shall be a date which is not earlier than the date of expiration of the '893 Patent and its patent term extension (September 24, 2009, with attached six months of pediatric exclusivity ending on March 24, 2010, to which FDA has previously ruled Pfizer is entitled).

(vii) Pursuant to 35 U.S.C. § 271 (e) (4) (B), defendants Ranbaxy Laboratories Limited and Ranbaxy Pharmaceuticals Incorporated, each of their officers, agents, servants, employees and attorneys, and those persons in active concert or participation with them or either of them were permanently enjoined from engaging in the manufacture, use, offer to sell, or sale within the United States, or importation into the United States, of any product comprising atorvastatin calcium covered by, or the use of which is covered by claims 1-4 and 8-9 of the '893 Patent or by claim 6 of the '995 Patent.

Respectfully submitted,

Jeffrey B. Bove
Connolly Bove Lodge & Hutz LLP

JBB/gm
Enclosures

cc: Steven K. Galson, M.D., M.P.H., Director (w/ enclosures)
Center for Drug Evaluation and Research

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

February 13, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

LABELING AMENDMENT

Reference: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg
ANDA – 76-477
Labeling Amendment – Update to RLD labeling approved in September 2005

Dear Sir/Madam,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40mg & 80 mg.

At this time we are hereby submitting revised package insert labeling for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40mg & 80 mg to be in line with new RLD labeling for Lipitor® approved in September 2005.

In accordance with the electronic labeling rule published December 11, 2003, (68FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004, the electronic labeling for this submission has been included on a CD in the archive copy of this submission. Please find enclosed the CD-ROM disk which contains all the relevant files.

Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott Tomsky
Associate Director, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

ORIGINAL

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540, PHONE: (609) 720-9200 FAX: (609) 720-1155

4/6/06
Abha Pant contacted to find out why a PIV cert has been made to the '893 + '995 patents when court decision was made against Ranbaxy

April 3, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

PATENT AMENDMENT

Reference: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg
ANDA – 76-477
Patent Amendment – Revised Patent Certification

Dear Sir/Madam,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40mg & 80 mg.

We hereby submit a revised Patent Certification and Exclusivity Statement, updated according to the current Electronic Orange Book listings. The revised Patent Certification and Exclusivity Statement along with the relevant pages of the Electronic Orange Book are enclosed.

If you have any questions, regarding this information, please call the undersigned at 609-720-8061, or Abha Pant at 609-720-5666.

Sincerely,

Usha Sankaran
Sr. Regulatory Affairs Associate (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
APR 0 5 2006
OGD / CDER

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540, PHONE: (609) 720-9200 FAX: (609) 720-3155

May 1, 2006

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

LABELING AMENDMENT

Reference: **Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg**
ANDA – 76-477
Labeling Amendment – Response to labeling deficiency dated March 27, 2006

Dear Sir/Madam,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40mg & 80 mg. Reference is also made to a labeling deficiency dated and received on March 27, 2006.

At this time we are hereby submitting a response to the above referenced labeling deficiency.

In accordance with the electronic labeling rule published December 11, 2003, (68FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004, the electronic labeling for this submission has been included on a CD in the archive copy of this submission. Please find enclosed the CD-ROM disk which contains all the relevant files.

Please contact me at 609-720-5609, or Abha Pant at 609-720-5666 if you have any questions regarding this amendment. Thank you.

Sincerely,

Scott Tomsky
Associate Director, Regulatory Affairs (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

ORIGINAL

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540, PHONE: (609) 720-9200 FAX: (609) 720-1155

September 13, 2006

ORIG AMENDMENT
N / AB

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

BIOEQUIVALENCE AMENDMENT

Reference: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg
ANDA – 76-477

Dear Sir/Madam,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40mg & 80 mg. Reference is also made to our minor amendment dated March 9, 2006 submitted in response to the CMC deficiency dated February 7, 2005.

Please note within the CMC deficiency dated February 7, 2005, reference was made to a bioequivalence deficiency dated November 18, 2003, however we have no record of receiving this bio deficiency. Therefore, we followed up with Agency and the same was faxed to us on September 11, 2006.

We are hereby submitting a complete response to the above referenced bioequivalence deficiency.

If you have any questions, regarding this information, please call the undersigned at 609-720-8061, or Abha Pant at 609-720-5666. Thank you.

Sincerely,

Usha Sankaran
Sr. Regulatory Affairs Associate (*for*)
Abha Pant
US Agent for Ranbaxy Laboratories Limited

RECEIVED
SEP 14 2006
OGD / CDER

BIOEQUIVALENCY AMENDMENT

ANDA 76-477

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

OCT 0 3 2006

APPLICANT: Ranbaxy Laboratories TEL: 609-720-5666

ATTN: Abha Pant FAX: 609-514-9797

FROM: Aaron Sigler PROJECT MANAGER: 301-827-5847

Dear Madam:

This facsimile is in reference to the bioequivalency data submitted on September 13, 2006, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached __3__ pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

BIOEQUIVALENCE DEFICIENCIES

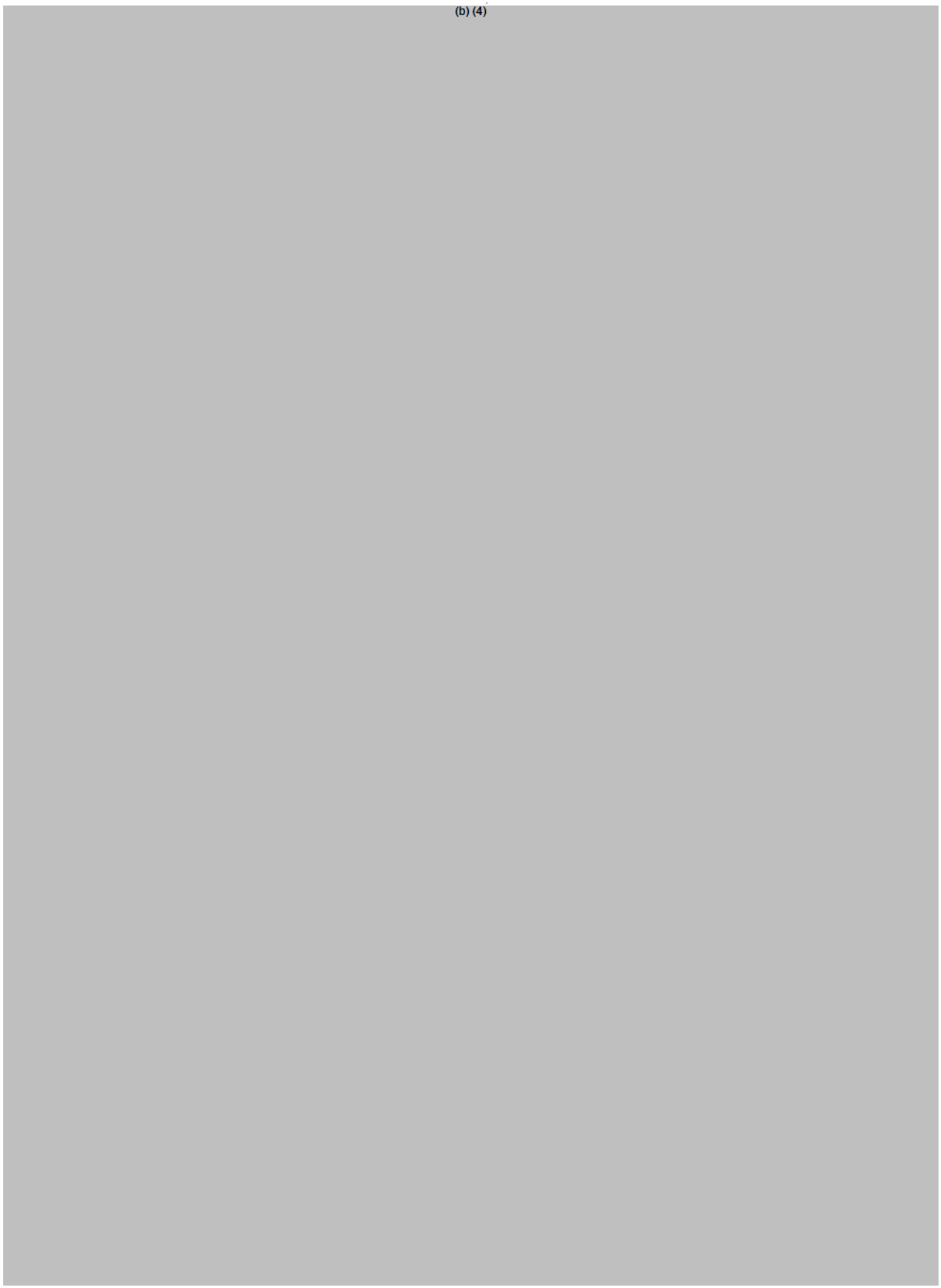
ANDA: 76-477 APPLICANT: Ranbaxy Laboratories

DRUG PRODUCT: Atorvastatin Calcium Tablets, 80 mg, 40 mg, 20 mg & 10 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

Your proposal for using the (b) (4) vessels in the dissolution testing of the test product is not acceptable for the following reasons:

(b) (4)


(b) (4)

(b) (4)

Your proposal of using (b) (4) ™ vessels in dissolution testing of the test product is denied at this time due to insufficient valid data to support the proposal.

Sincerely yours,

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

RANBAXY

RANBAXY USA INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

January 22, 2007

ORIG AMENDMENT

N/AA

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Gratuitous Amendment
Orders of District Court

Reference: **ANDA 76-477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to our pending Abbreviated New Drug Application 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. In this letter Ranbaxy is providing three separate orders from the District Court for the District of Delaware ("the District Court"). Thus, Ranbaxy is now permitted to launch upon expiry of US 4,681,893 and its associated pediatric exclusivity, i.e., March 24, 2010. The background for this is provided below.

The holder of the approved drug application for the listed drug, Pfizer Inc., was notified of Ranbaxy's ANDA 76-447 filing for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg with paragraph IV certifications to US 4,681,893 and US 5,273,995. Pfizer Inc. sued Ranbaxy for infringement of these two patents within 45 days of receiving the notification letters. The District Court ordered on January 3, 2006 that Ranbaxy had infringed both patents and ordered that Ranbaxy be enjoined from marketing its product until expiration of both patents. A copy of that first order is enclosed in **Attachment 1**.

Ranbaxy appealed the District Court's decision to the Court of Appeals from the Federal Circuit ("CAFC") which reversed the District Court's decision on US 5,273,995 and held invalid the sole claim of that patent asserted against Ranbaxy. The CAFC remanded the case to the District Court with an order to modify the permanent injunction with respect to US 5,273,995. The District Court then entered a modified order on November 7, 2006 removing one paragraph regarding US 5,273,995. A copy of this second order from the District Court is enclosed in **Attachment 2**. After being notified by Ranbaxy that another paragraph relating to US 5,273,995 inadvertently still remained from the first order, the District Court further modified its order of January 4, 2006, by entering an order dated November 30, 2006. A copy of this third order of the District Court is enclosed in **Attachment 3.**

Based on the court decisions and attached court orders, we request approval on March 24, 2010 upon expiry of the US 4,681,893 patent and its associated pediatric exclusivity.

Please note, effective January 1, 2007, Scott Tomsky has been appointed U.S. Agent. A revised U.S. Agent letter is provided following the 356h.

If you have any questions or comments regarding this submission, please call me at 609-720-8017 or Scott Tomsky at 609-720-5609.

Sincerely,

Brett Johnson (for)

Brett Johnson
Sr. Regulatory Affairs Associate (for)
Scott Tomsky
US Agent for Ranbaxy Laboratories Limited

RANBAXY

ORIGINAL

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: 609-720-9200 FAX: 609-720-1155

August 10, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS/FAX

BIOEQUIVALENCE
AMENDMENT

ORIG AMENDMENT

N/AB

RE: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
Response to Bioequivalence deficiency dated October 03, 2006

Dear Sir or Madam:

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the FDA Bioequivalence deficiency dated October 03, 2006.

We are hereby submitting, in duplicate, a complete response to the deficiencies noted in the above referenced FDA correspondence.

If you have any questions regarding this submission, please call Usha Sankaran at 609-720-8061 or Scott Tomsky at 609-720-5609.

Sincerely,

Rich Leone

Rich Leone, RAC
Manager, Regulatory Affairs (*for*)
Scott Tomsky
Director, Regulatory Affairs
U.S. Agent for Ranbaxy Laboratories Limited

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AUG 13 2007
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AUG 13 2007
OGD

RANBAXY

ORIGINAL

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

September 14, 2007

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

ADDITIONAL INFORMATION TO CMC

ORIG AMENDMENT
N / ~~AA~~

RE: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40mg & 80 mg
ANDA 76-477

Dear Sir/Madam:

Reference is made to our pending ANDA 76-477. Reference is also made to our submission dated June 18, 2007, in which we submitted revised stability data which had been updated where necessary. This was performed as part of our commitment to the Agency for the Warning Letter issued for our Paonta, India facility in June 2006.

Following additional discussions with CDER's Office of Compliance, we are hereby submitting additional details and information regarding the changes identified during the review the of the stability data. This submission contains the following:

1. The protocols for the retrospective stability review in **Attachment 1**.
2. A summary of the observations in which corrections have been made in the stability data in **Attachment 2**.
3. The updated Stability Reports in **Attachment 3**
4. The previously submitted Stability Reports in **Attachment 4**.

Please note that none of the changes affect previous conclusions about the product's stability.

Field Copy: We certify that a true copy of the technical section described in 21 CFR 314.94 (d)(5) of this original submission has been provided to the Food and Drug Administration, International Operations Group.

As part of our continuous improvement initiative, we will continue to make appropriate improvements. If you have any questions regarding this submission please call me at 609-720-5609.

Sincerely,

Rich Lenz (for)

Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RECEIVED
SEP 17 2007
OGD

BIOEQUIVALENCY AMENDMENT

ANDA 76-477

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (301-594-0320)

APPLICANT: Ranbaxy Laboratories TEL: 609-720-5609

ATTN: Scott Tomsky FAX: 609-514-9797

FROM: Keri Suh PROJECT MANAGER: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalency data submitted on August 10, 2007, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **one** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. Your cover letter should clearly indicate that the response is a "Bioequivalency Amendment" and clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this communication with your response. Please submit a copy of your amendment in both an archival (blue) and a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

In an effort to improve document flow and availability to review staff, please submit your response in electronic PDF format, with a signed cover letter and 356h form.

BIOEQUIVALENCE DEFICIENCIES

ANDA: 76-477 APPLICANT: Ranbaxy Laboratories Ltd.

DRUG PRODUCT: Atorvastatin Calcium Tablet,
80 mg, 40 mg, 20 mg and 10 mg

The Division of Bioequivalence has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiencies have been identified:

(b) (4)

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Barbara Davit
10/12/2007 04:19:54 PM
Signing for Dale P Conner

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

January 25, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

BIOEQUIVALENCY AMENDMENT

Reference: Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg
ANDA – 76-477

Dear Mr. Conner,

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets 10 mg, 20 mg, 40mg & 80 mg submitted to the Agency on August 19, 2002.

Reference is also made to the Bioequivalency deficiency comments received on October 12, 2007.

For your reference, please find enclosed a detailed summary and all relevant information supporting this bioequivalency amendment.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is placed on a CD-ROM and is approximately 1 MB in size. The contents of the CD have been scanned for viruses using McAfee VirusScan Enterprise 8.0.0 updated on January 23, 2008.

Please contact me at 609-720-5616, or Mr. Scott Tomsky at 609-720-5609 if you have any questions regarding this amendment. Thank you.

Sincerely,

Sanjeev Mohanty
Associate Director, Regulatory Affairs *(for)*
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

February 14, 2008

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS

AMENDMENT TO THE PENDING APPLICATION (CHEMISTRY & LABELING)

Reference: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA 76-477

Dear Sir/Madam,

Reference is made to Ranbaxy's ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the CMC Amendment dated March 9, 2006 and the Bioequivalence Amendment dated August 10, 2007.

Through this amendment we are proposing the following changes in the drug substance and the drug product:

1. Change in the API Manufacturing Process - Minor modifications to the API manufacturing process wherein (b) (4) .

2. Minor changes have been made in the quantitative composition of the drug product ((b) (4) '). Please note that the changes proposed in the formulation fall within Level 1 of the Guidance for Industry: IR Solid Oral Dosage Forms, Scale-up and Post Approval Changes; Chemistry, Manufacturing, and Controls, *In vitro* Dissolution Testing and *In vivo* Bioequivalence Documentation.

3. Minor Changes have been done in the drug product manufacturing process, equipments and the in-process parameters. These are fully explained in this amendment.

4. Drug product specifications for (b) (4) test have been revised to reflect the increased quantity of (b) (4) in the formulation.

5. The existing method for (b) (4) testing (by GC) has been replaced with the HPLC method. In addition, the testing method for determination of Related Substances (by HPLC) in the drug product has been revised and minor changes made to the sample preparation procedure in the Assay method for the drug product.

6. Minor change has been made in the description of drug product – debossing instead of imprinting (with the same code).

7. Additional bottle pack size and configurations and new pack - unit dose blister pack are being proposed for all the strengths of the drug product. The packaging configurations proposed also include new packaging components.

8. The labeling for Atorvastatin Calcium Tablets has been revised to incorporate the additional packs (90's count Bottle and Unit Dose Blister) for all the strengths. The updated labeling components including the container labels are provided in the CD enclosed.

Details of all the above changes along with the supporting data are provided on the following pages.

A comparative summary of the proposed changes Vs the original ANDA is also provided in **Attachment 1**.

Based on the information provided in this amendment, it is our opinion that the proposed changes have no potential for an adverse effect on identity, strength, quality, purity or potency of the drug product and in fact the testing results of the drug product batches (post change) indicate that the quality has been improved and the oxidative impurity levels have decreased.

If you have any questions regarding this submission, please contact the undersigned at 609-720-8061 or Mr. Scott Tomsky at 609-720-5609. Thank you.

Sincerely,

Usha Sankaran
Manager, Regulatory Affairs (*for*)
Scott Tomsky
U.S Agent for Ranbaxy laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

March 16, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS & FAX

PATENT AMENDMENT
(Revised Patent Certification)

Reference: **Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg**
ANDA 76-477

Dear Sir/Madam,

Reference is made to Ranbaxy's ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

At this time Ranbaxy is hereby submitting a revised patent certification to include the re-listed patent U.S. Patent No. RE 40, 667) for the reference listed drug, Pfizer's Lipitor® Tablets (NDA 20-702).

Please contact the undersigned at (609) 720-8066 or Ms. Usha Sankaran at (609) 720-8061 if you have any questions regarding this amendment. Thank you.

Sincerely,

Rich Leone, RAC
Manager, Regulatory Affairs (*for*)
Usha Sankaran
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

March 17, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS & FAX

PATENT AMENDMENT
(Revised Patent Certification)

Reference: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA 76-477

Dear Sir/Madam,

Reference is made to Ranbaxy's ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

At this time Ranbaxy is hereby submitting a revised patent certification to include the re-listed patent (U.S. Patent No. RE 40, 667) for the reference listed drug, Pfizer's Lipitor® Tablets (NDA 20-702).

Ranbaxy is providing this submission in an electronic PDF format. The submission is placed on a CD-ROM and is approximately 1 MB in size. The contents of the CD have been scanned for viruses with McAfee VirusScan Enterprise 8.0.0., updated on March 17, 2009.

Please contact the undersigned at (609) 720-8066 or Ms. Usha Sankaran at (609) 720-8061 if you have any questions regarding this amendment. Thank you.

Sincerely,

Rich Leone, RAC
Manager, Regulatory Affairs (*for*)
Usha Sankaran
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

March 18, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855

UPS & FAX

PATENT AMENDMENT
(Revised Patent Certification)

Reference: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA 76-477

Dear Sir/Madam,

Reference is made to Ranbaxy's ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

At this time Ranbaxy is hereby submitting a revised patent certification to include the re-listed patent (U.S. Patent No. RE 40,667) for the reference listed drug, Pfizer's Lipitor® Tablets (NDA 20-702). A copy of the relevant pages from the FDA's Electronic Orange Book is also included in this submission.

Ranbaxy is providing this submission in an electronic PDF format. The submission is placed on a CD-ROM and is approximately 1 MB in size. The contents of the CD have been scanned for viruses with McAfee VirusScan Enterprise 8.0.0., updated on March 18, 2009.

Please contact the undersigned at (609) 720-8066 or Ms. Usha Sankaran at (609) 720-8061 if you have any questions regarding this amendment. Thank you.

Sincerely,

Rich Leone, RAC
Manager, Regulatory Affairs (*for*)
Usha Sankaran
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

May 14, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS / FAX

PATENT AMENDMENT

Reference: ANDA 76-477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment – Notice of No Civil Action

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 76-477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the March 18, 2009 Patent Amendment submitted to the Agency.

In the Patent Amendment submitted on March 18, 2009, the patent certification submitted to the Agency for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg had claimed a paragraph IV certification to the reissued patent, U.S. Patent No. RE 40, 667.

Please note, the notices of certification of non-infringement for the above referenced product were sent to each owner of the patent and the holder of the approved application on March 18, 2009. The certified receipt was stamped by the United States Post Office on March 25, 2009. A copy of the notice, along with the certified mail receipts are provided in **Attachment 1** and **Attachment 2**, respectively.

As of today, (more than 45 days since notice was received), neither the patent holder nor the holder of the approved application has filed suit against Ranbaxy Laboratories Limited regarding the paragraph IV certification to the RLD's patent, Patent No. RE 40, 667.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is placed on a CD-ROM and is approximately 1 MB in size. The contents of the CD have been scanned for viruses using McAfee VirusScan Enterprise 8.0.0 updated on May 14, 2009.

If there are any questions regarding this submission, please contact the undersigned at 609-720-5354 or Usha Sankaran at 609-720-8061. Thank you.

Sincerely,

Lijie Wang, Ph.D.
Sr. Regulatory Affairs Associate *(for)*
Usha Sankaran
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

December 04, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

UPS

Gratuitous Amendment

RE: **Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg**
ANDA 76-477

Dear Sir/Madam:

Reference is made to our pending ANDA 76-477 for Atorvastatin Calcium Tablets,10 mg, 20 mg, 40 mg and 80 mg submitted to the Agency on August 19, 2002.

Ranbaxy Laboratories Ltd., Paonta Sahib, India was proposed as a manufacturing site for Atorvastatin Calcium Tablets,10 mg, 20 mg, 40 mg and 80 mg is in the original ANDA.

Through this amendment, Ranbaxy is proposing the following changes with respect to the original application:

Drug Substance

i) Change in the form of active pharmaceutical ingredient Atorvastatin Calcium from Amorphous to Crystalline.
ii) Change in the manufacturer of Atorvastatin Calcium active pharmaceutical ingredient from M/s Ranbaxy Laboratories Ltd. to M/s (b) (4).
iii) Revision in drug substance specifications and testing methods.

Drug Product

i) Addition of a new manufacturing site Ohm Laboratories Inc., Terminal Road, New Brunswick, New Jersey for the manufacture of the Drug Product.
ii) Addition of new analytical testing sites – Ohm Laboratories Inc. at 14 Terminal Road, NJ 08901 and 1385 Livingston Avenue, North Brunswick, NJ 08902.
iii) Qualitative and Quantitative changes in the Drug Product Formulation.
iv) Change in the manufacturing process of the Drug Product
v) Revision in drug product specifications and testing methods.
vi) Change in container closure system

Please find enclosed a detailed summary and all relevant information supporting the proposed changes.

Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 112 MB in size and is being submitted to the Agency through FDA's electronic

gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.0.0 updated on December 04, 2009.

If there are any questions regarding this supplement, please contact the undersigned at 609-720-5304, or Ms. Usha Sankaran at 609-720-8061.

Sincerely,

Sarika Jain

Sarika Jain
Regulatory Affairs Associate (for)
Usha Sankaran
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

December 09, 2009

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration,
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773.

UPS
Bio-Amendment to Gratuitous CMC
Amendment dated December 04, 2009

RE: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
ANDA 76-477

Dear Sir/Madam:

Reference is made to Ranbaxy's Gratuitous CMC Amendment dated December 04, 2009. The CMC amendment was submitted to the Agency to propose many changes including change in the polymorphic form of the drug substance, drug product formulation, the manufacturing process and manufacturing site of the drug product.

To support the changes proposed in the December 04, 2009 CMC amendment, Ranbaxy has performed bioequivalence studies on its Atorvastatin Calcium Tablets, 80 mg (Batch #RI560901) against the reference listed drug, Lipitor® Tablets, 80 mg of Pfizer.

This submission includes the following supporting information:

1. Bio-waiver Request Letter
2. Certificates of analysis of the Ranbaxy Laboratories Limited's Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg and Pfizer's Lipitor® Tablets, 10 mg, 20 mg, 40 mg and 80 mg as **Attachment-1**
3. Comparative in-vitro dissolution profiles of Ranbaxy Laboratories Limited's Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg and Pfizer's Lipitor® Tablets, 10 mg, 20 mg, 40 mg and 80 mg (provided in **Annexure 1 to the Bio-waiver request letter**)
4. Pivotal bioequivalence study under fasting condition (Study# R09-1032):
   4a. Clinical summary
   4b. Bio-summary tables
   4c. Complete study data
5. Pivotal bioequivalence study under fed condition (Study# R09-1033):
   5a. Clinical summary
   5b. Bio-summary tables
   5c. Complete study data

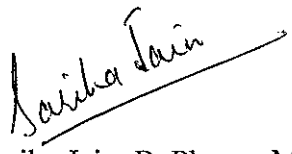
6. In accordance with the '*Requirements for Submission of Bioequivalence Data; Final Rule*, effective July 15, 2009', the pilot bioequivalence studies. As per the '*Guidance for Industry: Submission of Summary Bioequivalence Data for ANDAs'*, bioequivalence summary tables are being provided for the pilot bioequivalence studies.

To facilitate the navigation through the submission, table of contents has also been provided.

Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 350 MB in size and is being submitted to the Agency through FDA's electronic gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.0.0 updated on December 09, 2009.

If there are any questions regarding this supplement, please contact the undersigned at 609-720-5304 or Ms. Usha Sankaran at 609-720-8061.

Sincerely,



Sarika Jain, B. Pharm, M.Sc.
Regulatory Affairs Associate (for)
Usha Sankaran
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 12, 2010

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

ESG

Gratuitous Amendment
(CMC)

Reference: **ANDA 076477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Additional Source of API

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted to the Agency on August 19, 2002. Reference is also made to the December 4, 2009 Gratuitous Amendment.

Through this amendment, Ranbaxy is proposing the following:

1. Additional source of API - Ranbaxy Laboratories Limited's DMF 24139 for Atorvastatin Calcium, USP (crystalline).
2. Minor changes in the manufacturing process of the drug product manufactured using the proposed Ranbaxy API.

Please find enclosed the details of the changes and all relevant information supporting the proposed changes.

This amendment is submitting in an electronic PDF format. The submission is approximately 170 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses with McAfee Virus Scan Enterprise 8.0.0., updated on November 12, 2010. Please note the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

If you have any questions regarding this submission, please contact the undersigned at 609-720-5354 or Scott D. Tomsky at 609-720-5609. Thank you.

Sincerely,

Lijie Wang, Ph.D.
Sr. Regulatory Affairs Associate *(for)*
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 16, 2010

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855

ESG

LABELING AMENDMENT

Reference: **ANDA 076477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the November 12, 2010 Gratuitous CMC Amendment.

It has recently come to our attention that the November 12, 2010 submission (which was submitted in an electronic PDF format) included some labeling files under the folder titled "Labeling". We would like to inform the Agency that these files were inadvertently included in the submission. We request the Agency to disregard the labeling files in the November 12, 2010 submission. As on date, the labeling submitted in the December 4, 2009 Amendment is the current labeling for this application. We sincerely apologize for the oversight and any inconvenience this may have caused.

This amendment is being submitted in an electronic PDF format. The submission is less than 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses with McAfee Virus Scan Enterprise 8.0.0., updated on November 16, 2010. Please note the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

If you have any questions regarding this submission, please contact the undersigned at 609-720-8061 (email: usha.sankaran@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

Usha Sankaran
Associate Director, Regulatory Affairs *(for)*
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

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William B. Schultz
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February 14, 2011

VIA E-MAIL AND FEDERAL EXPRESS

Keith Webber
Acting Director
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place, HFD-600
Rockville, Maryland 20855

Orig-1, SD #60

Re: Response of Ranbaxy Laboratories Limited to Mylan, Inc.'s January 5, 2011, Letter Regarding 180-Day Exclusivity for Atorvastatin Calcium Tablets

Dear Mr. Webber:

We write on behalf of our client, Ranbaxy Laboratories Limited ("Ranbaxy"), in response to the January 5, 2011, letter from Mylan Inc. ("Mylan") regarding Ranbaxy's eligibility for 180-day exclusivity for Atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg (collectively, "Atorvastatin"). Mylan requests that the Food and Drug Administration ("FDA") deny Ranbaxy approval of its ANDA No. 76-477 and, as a result, determine that Ranbaxy is ineligible for exclusivity for Atorvastatin based solely on the Application Integrity Policy ("AIP") letter issued by the Agency to Ranbaxy on February 25, 2009.[1] For the reasons discussed below, including the fact that the Federal Food, Drug, and Cosmetic Act ("FFDCA") does not authorize the action requested by Mylan, Mylan's request to FDA should be denied.[2]

The ANDA application process, including the award and forfeiture of 180-day exclusivity, is governed exclusively by the FFDCA. Based solely on FDA's application of the

[1] Letter from Kurt R. Karst, counsel for Mylan, to Ralph S. Tyler and Keith O. Webber, FDA (Jan. 5, 2011) ("Mylan Petition").

[2] The Mylan Petition assumes that Ranbaxy's Atorvastatin product is manufactured at Paonta Sahib. Solely for purposes of this response, Ranbaxy accepts this assumption.

AIP to Ranbaxy's Paonta Sahib site, and its assumption that data from that site support Ranbaxy's Atorvastatin application, Mylan argues that FDA should immediately deny Ranbaxy approval for its Atorvastatin application under the FFDCA and FDA's regulations and thus strip Ranbaxy of its eligibility for 180 day exclusivity. Neither the law nor the facts support Mylan's position. FDA has not reached a determination on Ranbaxy's Atorvastatin application, and even though the Agency has invoked the AIP, the FFDCA and the AIP require an individualized review of the Atorvastatin application to determine whether it is entitled to approval under the very statutory and regulatory provisions cited by Mylan. Mylan has no right to force the FDA to make a decision before it has completed its review of the Atorvastatin application. Nor can Mylan argue that it will be prejudiced if such a decision is not made immediately, since, to Ranbaxy's knowledge, no generic product is either ready for approval or could be approved now even if Ranbaxy did not have exclusivity.

Mylan's argument that FDA should strip Ranbaxy of exclusivity based on the AIP fails. FDA's authority for approving ANDAs and awarding exclusivity is cabined by the FFDCA. The AIP itself is consistent with the FFDCA in this respect; it does not suggest that its invocation would be a basis for disapproving an ANDA and stripping a first filer of exclusivity. Nor could it; the AIP is nothing more than an FDA policy. It was neither enacted by Congress nor promulgated through notice and comment rulemaking, and it cannot function to expand or abrogate the FFDCA. In short, FDA simply has no lawful basis to take the action Mylan suggests.

I. FACTUAL BACKGROUND

Ranbaxy filed its abbreviated new drug application ("ANDA") for Atorvastatin in 2002. Based on the paragraph IV certifications in that application, including supplements, Ranbaxy believes it is eligible for 180-day marketing exclusivity.

On February 25, 2009, FDA issued an AIP letter to Ranbaxy based on certain information and data generated at Ranbaxy's Paonta Sahib site. *See* Letter from Janet Woodcock, FDA, to Malvinder Mohan Singh, Ranbaxy (Feb. 25, 2009) ("AIP Letter")) at 1. The main issues raised in the AIP Letter related to deficiencies in stability testing and data from Paonta Sahib that were used to support applications submitted by Ranbaxy.

The AIP is a policy that FDA developed to ensure the reliability of data called into question by alleged wrongful acts of the applicant. In such cases, FDA will conduct an investigation to identify all instances of wrongful acts, if any, and to determine the extent to which wrongful acts may have affected approved or pending applications. As a result of its investigation, FDA may refuse to approve or withdraw approval for applications. *See* Compliance Policy Guide § 7150.09, published at 56 Fed. Reg. 46191, 46199-200 (September

10, 1991). In short, the invocation of the AIP is the start of an investigative process in which both FDA and the applicant participate, not a final determination or finding as to any specific application.

In applying the AIP to Paonta Sahib, FDA stated it would conduct a validity assessment of the data and information that was generated at the site and relied on in Ranbaxy's applications. *See* AIP Letter at 5.

Ranbaxy has cooperated with FDA in the AIP data assessment process, and FDA's validity assessment is underway. FDA has not completed the AIP process, nor has it refused to approve or withdrawn approval of any application.

II. DISCUSSION

Mylan asserts five arguments in support of its request that FDA strip Ranbaxy of exclusivity for Atorvastatin. All five arguments are premised on the proposition that FDA must deny Ranbaxy's ANDA because of the AIP letter to Ranbaxy. All are based on incorrect factual assumptions and legal analysis. Each argument is discussed below in turn.

A. The AIP Letter Is Not a Basis for Denying Ranbaxy's Atorvastatin Application.

Mylan argues, based solely on the AIP Letter to Ranbaxy, that FDA "should immediately deny" approval of Ranbaxy's Atorvastatin application. Mylan Petition at 4. The AIP, by its own terms, does not authorize FDA to refuse to approve or to process an application and Mylan certainly has no right to use the device of a letter to the agency to force such a decision. As FDA has explained, the AIP "does not authorize FDA to refuse to process or review a particular application. Although deferral of substantive data review under the [AIP] may affect the timing and nature of FDA's final action on the application, it does not preclude review and approval of the application." Final FDA Policy, "Fraud, Untrue Statements of Material Facts, Bribery, and Illegal Gratuities," 56 FR 46,191, 46,193 (Sept. 10, 1991) (the "Final Policy). In addition, in responding to comments FDA stated:

> An agency decision to assess data prior to the normal scientific review of an application [i.e., to invoke the AIP] does not constitute a sanction or final agency action on the application. Deferral of substantive data review under these circumstances will help ensure that FDA's limited resources are not wasted in reviewing invalid data, and that applications are approved based on valid data.

Id.

Under the FFDCA, the FDA must review Ranbaxy's application and approve it if it meets the standards of the Act. Accordingly, Mylan's argument should be rejected.

B. The AIP Does Not Replace a Determination by FDA of Whether Ranbaxy Has Met the Applicable Statutory/Regulatory Standards for ANDA Approval.

As Mylan acknowledges, the requirements for refusing to approve an application are found in the FFDCA and FDA's regulations. *See* Mylan Petition at 4.[3] Mylan argues, however, based on the content of the AIP Letter to Ranbaxy, that Ranbaxy's Atorvastatin application should not be approved under various statutory and regulatory provisions. *See id.* at 4-5 (asserting Ranbaxy's ANDA should be denied under FFDCA §§ 505(j)(4)(A) & (K)). The grounds for not approving Ranbaxy's application cited by Mylan range from untrue statements in the Atorvastatin application to inadequate methods, facilities or controls for insuring the identity, strength, quality and purity of the drug to a lack of information in the ANDA showing bioequivalence to the listed drug. *See id.*

The AIP Letter to Ranbaxy did not make a determination as to the approvability of Ranbaxy's application on any of these bases, and Mylan cites no facts to support its assertions that Ranbaxy has not met or cannot meet the basic standards of the FFDCA. Ranbaxy is entitled to an individualized review of its application. Mylan has provided no information that would support denial of the Atorvastatin application.

Mylan does not allege, because it cannot, that FDA has completed the process that it is required to follow under the FFDCA for every application in order for it to determine whether Ranbaxy's Atorvastatin application may be approved or disapproved. *See* 21 U.S.C. § 355(j)(5)(A) and (E) (if FDA "decides to disapprove an application," then the Agency "shall give the applicant notice of an opportunity for a hearing . . . on the question of whether such application is approvable"). The FFDCA requires findings specific to the ANDA under review to disapprove an application. The AIP cannot and does not modify the statutory standard. The AIP simply creates a process for conducting a review intended in part to determine whether such a finding should be made as to a specific application.

[3] Ranbaxy is prepared to demonstrate to FDA that its Atorvastatin application does not contain any untrue statements of material fact.

C. The AIP Does Not Require Ranbaxy to File A New ANDA and Thus Lose Eligibility for 180 day Exclusivity.

Contrary to Mylan's assertions, Ranbaxy is not required to submit a new ANDA to replace its existing Atorvastatin application. *See* Mylan Petition at 6. There is no support for withdrawing the application, and Ranbaxy does not believe that there is anything about the application suggesting that withdrawal is required.

In further support of its argument that Ranbaxy should be required to file a new application, Mylan cites to 21 C.F.R. § 314.110(c). That regulation has no applicability here. It allows FDA to treat an application as withdrawn where an applicant fails to act after receiving a complete response letter in connection with the disapproval of an application. There has been no such disapproval by FDA of Ranbaxy's Atorvastatin application. Further, far from failing to act after receiving the AIP Letter, Ranbaxy has cooperated with FDA in the AIP data assessment process. There is no authority in the FFDCA or FDA's regulations, for FDA to "consider [Ranbaxy's] application withdrawn and [its] 180-day exclusivity extinguished." Mylan Petition at 6.

Mylan's assertions that FDA should refuse to approve Ranbaxy's Atorvastatin ANDA, and that Ranbaxy is required to submit a new application is belied by the AIP – which provides for a case-by-case assessment of the validity of the data contained in each ANDA, and the reasons for which the integrity of the data was called into question. *See id.* Further, under the AIP, the Agency has stated that in assessing affected ANDAs on a case-by-case basis, FDA has the authority to approve, and accept amendments or supplements to, ANDAs subject to the AIP. Indeed, the factors relevant to the review of an application and an applicant's eligibility for 180-day exclusivity may evolve during the Agency's evaluation of that particular application.

D. The AIP Does Not Authorize FDA to Strip Ranbaxy of 180-Day Exclusivity for Atorvastatin

In its petition, Mylan contends that the invocation of the AIP is a basis to strip Ranbaxy of its Atorvastatin exclusivity because to do otherwise "would run contrary to the purpose and intent of the AIP." Mylan Petition at 4. Just as FDA's decision to invoke the AIP does not provide a basis for the Agency to refuse to approve Ranbaxy's Atorvastatin ANDA, the AIP does not authorize FDA to strip a company of its marketing exclusivity. There is nothing in the AIP that even purports to address exclusivity or its forfeiture.[4] Even if the AIP

[4] The grounds for forfeiture are set forth in the FFDCA at section 505(j)(5)(D). Even if those forfeiture provisions applied to Ranbaxy's Atorvastatin application, which they do not since this ANDA was filed prior to the effective date of the Medicare Modernization Act ("MMA"), there is no forfeiture provision in the statue that

purported to authorize FDA to take the action Mylan seeks, which it does not, a policy that was neither enacted by Congress nor promulgated through notice and comment rulemaking cannot be utilized to strip Ranbaxy of its 180-day exclusivity for the Atorvastatin ANDA, an application for which Ranbaxy was first-to-file a substantially complete application containing a paragraph IV certification.[5]

E. Under These Circumstances, FDA Has No Inherent Authority to Strip Ranbaxy of Exclusivity.

Mylan contends that if Ranbaxy does not file a new ANDA, and FDA takes no action, Ranbaxy will block other generic manufacturers from manufacturing their Atorvastatin products, thereby "further denying [to consumers] access to lower cost Atorvastatin Calcium Tablets." *See* Mylan Petition at 6. It is true that Ranbaxy's Atorvastatin ANDA was filed prior to the effective date of the MMA. Accordingly, under the pre-MMA provisions that are applicable to Ranbaxy's ANDA, FDA may not grant final approval of another ANDA (such as the ANDA subsequently filed by Mylan) until 180 days after either (1) "the first commercial marketing of the drug" by Ranbaxy or (2) a court decision holding the relevant patent "to be invalid or not infringed." 21 U.S.C. § 355(j)(5)(B)(iv)(I)-(II).

Mylan's argument, however, is full of presumptions. Ranbaxy's Atorvastatin ANDA has, to date, caused no delay, and there is no particular reason to think that it will. Indeed, there a significant public health reason may prompt FDA to review Ranbaxy's application. In addition, a third party might trigger the exclusivity through a court decision. Further, to Ranbaxy's knowledge, there is no reason to believe that Mylan would be able to obtain approval of its ANDA any more quickly than Ranbaxy. For example, to Ranbaxy's knowledge, Mylan has not obtained a tentative approval, suggesting that Mylan's ANDA may not be ready for approval even if Ranbaxy's exclusivity were not blocking its approval.

---

would be triggered by the Agency's invocation of the AIP. *See* 21 U.S.C. § 355(j)(5)(D).

[5] The legality of the AIP is questionable for a number of reasons. For example, FDA did not follow notice and comment rulemaking procedures in promulgating the AIP. *See, e.g.*, *Community Nutrition Institute v. Young*, 818 F. 2d 943, 949 (D.C. Cir. 1987) (holding that FDA's "action levels" for certain unavoidable contaminates in food were treated "as substantive rules by FDA and, as such, c[ould] only be permitted if notice-and-comment procedures [wer]e applied"). Similarly, here, FDA has treated the AIP as a substantive rule. Under the AIP, it has bound itself to conduct a validity assessment of the data generated at Paonta Sahib. There is, however, no timeframe for completion of the assessment. In the interim, the applicant's rights to a review of and decision on its ANDA are placed on hold indefinitely. Further, it is significant that FDA did not issue the AIP as a non-binding guidance, but instead as a "policy." If FDA were to apply the AIP, as Mylan would have it, and determine that Ranbaxy forfeited its exclusivity because it is required to file a new application under the AIP, this would further demonstrate that the AIP is not a non-binding policy, but a substantive rule that required FDA to follow notice and comment rulemaking.

Finally, as discussed above, the FDA's decision to invoke the AIP does not provide a basis for the Agency to reject pending ANDAs, nor does it authorize FDA to strip an ANDA of its marketing exclusivity as Mylan contends. Despite this, Mylan argues that FDA has inherent authority to do so. Any inherent authority in this regard, however, is cabined by the FFDCA's provisions governing the approval of ANDAs. *See* 21 U.S.C. § 355(j)(5)(A) and (E) (if FDA "decides to disapprove an application," then the Agency "shall give the applicant notice of an opportunity for a hearing . . . on the question of whether such application is approvable"); 21 U.S.C. § 355(j)(5)(D) (establishing exclusive grounds under which a first applicant may lose its 180-day period of marketing exclusivity). Moreover, the two cases cited by Mylan in support of this argument have no application to this situation. In *Nilssen v. Osram Silvania, Inc.*, 528 F.3d 1352 (Fed. Cir. 2008), a patent case, the court affirmed an award of attorneys' fees pursuant to 35 U.S.C. § 285. That case did not involve any agency action, let alone any action by FDA that was taken based on its "inherent authority." *Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341 (2001), is similarly inapposite. The issue in *Buckman* was whether plaintiffs' state law claims were preempted based on the FFDCA, as amended by the Medical Devices Amendments. The Supreme Court did not consider whether, as Mylan argues here, FDA has the "inherent authority," in instances where the "the primary goal of the Hatch-Waxman Amendments . . . would otherwise be contravened," to act in a manner that is not authorized by the FFDCA. Mylan Petition at 6.

* * *

For the substantive reasons discussed above, FDA should deny Mylan's request that FDA strip Ranbaxy of exclusivity for Atorvastatin. In addition, regardless of the legal issues discussed herein, it would be premature for FDA to make any determination on Ranbaxy's Atorvastatin application.

Sincerely,

William B. Schultz

William B. Schultz
Alexandra W. Miller

ATTORNEYS FOR RANBAXY
LABORATORIES LIMITED

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ORIG-1
SD-61

March 17, 2011

ORIGINAL BY MAIL/COPY BY E-MAIL

Ralph S. Tyler, Esq.
Chief Counsel
Food and Drug Administration
10903 New Hampshire Avenue
White Oak 32, Room 4536
Silver Spring, Maryland 20993-0002

Keith O. Webber, Ph.D.
Acting Director, Office of Generic Drugs
Food and Drug Administration
7519 Standish Place, Room 3020
Rockville, Maryland 20855

RE: ATORVASTATIN CALCIUM TABLETS, 10 mg, 20 mg, 40 mg, and 80 mg; Ranbaxy's 180-Day Exclusivity Status for Generic LIPITOR® (Atorvastatin Calcium) Tablets

Dear Mr. Tyler and Dr. Webber:

Attached is Mylan Inc.'s response to Ranbaxy Laboratories, Inc.'s letter dated February 14, 2011 relating to Ranbaxy's ANDA No. 76-477 for a generic version of LIPITOR® (atorvastatin calcium) Tablets, 10 mg, 20 mg, 40 mg, and 80 mg. With the exception of certain information relating to Matrix's pending ANDA for Atorvastatin Calcium tablets, the attached letter, which may be made available to Ranbaxy, contains substantive points made in a separate letter we sent to FDA addressing Ranbaxy's February 14th letter, and that was submitted as an amendment to Matrix's pending ANDA No. 91-226 for Atorvastatin Calcium Tablets.

Sincerely,

Kurt R. Karst
Counsel to Mylan Inc.

KRK/eam

cc: Eric M. Blumberg, Esq.
Deputy Chief Counsel, Litigation, FDA
Elizabeth H. Dickinson, Esq.
Office of Chief Counsel, FDA
David T. Read, Esq.
Office of Generic Drugs, FDA

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March 17, 2011

ORIGINAL BY MAIL/COPY BY E-MAIL

Ralph S. Tyler, Esq.
Chief Counsel
Food and Drug Administration
10903 New Hampshire Avenue
White Oak 32, Room 4536
Silver Spring, Maryland 20993-0002

Keith O. Webber, Ph.D.
Acting Director, Office of Generic Drugs
Food and Drug Administration
7519 Standish Place, Room 3020
Rockville, Maryland 20855

RE: ATORVASTATIN CALCIUM TABLETS, 10 mg, 20 mg, 40 mg, and 80 mg; Ranbaxy's 180-Day Exclusivity Status for Generic LIPITOR® (Atorvastatin Calcium) Tablets

Dear Mr. Tyler and Dr. Webber:

On behalf of Mylan Inc. ("Mylan"), we write to respond to certain arguments made by Ranbaxy Laboratories, Inc. ("Ranbaxy") in its February 14, 2011 letter ("Ranbaxy Letter") relating to Ranbaxy's Abbreviated New Drug Application ("ANDA") No. 76-477 for a generic version of LIPITOR® (atorvastatin calcium) Tablets, 10 mg, 20 mg, 40 mg, and 80 mg ("Ranbaxy's generic LIPITOR® ANDA").[1]

[1] For purposes of this letter, Mylan assumes that Ranbaxy's generic LIPITOR® ANDA is an application that is affected by the Application Integrity Policy ("AIP") and falls within one of the first three "buckets" discussed in Section II of this letter.

The facts and circumstances surrounding generic LIPITOR® are unique for two key reasons. First, the ANDA of the sole company eligible for 180-day exclusivity for generic LIPITOR®, Ranbaxy, appears to be covered by the AIP, which FDA has invoked against Ranbaxy's Paonta Sahib manufacturing site based on a litany of findings, potentially rendering data in the pending ANDA unreliable. Second, LIPITOR® is the most widely prescribed drug product in the United States, with ***over two billion doses dispensed per year***. As such, generic LIPITOR® is anticipated to be the largest U.S. launch of a generic drug. It is estimated that a high-quality and more affordable generic version of the drug could save United States consumers and the government between $10.9 million and $18.6 million per day, which equates to potentially $3.97 billion to $6.8 billion in savings per year. Given the efforts necessary to launch a generic product of this market size, including determining how to best handle manufacturing capacity, a significant amount of lead time is required.

These circumstances, coupled with the findings that led to the imposition of the AIP to the only first-filer, require FDA's immediate action.

The Ranbaxy Letter puts forth an untenable interpretation of the statutory scheme. In essence, Ranbaxy's position is that ANDA No. 76-477 must receive market exclusivity even if the application is so fatally tainted that FDA cannot approve it. Of course, if Ranbaxy's position is adopted, then no other generic versions of LIPITOR® will be able to reach the market either. This approach threatens FDA's ability to properly administer the statutory scheme. If Ranbaxy's generic LIPITOR® ANDA is covered by the AIP, then Ranbaxy should not be allowed to game the system and leverage what FDA has concluded was Ranbaxy's "pattern and practice" of misconduct to prevent the emergence of generic competition to LIPITOR® for an indefinite period. Indeed, the burden is on Ranbaxy to prove to FDA that Ranbaxy's generic LIPITOR® ANDA contained data and information that was neither false nor unreliable, which under the circumstances appears to be impossible. If Ranbaxy cannot promptly ***and lawfully*** obtain approval of its ANDA according to applicable law, regulations and FDA policy, then other ANDA sponsors who have not subverted the review process should be permitted to reach the market in a timely fashion. It is critical for FDA to make a decision now in order to serve market needs and not deprive patients of access to more affordable versions of generic LIPITOR® for a single day beyond the earliest possible entry date.

The Ranbaxy Letter makes it clear that FDA must promptly determine and publicly announce that Ranbaxy is not entitled to 180-day exclusivity in connection with its ANDA No. 76-477. This determination can and should be based on the language and policies in the Federal Food, Drug, and Cosmetic Act ("FDC Act") and applicable regulations, supplemented by the Agency's practices and guidelines. The necessity for this determination naturally flows from the public record and from what Ranbaxy did and did not state in the Ranbaxy Letter.

First, we note that the Ranbaxy Letter does ***not*** deny that Ranbaxy manufactured atorvastatin at its Paonta Sahib site for data submissions in its ANDA. See Ranbaxy Letter at footnote 2. Nor does Ranbaxy deny that the data on which Ranbaxy's generic LIPITOR® ANDA are based are affected by, or are the same as or similar to, the data that resulted in the conclusions that FDA publicly made about the Paonta Sahib site when FDA invoked the AIP against that site. Further, Ranbaxy has acknowledged, see Ranbaxy Letter at 2, that the Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA, to Mr. Malvinder Mohan Singh, CEO & Managing Director, Ranbaxy Laboratories Limited (Feb. 25, 2009) ("Woodcock Letter"), addressed "deficiencies" in "stability testing and data from Paonta Sahib that were used to support applications submitted by Ranbaxy," which apparently included Ranbaxy's generic LIPITOR® ANDA.

In light of this factual background, Ranbaxy does the only thing the company can do to avoid the necessary effect of FDA's already public findings: Ranbaxy launches a frontal and misplaced assault on the validity of the AIP and attempts to undermine FDA's ability to carry out the Agency's statutory obligation to approve only those drug applications that are free of unreliable data. If Ranbaxy's arguments are rejected, as they should be, then FDA can authorize generic versions of LIPITOR® to enter the marketplace as early as June 28, 2011.

The inherent unreliability of the data supporting and surrounding Ranbaxy's generic LIPITOR® ANDA, and Ranbaxy's failure to (indeed its legal inability to) amend or replace that data, must lead FDA to the only place that the Agency can go: FDA must require Ranbaxy, if Ranbaxy desires, to submit, and pursue approval of, an entirely new ANDA with valid data for its generic LIPITOR® product and, consequently, determine that Ranbaxy is not entitled to 180-day exclusivity in connection with ANDA No. 76-477.

I. The FDC Act and FDA's Regulations Dictate that FDA Must Deny Ranbaxy's Generic LIPITOR® ANDA and Any Associated 180-Day Exclusivity

There is more than sufficient statutory and regulatory authority (and indeed an obligation) for FDA to conclude that Ranbaxy's generic LIPITOR® ANDA cannot stand, and, as a consequence, deny Ranbaxy any associated 180-day exclusivity. The FDC Act prohibits FDA from approving an ANDA that is tainted with unreliable data or statements as described in the Woodcock Letter. After years of investigating Ranbaxy's Paonta Sahib manufacturing site, FDA certainly must recognize, and be aware of, the extent to which Ranbaxy's pending applications originating from this site are tainted with such data, rendering the applications unapprovable.[2]

Under the plain language of the FDC Act, FDA is ***not*** authorized to approve an ANDA where: (a) "the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity;" (b) "the application contains an untrue statement of material fact;" or (c) "the application does not meet any other requirement of [21 U.S.C. at § 355(j)(2)(A)]." 21 U.S.C. § 355(j)(4); see also 21 C.F. R. § 314.127(a). It is noteworthy that nowhere in the Ranbaxy Letter is there any indication that Ranbaxy disagrees with this fundamental assertion.

If FDA determines that an ANDA contains unreliable or false data and information, then to the extent the Agency invokes the AIP, these "defects" cannot be cured with an amendment, including an amendment to change the product to a new manufacturing site. This policy was spelled out many years ago in the AIP. See AIP at 1. It is again noteworthy that Ranbaxy does ***not*** deny that this is FDA's practice. Nor does Ranbaxy take issue with the FDA practice of prohibiting defects to be cured with an amendment, or suggest that FDA must approve a tainted application, rather than insist that the sponsor submit a new ANDA. Indeed, both the policy and FDA's requirement

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[2] FDA has been aware of significant problems at the Paonta Sahib manufacturing site since at least a February 2006 inspection, which led to a June 15, 2006 Warning Letter. Just a few months before imposing the AIP, FDA, in September 2008, issued another Warning Letter with respect to this same Ranbaxy facility (as well as others) and issued an Import Alert.

for a sponsor to submit a new application rather than submit an amendment in an effort to cure unreliable data is entirely consistent with the FDC Act.

Additionally, FDA's implementing regulations state, in relevant part, that FDA may consider an ANDA sponsor's failure to take certain actions with respect to its pending ANDA "to be a request by the applicant to withdraw the application." 21 C.F.R. § 314.110(c)(1).[3] This regulation clearly shows that FDA has the authority to deem an application to be withdrawn under appropriate circumstances. But regardless of how FDA gets there, it is clear that Ranbaxy cannot, pursuant to the FDC Act, the AIP, and FDA practice, amend its ANDA or retain 180-day exclusivity.

Indeed, if FDA cannot approve a tainted application, how can the Agency possibly determine that a sponsor is entitled to 180-day exclusivity ***as a result of that application***? Based on the statutory scheme and FDA's policies, the answer to the question is that the FDA cannot lawfully do so. "It is a 'fundamental canon of statutory construction that the words of a statute must be read in their context and with a view to their place in the overall statutory scheme.'" FDA v. Brown & Williamson Tobacco Corp., 529 U.S. 120, 133 (2000). To do so, one must interpret a statute "'as a symmetrical and coherent regulatory scheme,'" and "'fit, if possible, all parts into a harmonious whole.'" Id. (citations omitted).

II. The Available Record Demonstrates that Ranbaxy's Generic LIPITOR® ANDA Almost Surely Cannot Meet the Statutory Criteria for Approval

There are arguably four categories – or "buckets" – into which pending ANDAs can be placed with regard to the types of unreliable data described in the Woodcock Letter:

(1) ANDAs containing blatantly unreliable data;

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[3] Ranbaxy asserts that this regulation has no direct applicability here. See Ranbaxy Letter at 5. Ranbaxy misses the mark. The regulation demonstrates that FDA has the right to declare, under appropriate circumstances, including those found here, that an application must be deemed to be withdrawn, at least for purposes of clearing the approval bottleneck Ranbaxy created through its "pattern and practice" of conduct described in the Woodcock Letter.

(2) ANDAs for which the applicant has failed to provide data and information upon which FDA can rely to approve the ANDA because of findings that affect the entire manufacturing site (e.g., campus-wide systemic concerns);

(3) ANDAs for which the applicant has failed to provide data and information upon which FDA can rely to approve the ANDA because of manufacturing site concerns that could affect the particular type of drug product or a particular ANDA component (e.g., a silo approach under which there are concerns with a particular campus building, such as one with dedicated blocks for manufacturing tablets, or with a particular site function, such as quality control/quality assurance); and

(4) ANDAs not containing any unreliable data and otherwise not related to any manufacturing site concerns.

The Woodcock Letter demonstrates that it is almost certain that Ranbaxy's generic LIPITOR® ANDA cannot fit into bucket 4. As indicated in the Woodcock Letter, Ranbaxy submitted information in certain pending and approved ANDAs that had been derived from Ranbaxy's Paonta Sahib manufacturing site.

If Ranbaxy's generic LIPITOR® ANDA fits within buckets 1 or 2, then the FDC Act and FDA's implementing regulations make clear that FDA should immediately deny Ranbaxy's generic LIPITOR® ANDA, and consequently, Ranbaxy will lose any eligibility for 180-day exclusivity. If Ranbaxy's generic LIPITOR® ANDA falls within bucket 3, and Ranbaxy has failed to meet its burden of proving that the data contained in its ANDA are indeed reliable, then, in accordance with the applicable statutes and regulations, the conclusion is the same as buckets 1 and 2. Clearly, a company whose own misconduct caused imposition of the AIP should not be permitted to single-handedly hold up otherwise eligible generic applicants and deprive consumer access while Ranbaxy struggles to prove what the company obviously has been unable to demonstrate for at least two years since the AIP was invoked.

The Woodcock Letter includes a litany of findings with respect to stability test results Ranbaxy submitted to FDA, and untrue statements to support the approval of certain of the company's ANDAs. FDA stated that the Agency's investigation had demonstrated that there was "a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information contained in applications (pending and approved)

that [Ranbaxy] has filed with the Agency and which contain data developed at the Ranbaxy Laboratories, Paonta Sahib site." Id. at 5. Other findings were that:

- Ranbaxy "submitted untrue statements of material fact in abbreviated and new drug applications." Id. at 1.

- "Ranbaxy submitted stability information in numerous approved and pending applications that contain untrue statements of material fact." Id. FDA explained that Ranbaxy had failed to include critical information about the storage and testing of products. The Agency found that Ranbaxy had improperly stored stability samples in refrigerators but the "sample logbooks did not identify the samples that were being held in the refrigerators." Assuming Ranbaxy was generating stability samples relating to atorvastatin at this facility during the period when FDA found this serious violation of the FDC Act, how could Ranbaxy ever demonstrate that the data with regard to the atorvastatin samples were "reliable"? In other words, if Ranbaxy's own logbooks did not identify the samples that were improperly stored, Ranbaxy cannot prove to FDA that the information it submitted to FDA with regard to the atorvastatin samples was both true and reliable.

- Ranbaxy's "unusual storage condition for stability testing was not defined in the submitted protocol for U.S. drug applications, [which presumably included the pre-2003 atorvastatin application] and prior to the February 2006 inspection, was not reported to FDA." Id. at 2.

- A Ranbaxy audit of stability data in an unidentified number of "pending ANDAs found 2257 errors in entries for the dates of analysis." Id. at 3.

- "These submissions of false information about the stability testing of the product were material to FDA's review of these applications." Id.

As a result, FDA stated that if Ranbaxy wished to replace the unreliable data with a new submission, the new submission had to be in the form of a new application. Id. at 6 (citing the AIP). Although Ranbaxy has challenged this basic proposition, Ranbaxy has provided no legal support for its bald conclusion.

Ranbaxy obviously knows the extent to which these findings directly implicate Ranbaxy's generic LIPITOR® ANDA. However, we can glean how that product is implicated by the FDA findings discussed above and by reviewing the Ranbaxy Letter.

First, Ranbaxy did not deny, and basically conceded, that atorvastatin was manufactured at the Paonta Sahib site. See Ranbaxy Letter at 1. Second, although the Ranbaxy Letter contains a detailed discussion of the applicability of the Woodcock Letter to FDA's legal ability to determine the 180-day exclusivity issues, see id. at 4, Ranbaxy does ***not*** assert that the general conclusions outlined in the Woodcock Letter do ***not*** apply to atorvastatin.[4] Thus, the Ranbaxy Letter naturally implies that the conclusions set forth in the Woodcock Letter do indeed apply to Ranbaxy's generic LIPITOR® ANDA, and therefore FDA can take action now by deciding that 180-day exclusivity is inapplicable to Ranbaxy's generic LIPITOR® ANDA.

III. FDA Has Ample Authority to Rule that Ranbaxy Is Not Entitled to 180-Day Exclusivity

As discussed above, if FDA finds that Ranbaxy's data are unreliable, then Ranbaxy's pending generic LIPITOR® ANDA cannot be approved. If the ANDA cannot be approved, then the practical question arises about the disposition of 180-day exclusivity associated with Ranbaxy's generic LIPITOR® ANDA. If 180-day exclusivity is maintained by a company that does not have an approvable application, then the entire market for generic LIPITOR® will be blocked for an indefinite period. As discussed below, we do not agree with Ranbaxy that FDA is required to maintain 180-day exclusivity for Ranbaxy's generic LIPITOR® ANDA.

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[4] Ranbaxy asserts that the AIP does not authorize FDA to strip Ranbaxy of 180-day exclusivity because the AIP is only a policy that was not promulgated through notice-and-comment rulemaking. See Ranbaxy Letter at 5-6. Ranbaxy's argument misses the mark with regard to Mylan's arguments. Mylan submits that FDA's legal duty to refuse to approve Ranbaxy's generic LIPITOR® ANDA and deny Ranbaxy exclusivity for a tainted application is based on the mandates of the FDC Act, whether or not the AIP is a rule. However, we submit that a court could well rule that FDA's AIP is indeed a rule or regulation because FDA has applied the AIP for almost 20 years. See Teva v. Sebelius, 595 F.3d 1303, 1309 (D.C. Cir. 2010) (so-called "policy" was ripe for challenge in court because FDA had applied that policy on two prior occasions).

The Ranbaxy Letter states that "[a]ny inherent authority in this regard, however, is cabined by the FFDCA's provisions governing the approval of ANDAs." Ranbaxy Letter at 7. Apparently, Ranbaxy is trying to apply a hyper-technical limit on the FDC Act by arguing that unless the FDC Act and FDA's implementing regulations precisely address this fact pattern in the statutory text, then FDA is powerless and cannot conclude that 180-day exclusivity is lost. This is clearly a flawed interpretation, as FDA's "inherent" authority has been widely recognized by both the FDA and the courts.

Indeed, FDA's "inherent" authority has been the subject of litigation involving ANDAs tainted by the type of unreliable data described in the Woodcock Letter. In American Therapeutics v. Sullivan, 755 F. Supp. 1 (D.D.C. 1990), FDA withdrew approval of an ANDA because the Agency concluded that the approval was a mistake. The plaintiff argued that FDA had no authority to withdraw the approval because FDA had not followed the statutorily-mandated procedures in Section 505 of the FDC Act for withdrawing ANDA approvals. The Court disagreed and observed that even without following those procedures, courts defer to FDA so that the Agency can remedy "mistakes" even though there was no explicit language in the FDC Act that authorized FDA's actions. Id.; see also Boesche v. Udall, 373 U.S. 472, 476-78 (1963) (the overall language of the statute and its legislative history did not affect the government's "traditional administrative authority" to do what the statute did not on its face specifically authorize); Gun South, Inc. v. Brady, 877 F.2d 858, 862 (11th Cir. 1989) (implied authority to rectify errors).

Moreover, the courts have found that agencies have "inherent" authority to protect the integrity of the agency's administrative processes. See Checkosky v. SEC, 23 F.3d 452, 455 (D.C. Cir. 1994) (Concurring Opinion of Silberman, J.); Touche Ross & Co. v. SEC, 609 F.2d 570, 582 (2d Cir. 1979). That is exactly what is necessary here, consistent with the text of, and the goals set forth in, the FDC Act.

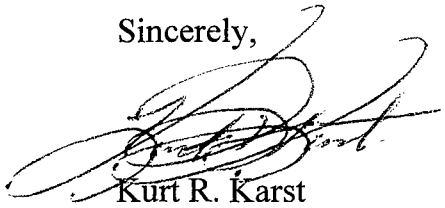
FDA's hands are not tied in the face of Ranbaxy's "pattern and practice" of misconduct described in the Woodcock Letter. Indeed, how could Congress ever have envisioned that a company could gain 180-day exclusivity for an application that, as a matter of law, FDA cannot approve? FDA has both ample authority, and indeed the obligation, to determine that Ranbaxy has lost any 180-day exclusivity in connection with ANDA No. 76-477, unless Ranbaxy can fulfill its burden to prove to FDA that Ranbaxy's generic LIPITOR® ANDA contained data and information that were neither false nor unreliable, which, under the circumstances, appears to be impossible.

CONCLUSION

FDA has all of the information the Agency needs to decide now whether Ranbaxy's generic LIPITOR® ANDA can stand or whether Ranbaxy must submit an entirely new ANDA with valid data, and, as a consequence, any 180-day exclusivity associated with Ranbaxy's generic LIPITOR® ANDA is lost in its entirety. If for some reason FDA is unable to promptly decide how to resolve Ranbaxy's generic LIPITOR® ANDA (i.e., deemed withdrawn, denied or otherwise), FDA should nonetheless decide that Ranbaxy is not eligible for 180-day exclusivity because, since FDA cannot approve a tainted application, the Agency cannot possibly determine under the FDC Act that the sponsor (here, Ranbaxy) is entitled to 180-day exclusivity as a result of that application. A sponsor whose own behavior has created this circumstance should not be permitted to hold up the introduction of otherwise eligible approvals and further deny consumers access to generic LIPITOR®.

With billions of dollars in annual savings at stake, each day FDA fails to take action to ensure generic LIPITOR® is available on the earliest possible date represents a substantial cost savings loss to the American public by depriving patients of earlier access to a more affordable generic after 15 years of a brand-only market.

Sincerely,



Kurt R. Karst
Counsel to Mylan Inc.

KRK/eam
cc: Eric M. Blumberg, Esq.
Deputy Chief Counsel, Litigation, FDA
Elizabeth H. Dickinson, Esq.
Office of Chief Counsel, FDA
David T. Read, Esq.
Office of Generic Drugs, FDA

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 076477

Kate C. Beardsley, Esq.
Buc & Beardsley, LLP
P.O. Box 5769
Washington, DC 20016

Carmen M. Shepard
Zuckerman Spaeder, LLP
1800 M Street, N.W., Suite 1000
Washington, D.C. 20036

Dear Ms. Beardsley and Ms. Shepard:

Your client Ranbaxy Laboratories Ltd. has a pending ANDA for a generic form of Pfizer's Lipitor (atorvastatin calcium) tablets. This ANDA was received by FDA in August 2002. Ranbaxy believes its ANDA was the first submitted for atorvastatin calcium and is thus eligible for 180-day exclusivity under section 505(j)(5)(B)(iv) of the Federal Food, Drug, and Cosmetic Act (the Act), as in effect prior to the amendments to section 505 of the Act made by the Medicare Prescription Drug, Improvement, and Modernization Act of 2003 (Public Law 108-173).

CDER is assessing whether Ranbaxy's eligibility for exclusivity for atorvastatin is affected by agency findings, as described in FDA's February 25, 2009 letter to Ranbaxy, that have raised significant questions regarding the reliability of data and information that was developed at the Ranbaxy Laboratories Paonta Sahib site and is contained in pending applications. To be eligible for 180-day exclusivity, an application must be the first substantially complete ANDA for the drug product to contain a patent challenge to a listed patent. See 21 CFR 314.107(c). In light of the concerns about the reliability of certain Ranbaxy data, CDER is actively considering whether the Ranbaxy atorvastatin ANDA was, in fact, substantially complete when it was received in August 2002.

Ranbaxy has asked for the opportunity to provide FDA with information to support that the atorvastatin ANDA was substantially complete when it was received in August 2002. I am writing now to memorialize our recent conversations in which I notified you that FDA will review information Ranbaxy submits to support its claim that the application was substantially complete in August 2002. As I noted, Ranbaxy should submit the information in an easily reviewable format.

It is my understanding that Ranbaxy expects to submit the relevant data and information by March 31, 2011.

If you have any questions, I can be reached at 240-276-9320.

Sincerely,

{See appended electronic signature page}

David T. Read
Regulatory Counsel
Office of Generic Drugs
Center for Drug Evaluation and Research

cc: Office of Chief Counsel, FDA

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DAVID T READ
03/24/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993-0002

MAY

Mr. Arun Sawhney
CEO and Managing Director
Ranbaxy Laboratories Limited
Corporate Office
Plot No. 90, Sector 32
Gurgaon, 122001 (Haryana), India
Telephone: 91-124-4135000
Facsimile: 91-124-4135001

Dear Mr. Sawhney:

The Center for Drug Evaluation and Research has determined that the Office of Generic Drugs will review your firm's ANDA 76-477 (Atorvastatin Calcium 10 mg, 20 mg, 40 mg, 80 mg tablets) under an exception to the Application Integrity Policy.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Kate C. Beardsley
Carmen Shepard
Zuckerman Spaeder LLP
1800 M Street, NW
Suite 1000
Washington, DC 20036-5807

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DOUGLAS A CAMPBELL

05/16/2011

This "AIP Exception" communication was initially issued by the FDA on May 16th, 2011. It is a hard copy, hand signed communication issued by the Office of the Center Director in collaboration with the Office of Compliance. This communication was checked into DARRTS on December 2nd, 2011 for records management and repository purposes. The DARRTS system date is being set to the date the communication was actually issued for archival accuracy and for accurate calculation of the status date. It is a copy of the original communication issued.

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

June 2, 2011

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855-2773

ESG
GRATUITOUS LABELING AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Gratuitous Labeling Amendment

Dear Sir/Madam:

Reference is made to Ranbaxy's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the following:

1. Gratuitous Amendment submitted on December 04, 2009. Through this amendment, Ranbaxy proposed multiple changes including:
   - Changes in the qualitative and quantitative composition of the drug product
   - Proposed Ohm Laboratories Inc.'s Terminal Road facility as the manufacturing site of the drug product
   - Proposed the use of Atorvastatin Calcium Crystalline API from (b) (4) in the drug product

   This gratuitous amendment also included revised labeling to reflect the changes proposed as mentioned above.
2. Gratuitous Amendment submitted on November 12, 2010. Through this amendment, an additional source of the API – Ranbaxy Laboratories Limited was proposed. Ranbaxy's DMF for Atorvastatin Calcium, USP (DMF 24139) includes two manufacturing processes for the API – Process I and Process II, and both Process I and Process II were proposed in this gratuitous amendment.

Through this gratuitous labeling amendment, Ranbaxy is hereby proposing additional changes to the drug product labeling based on comments from the Agency for ANDA (b) (4) The details of the changes are provided in **Attachment 1.**

Ranbaxy is hereby submitting its revised container and insert labeling. In addition, Ranbaxy is herewith submitting the Final Printed Labeling and Structured Product Labeling with this e-labeling submission. For ease of reference an annotated side-by-side comparison of revised vs. previously submitted Package Insert has also been included with this e-labeling submission.

In accordance with the electronic labeling rule published December 11, 2003, (68FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004, the labeling for this submission has been submitted through the FDA-ESG and is approximately 6 MB in size. The contents of the submission have been scanned for viruses using McAfee Virus Scan Enterprise 8.5 updated on June 2, 2011.

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

Please contact the undersigned at 609-720-8057 (email: manisha.sharma@ranbaxy.com) or Mr. Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission.

Sincerely,

Manisha Sharma
Senior Regulatory Associate (*for*)
Scott D. Tomsky
Official Agent for Ranbaxy Laboratories Inc.

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 11, 2011

FROM: Director, Office of Compliance

TO: Director, Center for Drug Evaluation and Research

SUBJECT: Proposal to Review Ranbaxy's Atorvastatin ANDA

ISSUE:

CDER's Application Integrity Policy (AIP) has been applied to Ranbaxy's Paonta Sahib site. Among the (b)(4) applications listed in CDER's AIP letter as originating from Paonta Sahib is Ranbaxy's ANDA 76-477 (atorvastatin calcium, 10, 20, 40 and 80 mg). After being put on the AIP, Ranbaxy submitted comprehensive amendments to this ANDA that, among other things, move manufacture of the atorvastatin product to a site in New Jersey.

This memo addresses the question of whether OGD should proceed with the review of the Ranbaxy ANDA, as amended.

BACKGROUND:

Pfizer's Lipitor (atorvastatin calcium) is a cholesterol-lowering agent that has been very widely prescribed for many years. Ranbaxy submitted its atorvastatin ANDA in 2002. It was the first generic applicant to submit an ANDA for atorvastatin. Ranbaxy challenged all the patents listed by Pfizer as covering Lipitor. By being the first to challenge the Lipitor patents, under the FD&C Act, Ranbaxy became eligible for 180 days of generic drug exclusivity.[1] As a pre-MMA ANDA, the Ranbaxy ANDA is not subject to the forfeiture provisions now found in the 180-day exclusivity provisions of the Act (e.g., forfeiture of eligibility for exclusivity if an applicant fails to obtain a tentative approval for its application within 30 months of submission). This means that unless Ranbaxy relinquishes its exclusivity, or the agency takes the unprecedented step of

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[1] Certain "subsequent applicants" (i.e., those applicants whose ANDAs would not be approved prior to or during Ranbaxy's 180-day exclusivity period) have written the agency and stated that the agency should declare Ranbaxy ineligible for 180-day exclusivity (in short, because of the AIP). Mylan recently brought suit against the agency on this point. No decision has been made at this time about the status of Ranbaxy's eligibility for 180-day exclusivity. Issues related to Ranbaxy's eligibility for exclusivity are not addressed in this memorandum.

revoking Ranbaxy's eligibility for 180-day exclusivity, ANDAs other than Ranbaxy's could not be approved until 180 days after Ranbaxy's exclusivity has been triggered by marketing or a court decision.[2]

In a letter dated February 25, 2009, CDER informed Ranbaxy that CDER was applying the AIP to the (b) (4) applications CDER identified as originating from Ranbaxy's Paonta Sahib site in India. CDER concluded that there was:

> a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information contained in applications … developed at the Ranbaxy Laboratories, Paonta Sahib site.

CDER cited examples to support this conclusion. Most of the examples pertained to irregularities with respect to stability data. ANDA 76-477 (atorvastatin calcium, 10, 20, 40 and 80 mg) was among the (b) (4) ANDAs listed as originating from Paonta Sahib, although it was not among the examples cited in the letter.

In the February 25, 2009, AIP letter to Ranbaxy, the agency stated the following in explaining the process to assess the validity of the data in the affected applications:

> This means that the Agency does not intend ordinarily to conduct or to continue its normal substantive scientific review (including review of data and labeling) of any such pending application or supplement, or of any new application or supplemental applications filed after the date of this letter, that contain data developed at the Paonta Sahib site, during a validity assessment of that application.

In December 2009, about 10 months after issuance of the AIP letter, Ranbaxy submitted a major amendment to its atorvastatin ANDA for the following changes:

> Drug Substance:
> - Change in the form of the drug substance Atorvastatin Calcium from amorphous to crystalline
> - Change in drug substance manufacturer from Ranbaxy Laboratories Ltd. to (b) (4)
> - Revisions to drug substance specifications and test methods

[2] On March 23, 2011, counsel for Ranbaxy notified FDA that if it does not receive final approval by March 1, 2012, Ranbaxy will not object to FDA's approval of any other ANDA for atorvastatin after May 30, 2012 (i.e., the approximate date upon which Ranbaxy's exclusivity would expire if its ANDA were approved and Ranbaxy began commercial marketing promptly after November 30, 2011, as permitted in its settlement agreement with Pfizer). Ranbaxy's representations diminish significantly, but do not completely eliminate, the possibility that its eligibility for exclusivity could result in an indefinite delay in approval of generic Lipitor. Among other things, Ranbaxy could attempt to withdraw the commitment made in the letter.

Drug Product:

- Addition of Ohm Laboratories Inc., New Brunswick, NJ, as new drug product manufacturing site
- Addition of Ohm Laboratories Inc., Terminal Road and Livingston Avenue, New Brunswick, NJ, as new analytical testing sites
- Qualitative and quantitative changes to the drug product formulation
- Changes to the drug product manufacturing process
- Revisions to the drug product specifications and test methods
- Change in the container closure system.

This was accompanied by new bioequivalence studies.

In November 2010, Ranbaxy submitted another major amendment for the following changes:

- Additional drug substance source: DMF 24139, Atorvastatin Calcium, USP (crystalline), Ranbaxy Laboratories Ltd., Vill. Toansa, Punjab, India
- Minor changes to the drug product manufacturing process using the new Ranbaxy drug substance.

Pursuant to the AIP, neither of these amendments has been reviewed.

The amendments to the Ranbaxy application necessitate, in essence, a new full review of the main elements of the ANDA, including the CMC information, bioequivalence studies, and labeling. In addition, to ensure data reliability of the new Ranbaxy submissions from Ohm Laboratories, we need to determine that they are free of the concerns which gave rise to the AIP. Among the factors to be assessed are the following:

- Have data from Paonta Sahib or other facilities with significant cGMP or data reliability concerns been included in the Ohm Laboratories submission?
- Have data "migrated" from earlier submissions into the amendments?
- Does the application adequately address known areas of concern, including dissolution, stability, other analytical data, and exhibit batch production records?

November 30, 2011, is the earliest date Ranbaxy could market its atorvastatin product under its 2008 settlement agreement with Pfizer. If Ranbaxy were to retain eligibility for exclusivity, obtain approval of its ANDA, and market immediately, its exclusivity would expire at the end of May 2012.

Those subsequent applicants who would have us revoke Ranbaxy's eligibility for exclusivity point to June 28, 2011 (the expiration date of the pediatric exclusivities attaching to two key patents), as the date on which they should be eligible for approval and immediate marketing. It is possible that Ranbaxy will lose its eligibility for exclusivity either by relinquishing it or as a

result of a determination by the agency that Ranbaxy is not eligible for the exclusivity (e.g., because Ranbaxy's ANDA was not "substantially complete" at the time of its submission). In anticipation that either of these events could occur and result in subsequent applicants being eligible for approval earlier than they would be if Ranbaxy retained its exclusivity (i.e., before May 2012), OGD is expediting the review of ANDAs for which there is no statutory impediment to approval (e.g., 30-month stay) as of June 28, 2011.

If Ranbaxy retains its eligibility for exclusivity (that is Ranbaxy does not relinquish it and FDA does not revoke it) FDA will be prohibited from approving other atorvastatin ANDAs until 180 days after Ranbaxy initiates marketing.[3] If Ranbaxy does not obtain approval or its approval is significantly delayed, then the approval of all other ANDAs will be delayed.

For the reasons set forth below, we are proposing that OGD review the pending Ranbaxy ANDA 76-477. This will include an assessment of the reliability of the data and information in the pending ANDA as amended, as well as a review to determine whether the application meets the approval requirements under the statute and regulations.

DISCUSSION

The agency's AIP provides for exceptions under which the agency may review an application otherwise subject to the policy. The policy includes certain specific bases for reviewing an application after the AIP is invoked, and further provides that "A Center may have additional reasons that justify continuing or resuming review." *See* Application Integrity Policy Procedures § 1-1-6, " (found at

).

We have considered the complicated circumstances related to Ranbaxy's atorvastatin ANDA, and concluded that they support review of the ANDA. The review of ANDA 76-477, including the December 2009 and November 2010 amendments, is appropriate because, among other things: (1) the initial findings of the third party auditor conducting the internal review at Paonta Sahib indicate that the practices at issue arose during a time period after 2002; (2) this and other evidence currently available to FDA suggests that the pattern of activity discussed in the AIP letter would not have affected the originally filed 2002 ANDA (e.g., the untrue statements identified by FDA occurred subsequent to the original ANDA filing); (3) the ANDA, as amended, purportedly does not contain data from the Paonta Sahib facility; (4) at this time, FDA is not aware of evidence that the application for which Ranbaxy is seeking approval (i.e., as amended in 2009 and 2010) contains unreliable data or information; (5) review may be necessary to avoid a situation in which the statutory 180-day exclusivity blocks approval of any ANDA for

[3] The possibility of a court decision triggering Ranbaxy's exclusivity appears increasingly remote, but is still not entirely impossible. One subsequent applicant has been trying to accomplish this by means of a declaratory judgment.

atorvastatin; and (6) the overall circumstances are such that the agency believes it will be able to determine whether the data and information in the application as amended are reliable and whether the ANDA meets the requirements for approval. If the data are found to be unreliable, or the application otherwise does not meet the requirements for approval, FDA would not approve the ANDA.

The Ranbaxy application presents an unusual situation in which an applicant eligible for 180-day exclusivity under the pre-MMA provisions (in which there are no forfeiture provisions) is subject to the AIP. This is not a case in which an exception to the AIP is sought to permit approval of an additional generic drug; this is a case in which the application subject to the AIP has the potential to significantly delay the approval of any ANDA for the drug. For FDA to apply the AIP in such a way as to permit the 180-day exclusivity provisions to unduly delay approval of all generic versions of the drug is inconsistent with both the specific goals of the exclusivity and the broader goals of Hatch-Waxman. Court decisions, including *Mova Pharmaceutical Corp., v. Shalala*, 140 F.3d 1060, 1074 (D.C.Cir. 1998), observe that the 180-day exclusivity period is intended as a reward to the ANDA applicant who challenges a listed patent, thus making it possible that generic drugs might be approved before the expiration date of the challenged patent. The exclusivity was not intended to act as an undue barrier to approval of generic drug products.

November 30, 2011, the earliest date Ranbaxy can market its atorvastatin product under its 2008 settlement with Pfizer, is about 7 months away. We anticipate that FDA's review of this ANDA can be completed by that date. If this application is granted an exception from the AIP's restriction on review, OGD proposes that expedited review of this ANDA both for reliability and approvability commence immediately. Prompt review of the ANDA does not, of course, guarantee that the application will be ready for final approval by November 30, 2011. To be approved, any ANDA for atorvastatin must meet the requirements under section 505(j) of the FD&C Act and applicable regulations.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEIGH A SEARS
06/02/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993-0002

MAY

Mr. Arun Sawhney
CEO and Managing Director
Ranbaxy Laboratories Limited
Corporate Office
Plot No. 90, Sector 32
Gurgaon, 122001 (Haryana), India
Telephone: 91-124-4135000
Facsimile: 91-124-4135001

Dear Mr. Sawhney:

The Center for Drug Evaluation and Research has determined that the Office of Generic Drugs will review your firm's ANDA 76-477 (Atorvastatin Calcium 10 mg, 20 mg, 40 mg, 80 mg tablets) under an exception to the Application Integrity Policy.

Sincerely,

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research
Food and Drug Administration

cc: Kate C. Beardsley
Carmen Shepard
Zuckerman Spaeder LLP
1800 M Street, NW
Suite 1000
Washington, DC 20036-5807

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/s/

LEIGH A SEARS
06/02/2011

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

June 3, 2011

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773

PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment – Update Regarding Settlement

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Through this patent amendment Ranbaxy is hereby informing the Agency about the settlement agreement between Ranbaxy and Pfizer (RLD holder). A revised patent certification is appended as **Attachment 1**.

With reference to the U.S. Patent numbers 5,273,995, RE 40,667, 5,686,104; 5,969,156 and 6,126,971 Ranbaxy has maintained a Paragraph IV certification against each of these Patents. Ranbaxy informed the Agency in a letter dated April 17, 2003 that it was sued by Pfizer on U.S. Patent numbers 4,681,893 and 5,273,995 at the U.S. District Court for the District of Delaware on February 21, 2003, in response to Ranbaxy's P-IV certifications against these patents filed in connection with this ANDA (03-cv-0209). The case was appealed to the Court of Appeals for the Federal Circuit in December 2006 (06-1179). Pfizer and Ranbaxy settled their litigation on June 17, 2008 (the "Settlement"). As part of the Settlement, and amendments thereto, (b) (4) [redacted] Provided in **Attachment 2** are excerpts from the settlement agreement.

US Patent No. 5,969,156 claims, among other things, crystalline form I atorvastatin hydrate, including the trihydrate. Ranbaxy's amended ANDA product (through letter dated December 4,

Please note that this letter and the corresponding attachments contain trade secrets/confidential commercial information. Ranbaxy, therefore, claims confidentiality under 18 U.S.C. § 1905, 21 U.S.C. § 331(j) and FDA's regulations implementing the Freedom of Information Act at 21 C.F.R. § 20.61 for all this information.

2009) now uses [redacted] (as the trihydrate). As mentioned above, under the Settlement, Ranbaxy has a license to US Patent No. 5,969,156, and, therefore, to use [redacted]

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is placed on a CD-ROM and is approximately 1 MB in size. The contents of the CD have been scanned for viruses using McAfee VirusScan Enterprise 8.0.0 updated on June 3, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-5609. Thank you.

Sincerely,

Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

Attachments:

1. Amended Patent certification
2. Excerpts from the 2008 Settlement between Pfizer and Ranbaxy, including provisions that discuss patent licenses and launch date.
3. [redacted]

Please note that this letter and the corresponding attachments contain trade secrets/confidential commercial information. Ranbaxy, therefore, claims confidentiality under 18 U.S.C. § 1905, 21 U.S.C. § 331(j) and FDA's regulations implementing the Freedom of Information Act at 21 C.F.R. § 20.61 for all this information.

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

June 7, 2011

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855-2773

ESG
GRATUITOUS CMC AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

Dear Sir/Madam:

Reference is made to Ranbaxy's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

This ANDA was submitted to the Agency on August 19, 2002. In the original ANDA, Atorvastatin Calcium (Amorphous) was proposed as the API and Ranbaxy Laboratories Ltd.'s Paonta Sahib facility in India was proposed as the drug product manufacturing site for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Subsequently, the ANDA has been amended. The following are the key amendments submitted to this ANDA:

1. December 4, 2009 - A Gratuitous CMC Amendment was submitted wherein the following changes were proposed:
   - Change in the API from the original Ranbaxy API to Atorvastatin Calcium from (b) (4)
   - Changes in the qualitative and quantitative composition of the drug product
   - Change to Ohm Laboratories Inc.'s Terminal Road facility in New Jersey, USA as the manufacturing site of the drug product
   - Revised labeling to reflect the changes proposed

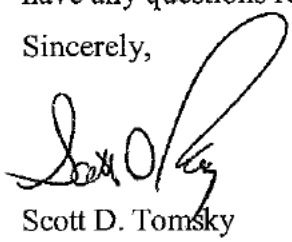
2. December 9, 2009 - New bioequivalence studies were submitted to support the changes proposed in the December 4, 2009 CMC amendment.

3. November 12, 2010 - A Gratuitous CMC Amendment was submitted wherein an additional source of the API – Ranbaxy Laboratories Limited was proposed.

Through this amendment, Ranbaxy hereby commits that all future batches of the drug product will be manufactured at Ohm Laboratories Inc.'s Terminal Road facility in New Jersey, USA; using only the API proposed in the December 4, 2009 or the Nov 12, 2010 amendments mentioned above; and using the revised qualitative and quantitative composition of the drug product, as proposed in the December 4, 2009 amendment.

Please contact the undersigned at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission.

Sincerely,



Scott D. Tomsky
US Agent for Ranbaxy Laboratories Inc.

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

June 14, 2011

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room,
Metro Park North - VII
7620 Standish Place,
Rockville, MD 20855

Patent Amendment

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment – Notice of certification of non-infringement

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, reference is also made to the patent amendment dated June 03, 2011.
It has come to our attention that the patent amendment sent on June 03, 2011 as referenced above was sent to an incorrect address. Upon tracking we found that this submission was delivered to Ammendale Road, Beltsville MD. We are therefore re-submitting the patent amendment dated June 03, 2011 along with this Amendment (see **Attachment 1**).

With this amendment Ranbaxy Laboratories Limited hereby certifies that pursuant to 21 C.F.R. § 314.95(a), notice of certification of non-infringement of the above referenced product has been provided to:

(1) The owner of the patent which is the subject of the certification or the representative designated by the owner to receive the notice and
(2) The holder of the approved application under section 505(b) of the act for the listed drug that is claimed by the patent and for which the applicant is seeking approval.

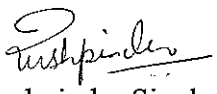
Ranbaxy Laboratories Limited also certifies that the notice meets the content requirement as described in 21 C.F.R. § 314.95(c).

Notice was sent to the appropriate owner on June 06, 2011 by certified mail. The USPS receipt confirmed the delivery on June 08, 2011. A copy of the notice along with the delivery confirmation receipt is provided in **Attachment 2**.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is placed on a CD-ROM and is approximately 1 MB in size. The contents of the CD have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on June 14, 2011.

Please contact the undersigned at 609-720-5334 (email: pushpinder.singh@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission. Thankyou.

Sincerely,



Pushpinder Singh
Regulatory Affairs Associate *(for)*
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

QUALITY DEFICIENCY - MINOR

ANDA 076477

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: Ranbaxy Laboratories Limited TEL: 609-720-5609

ATTN: Scott Tomsky FAX: 609-514-9797

FROM: Leigh Ann Sears FDA CONTACT PHONE: (240) 276-8453

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 19, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to your amendment dated December 4, 2009 and November 12, 2010.

The Division of Chemistry has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **5** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard copy will not be mailed.

Your amendment should respond to all of the deficiencies listed. **Facsimiles or partial replies will not be considered for review**, nor will the review clock be reactivated until all deficiencies have been addressed. The response to this facsimile will be considered to represent a MINOR AMENDMENT and will be reviewed according to current OGD policies and procedures. Your cover letter should clearly indicate that the response is a ***QUALITY MINOR AMENDMENT / RESPONSE TO INFORMATION REQUEST*** and should appear prominently in your cover letter.

We also request that you include a copy of this communication with your response. Please direct any questions concerning this communication to the project manager identified above.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents will be:*

Office of Generic Drugs, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

All ANDA documents will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

36. CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 76-477 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

The deficiencies presented below represent MINOR deficiencies.

A. Deficiencies:

1. Please revise the drug product composition table and other related sections of your document to label the drug substance as Atorvastatin calcium, USP.

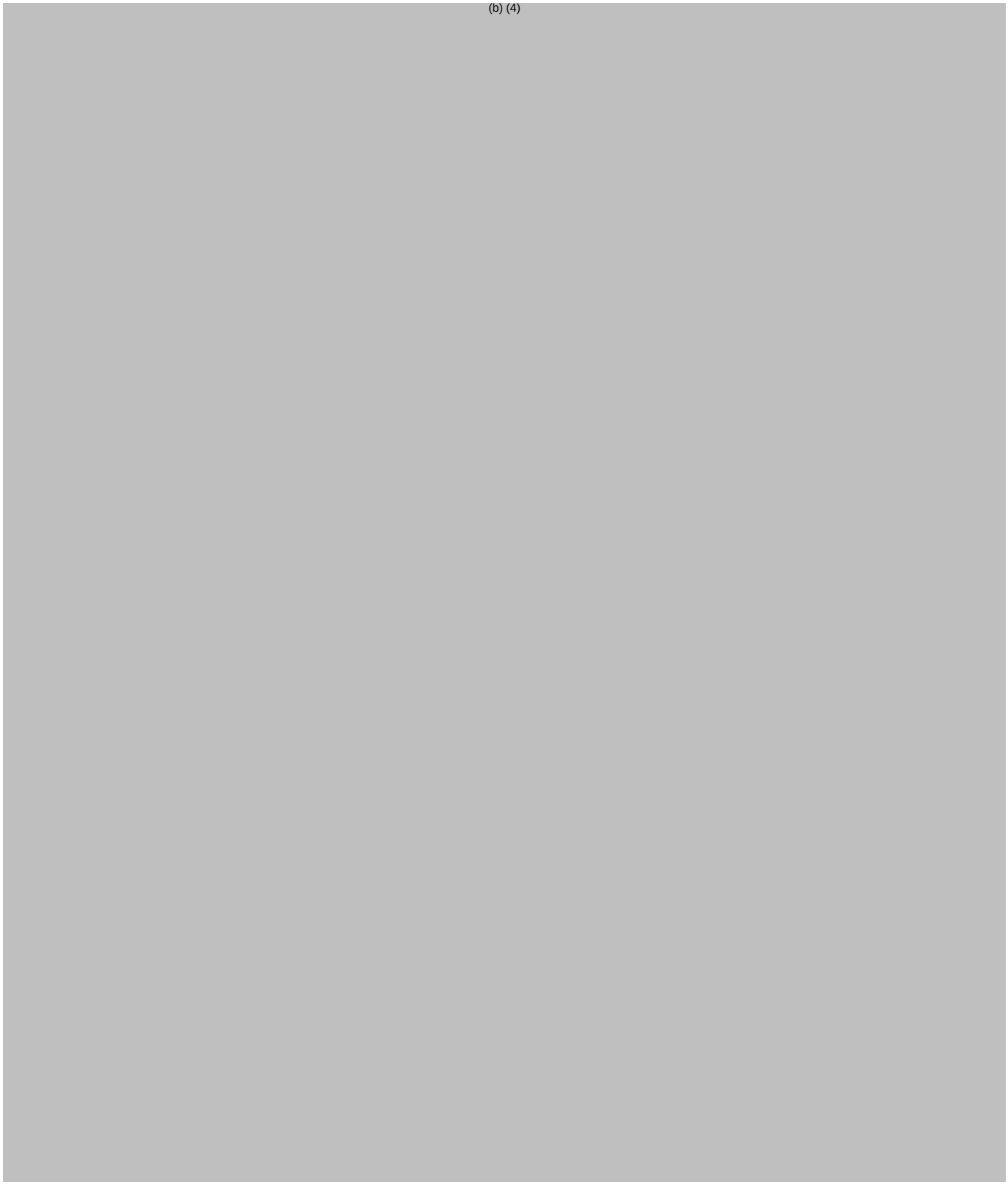
2. Please provide a comparable composition table for your test product with that of RLD.

3. DMF # (b) (4) and DMF #24139 are currently inadequate. Please do not respond to this letter until the DMF holders have notified you that they have responded to the deficiencies. Please revise the drug substance specifications and test methods as necessary.

4. With regard to your API release specification:

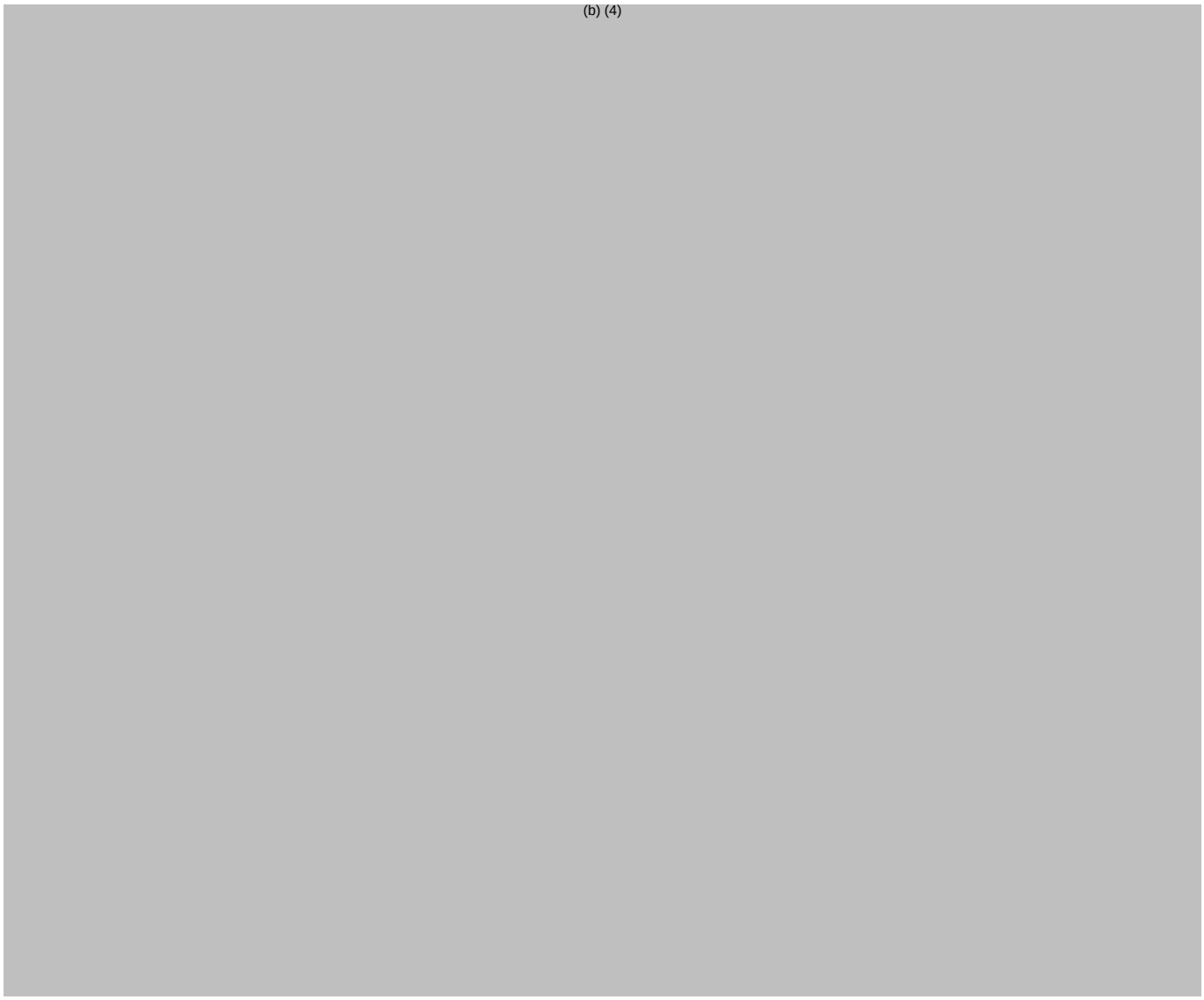
(b) (4)

(b) (4)



9. With regard to your drug product release and stability specification, please address the following comments:

(b) (4)



B. In addition to responding to the deficiencies presented above, please note and acknowledge the following comments in your response:

1. Please provide all available long-term stability data.

2. The labeling and bioequivalence portions of your application are pending. Deficiencies, if any, will be conveyed to you under separate covers.

3. A satisfactory cGMP compliance evaluation for the firms referenced in the ANDA is required for approval. We have requested an evaluation from the Division of Manufacturing and Product Quality.

4. Please be advised that the use of in-house analytical methods does not relieve you from meeting the compendial standards. In the event of a dispute, the official USP methods will prevail.

Sincerely yours,

{See appended electronic signature}

Vilayat A. Sayeed, Ph.D.
Director
Division of Chemistry III
Office of Generic Drugs
Center for Drug Evaluation and Research

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/s/

LEIGH A SEARS
06/14/2011

MOHAMMED K AHMED
06/14/2011

BIOEQUIVALENCE AMENDMENT

ANDA 076477

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Ranbaxy Laboratories Ltd.

TEL: 609-720-5609

ATTN: Scott D. Tomsky

FAX: 609-514-9797

FROM: Teresa Ramson

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on August 19, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to amendments submitted on December 9, 2009 and on November 12, 2010.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **1** page. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

ANDA:	076477
APPLICANT:	Ranbaxy Laboratories Ltd.
DRUG PRODUCT:	Atorvastatin Calcium Tablet 10, 20 , 40 and 80 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

In the amendments dated December 9, 2009 and November 12, 2010, you submitted the dissolution data for all strengths of the reference product and the test products with the (b) (4) Active Pharmaceutical Ingredient (API), and Ranbaxy's API (manufactured from Process I and Process II) to support the API and other manufacturing changes. Your dissolution testing data using the FDA-recommended method are insufficiently discriminating, with greater than 85% of the drug in the dosage form dissolved in 10 minutes. Therefore, please conduct additional dissolution testing for 12 units of each strength of each of the three proposed test products manufactured with (b) (4) API, Ranbaxy Process-1 API, and Ranbaxy Process-II API, compared to the respective strengths of the reference (Lipitor®) products, using the reduced paddle speed of 50 rpm, as follows:

Medium: 0.05M Phosphate Buffer, pH 6.8 at 37^0C
Volume: 900 mL
USP Apparatus: II (Paddle) at 50 rpm
Recommended Sampling Times: 10, 15, 20, 30, 45 minutes and until at least (b) (4) % is dissolved.

[NOTE: The method should use conventional USP II Vessels, and not (b) (4) ® Vessels.]

Sincerely yours,

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA V RAMSON
06/13/2011

DALE P CONNER
06/20/2011

RANBAXY

RANBAXY LABORATORIES INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200. FAX: (609) 720-1155

July 18, 2011

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

ESG
BE Amendment
Bioequivalence Response to Information Request

Reference: **ANDA 076477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Bioequivalence Response to Information Request dated June 20, 2011
(Dissolution Data)

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg submitted to the Agency on August 19, 2002. Reference is also made to the deficiency letter dated June 20, 2011 received from the Division of Bioequivalence, FDA.

Ranbaxy is hereby submitting a complete response to the above referenced request.

Ranbaxy is providing this submission in an electronic PDF format. The submission is approximately 2.5 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses with McAfee Virus Scan Enterprise 8.5., updated on July 18, 2011. Please note the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-8069 (email: sreelatha.panicker@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission.

Sincerely,

Sreelatha

Sreelatha Panicker
Regulatory Affairs Associate *(for)*
Scott D. Tomsky
US Agent for Ranbaxy Laboratories Ltd.

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

June 2, 2011

Office of Generic Drugs
Document Control Room
7620 Standish Place
Rockville, MD 20855-2773

ESG
GRATUITOUS LABELING AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Gratuitous Labeling Amendment

Dear Sir/Madam:

Reference is made to Ranbaxy's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the following:

1. Gratuitous Amendment submitted on December 04, 2009. Through this amendment, Ranbaxy proposed multiple changes including:
   - Changes in the qualitative and quantitative composition of the drug product
   - Proposed Ohm Laboratories Inc.'s Terminal Road facility as the manufacturing site of the drug product
   - Proposed the use of Atorvastatin Calcium Crystalline API from (b) (4) in the drug product

   This gratuitous amendment also included revised labeling to reflect the changes proposed as mentioned above.
2. Gratuitous Amendment submitted on November 12, 2010. Through this amendment, an additional source of the API – Ranbaxy Laboratories Limited was proposed. Ranbaxy's DMF for Atorvastatin Calcium, USP (DMF 24139) includes two manufacturing processes for the API – Process I and Process II, and both Process I and Process II were proposed in this gratuitous amendment.

Through this gratuitous labeling amendment, Ranbaxy is hereby proposing additional changes to the drug product labeling based on comments from the Agency for ANDA (b) (4) The details of the changes are provided in **Attachment 1.**

Ranbaxy is hereby submitting its revised container and insert labeling. In addition, Ranbaxy is herewith submitting the Final Printed Labeling and Structured Product Labeling with this e-labeling submission. For ease of reference an annotated side-by-side comparison of revised vs. previously submitted Package Insert has also been included with this e-labeling submission.

In accordance with the electronic labeling rule published December 11, 2003, (68FR 69009) that requires submission of labeling content in electronic format effective June 8, 2004, the labeling for this submission has been submitted through the FDA-ESG and is approximately 6 MB in size. The contents of the submission have been scanned for viruses using McAfee Virus Scan Enterprise 8.5 updated on June 2, 2011.

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

Please contact the undersigned at 609-720-8057 (email: manisha.sharma@ranbaxy.com) or Mr. Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission.

Sincerely,

Manisha Sharma
Senior Regulatory Associate (*for*)
Scott D. Tomsky
Official Agent for Ranbaxy Laboratories Inc.

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

July 27, 2011

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

ESG

QUALITY MINOR AMENDMENT
RESPONSE TO INFORMATION REQUEST

Reference: **ANDA 076477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Response to Information Request dated June 14, 2011

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the quality minor deficiency letter dated June 14, 2011.

Ranbaxy is hereby submitting a complete response to the above referenced request.

Please note, in the above referenced quality deficiency, the Agency indicated that (b) (4) DMF (b) (4) and Ranbaxy's DMF 24139 have been found inadequate and that the ANDA deficiency response should be submitted only after the DMF deficiencies have been responded. Ranbaxy has responded to the deficiencies for DMF 24139 on July 20, 2011. However, (b) (4) has not yet responded to the deficiencies for DMF (b) (4) Based on the telephone conversation with Mr. Robert West, OGD on July 25, 2011, we are submitting the ANDA deficiency response even though the DMF holder has not responded to the DMF deficiencies. Ranbaxy commits that if any changes to the API specifications or test methods are required based on the (b) (4) DMF response, all such changes will be made to the relevant documents in the ANDA, in a timely manner, prior to approval of the ANDA.

Ranbaxy is providing this submission in an electronic PDF format. The submission is approximately 85 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses with McAfee Virus Scan Enterprise 8.5., updated on July 27, 2011. Please note the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-5605 (email: vijayata.sharma@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission.

Sincerely,

Vijayata Sharma, Ph.D.
Regulatory Affairs Associate *(for)*
Scott D. Tomsky
US Agent for Ranbaxy Laboratories Ltd.

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

July 28, 2011

Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
Document Control Room,
Metro Park North - VII
7620 Standish Place,
Rockville, MD 20855

FDA-ESG
Patent Amendment

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment – Notice of no civil action

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, reference is also made to the patent amendment dated June 14, 2011.

On June 14, 2011, a patent amendment (revised patent certification) has been submitted to the Agency for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Ranbaxy Laboratories Limited has complied with the requirements under 21 CFR 314.95(a) with respect to providing a notice to each owner of the patent or their representatives and to the holder of the approved drug application for the listed drug and with the requirements under 21 CFR 314.95(c) with respect to the contents of the notice.

As of today, (more than 45 days since we notified the patent holder or holder of the approved application), neither the patent holder nor the holder of the approved application has commenced any civil action pursuant to 21 CFR § 314.107(b)(3) against Ranbaxy Laboratories Limited on any of the patents against which a paragraph IV certification was made.

Please note that Pfizer and Ranbaxy settled their litigation on June 17, 2008 (the "Settlement"). As part of the Settlement, and amendments thereto, (b) (4)

(b) (4)

Ranbaxy is providing this submission in a PDF format. The submission is approximately 1 MB in size and is being submitted to the Agency through FDA's electronic submission gateway. The contents of the submission have been scanned for viruses with McAfee Virus Scan Enterprise 8.5, updated on July 28, 2011. Please note the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-5362 (email: johanan.jeyaraj@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission. Thank you.

Sincerely,

Johanan Jeyaraj
Regulatory Affairs Associate (for)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: July 29, 2011

FROM: Martin Shimer, Branch Chief
Regulatory Support Branch
Office of Generic Drugs

THROUGH: Keith O. Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science

SUBJECT: Re-examination of ANDA 076477 for Substantial/Sufficient Completeness

TO: ANDA 076477 – Ranbaxy Laboratories Limited
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg

I. BACKGROUND

The purpose of this memorandum is to document the re-examination of whether ANDA 076477 was substantially/sufficiently complete when submitted to the agency in 2002. It is extremely unusual for the agency to undertake such a re-examination, especially in a case such as this when the ANDA in question was received (and therefore determined to be sufficiently complete) many years ago. However, the unusual facts surrounding ANDA 076477, summarized below, compel such a re-examination.

Ranbaxy Laboratories Limited (Ranbaxy) is the sponsor of ANDA 076477 (atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg and 80 mg). The reference listed drug (RLD) is Pfizer's Lipitor. ANDA 076477 was received by the Office of Generic Drugs (OGD) on August 19, 2002, and was the first ANDA for atorvastatin submitted to the agency. ANDA 076477 also contained the first paragraph IV patent certifications to all the patents that are still listed in the Orange Book for Lipitor. By being the first to challenge the Lipitor patents, Ranbaxy became eligible for 180 days of generic drug exclusivity under the Federal Food, Drug, and Cosmetic Act (the Act).[1]

[1] The Medicare Prescription Drug, Improvement and Modernization Act (MMA)(Public Law 108-173) was enacted on December 8, 2003. ANDA 076477, having been received prior to enactment of the MMA, is not subject to the forfeiture provisions now found in the 180-day exclusivity provisions of the Act, e.g., forfeiture of eligibility for exclusivity if an applicant fails to obtain a tentative approval for its application within 30 months of submission.

(b) (4) generic applicants, in addition to Ranbaxy, have submitted ANDAs for atorvastatin. As part of the 2008 resolution of its patent case with Pfizer, Ranbaxy entered into a settlement agreement under which the earliest date Ranbaxy could market its atorvastatin product is November 30, 2011. But for Ranbaxy's eligibility for 180-day exclusivity, one or more of the other generic applicants could possibly be eligible for approval prior to November.

About 6½ years after submission of ANDA 076477, in a letter dated February 25, 2009, CDER informed Ranbaxy that it was applying CDER's Application Integrity Policy (AIP) to the 85 applications CDER identified as originating from Ranbaxy's Paonta Sahib site in India. CDER concluded that there was:

> a pattern and practice of submitting untrue statements of material fact and other wrongful conduct, which raise significant questions regarding the reliability of the data and information contained in applications … developed at the Ranbaxy Laboratories, Paonta Sahib site.

CDER cited examples to support this conclusion. Most of the examples pertained to irregularities with respect to post-market stability data. ANDA 076477 was among the (b) (4) ANDAs listed as originating from Paonta Sahib. However, it was not among the examples of specific applications with data irregularities cited in the letter.

CDER has also noted that the first problems with data reliability that formed the basis for putting the site on the AIP appear to date from 2004.

Teva, Apotex, and Matrix/Mylan, who are among the subsequent applicants whose ANDAs would not be approved prior to or during Ranbaxy's 180-day exclusivity period, have written the agency and stated that the agency should declare Ranbaxy ineligible for 180-day exclusivity (in short, because of the AIP).[2]

The agency does not regard the AIP as necessarily conferring any automatic status on those applications subject to the AIP, other than that the agency generally will not conduct a review of relevant applications (with some exceptions) until certain remedial measures have been taken by the affected company. The status of any particular application, including whether an ANDA is eligible for 180-day exclusivity, is a fact-based determination made on a case-by-case basis.

As noted above, ANDA 076477 is a pre-MMA ANDA and is therefore not subject to the forfeiture provisions now a part of the Act. As a result, there are only two relatively straightforward bases at this juncture for considering Ranbaxy ineligible for 180-day exclusivity with respect to ANDA 076477 (which is not yet tentatively approved nearly nine years after

[2] On March 18, 2011, Mylan sued the agency, arguing that since Ranbaxy's ANDA 076477 originated from the Paonta Sahib site, it should be rejected, and that any applicable 180-day exclusivity period is extinguished. On May 2, 2011, the case was dismissed for Mylan's lack of standing, largely based on the fact that its ANDA has not yet been tentatively approved. As of the date of this memorandum, no atorvastatin ANDA has been tentatively approved.

submission).[3] The regulations provide that exclusivity can be lost if the eligible applicant is "not actively pursuing approval of its abbreviated application." 21 C.F.R. § 314.107(c)(3). Although the Ranbaxy application was, for a significant period, not under active review by OGD, this lull was a function of the AIP status of the ANDA, rather than a result of Ranbaxy's failure to pursue approval. Therefore, this regulation (which has never been applied in practice) does not appear to be an appropriate basis on which to deny Ranbaxy eligibility for exclusivity. A second basis for finding Ranbaxy ineligible for 180-day exclusivity would be a determination that ANDA 076477 was not substantially complete when received in 2002, and therefore did not qualify for the exclusivity under 21 C.F.R. § 314.107(c)(2). In order to provide a clear answer to the question of whether ANDA 076477 was substantially complete when it was submitted, the agency has conducted a re-examination of the ANDA as submitted in 2002.[4]

II. ELIGIBILITY FOR 180-DAY EXCLUSIVITY

Ranbaxy's eligibility for 180-day exclusivity is governed by section 505(j)(5)(B)(iv) as in effect before passage of the MMA. This section provides that if a subsequent ANDA contains a paragraph IV certification and is for a drug "for which a previous application has been submitted [containing] such a [paragraph IV] certification," the subsequent ANDA will not be approved until the exclusivity expires. FDA promulgated regulations implementing this exclusivity. These regulations require that, to be eligible for exclusivity, an ANDA must, among other things, contain a specific quantum and type of information when submitted; that is, the application must be "substantially complete."

A. Substantially/Sufficiently Complete

With respect to ANDAs that may be eligible for generic drug exclusivity, the relevant regulations state the following:

> (c) *Subsequent abbreviated new drug application submission.* (1) If an abbreviated new drug application contains a certification that a relevant patent is invalid, unenforceable, or will not be infringed and the application is for a generic copy of the same listed drug for which one or more substantially complete abbreviated new drug applications were previously submitted containing a certification that the same patent was invalid, unenforceable, or would not be infringed ….

[3] Of course, if FDA were to determine that Ranbaxy's application was not approvable and to prevail in any appeals of that decision, Ranbaxy would ultimately lose eligibility for exclusivity because it would no longer have an application to support such exclusivity.

[4] FDA originally notified Ranbaxy on October 10, 2002, that ANDA 076477 had been received as acceptable for filing as of August 19, 2002, its original submission date. After questions were raised regarding Ranbaxy's eligibility for exclusivity in light of the AIP, Ranbaxy asked FDA for an opportunity to address whether its atorvastatin ANDA was substantially complete when submitted. On March 25, 2011, OGD corresponded with Ranbaxy regarding a submission on this issue. On April 1, 2011, Ranbaxy submitted arguments and information in support of its position that ANDA 076477 was substantially complete when it was submitted in 2002.

(2) For purposes of paragraph (c)(1) of this section, the "applicant submitting the first application" is the applicant that submits an application that is both substantially complete and contains a certification that the patent was invalid, unenforceable, or not infringed prior to the submission of any other application for the same listed drug that is both substantially complete and contains the same certification. A "substantially complete" application must contain the results of any required bioequivalence studies, or, if applicable, a request for a waiver of such studies.

21 C.F.R. §§ 314.107(c)(1) and (2) (emphasis added).

The regulations at 21 C.F.R. §§ 314.101(b) and (d) state the following:

(b)(1) An [ANDA] will be reviewed after it is submitted to determine whether the [ANDA] may be received. Receipt of an [ANDA] means that FDA has made a threshold determination that the [ANDA] is sufficiently complete to permit a substantive review.
(2) If FDA finds that none of the reasons in paragraphs (d) and (e) of this section for considering the [ANDA] not to have been received applies, the agency will receive the [ANDA] and notify the applicant in writing.
(3) If FDA considers the [ANDA] not to have been received under paragraph (d) or (e) of this section, FDA will notify the applicant, ordinarily by telephone. The applicant may then:

(i) Withdraw the [ANDA] under 314.99; or
(ii) Amend the [ANDA] to correct the deficiencies; or
(iii) Take no action, in which case FDA will refuse to receive the [ANDA].

…

(d) FDA may refuse to file an application or may not consider an abbreviated new drug application to be received if any of the following applies:
(1) The application does not contain a completed application form.
(2) The application is not submitted in the form required under Sec. 314.50 or Sec. 314.94.
(3) The application or abbreviated application is incomplete because it does not on its face contain information required under section 505(b), section 505(j), or section 507 of the act and Sec. 314.50 or Sec. 314.94.

In sum, as a threshold matter, and regardless of whether it contains a paragraph IV certification, any ANDA must be "sufficiently complete" in order to be received for review by the agency, and must be "substantially complete" for it to be eligible for 180-day exclusivity.[5]

[5] This standard is now expressly set forth in the Act, as a result of the amendments made by the MMA. See section 505(j)(5)(B)(iv)(II)(bb). A "substantially complete application" is an application that "on its face is sufficiently complete to permit substantive review and contains all the information required by [section 505(j)(2)(A)]." Section 505(j)(5)(B)(iv)(II)(cc).

As the legislative history makes clear, Congress was concerned about the submission of incomplete ANDAs:

> Congress did "not intend that applicants be permitted to circumvent this notice requirement [proposed 21 C.F.R. § 314.95(b)] by filing sham ANDA's or ANDA's which are substantially incomplete."

59 FR 50338, 50349 (Oct. 3, 1994) (quoting H. Rept. 857, 98th Cong. 2d Sess. 24 (1984)). This concern was shared by the FDA as reflected in its preamble discussion:

> As written, § 314.95(b) is consistent with the legislative history because it requires the ANDA applicant to provide notice once FDA has determined that the ANDA is substantially complete to permit a substantive review. To permit an ANDA applicant to provide notice before FDA has determined whether the ANDA is sufficiently complete would be contrary to the legislative history because it would only encourage ANDA applicants to file incomplete or "sham" ANDA's and to supplement them later to secure a place in the review queue in an attempt to secure the first ANDA approval.

59 FR 50338, 50350 (Oct. 3, 1994).

FDA regulations distinguish between an ANDA that "on its face" is sufficiently complete to permit a substantive review and an application that will ultimately be approvable. Prior to the passage of the MMA (when Congress incorporated into the statute the concept of an application being sufficiently complete "on its face" to permit a substantive review) this distinction had been recognized by the courts:

> Under the FDCA and FDA regulations, the ANDA procedure is only available after the FDA makes a "threshold determination that the ANDA is sufficiently complete to permit a substantive review." 21 C.F.R. § 314.101(b)(1). An ANDA must contain, *inter alia*, information to show that (1) the active ingredient(s), (2) the route of administration, (3) the dosage form, and (4) the strength of the proposed generic drug are the "same as" those of the pioneer drug. 21 U.S.C. § 355(j)(2)(A)(ii) and (iii); 21 C.F.R. § 314.94(a)(5) and (6). [footnote omitted] If the FDA finds that the ANDA "on its face" contains this required information, then the FDA proceeds to the more in depth substantive review phase of the ANDA process to determine whether to approve the proposed generic drug for marketing and use. If, on the other hand, the FDA determines that an ANDA does not "on its face" contain certain required information, the FDA may refuse to receive it, and the review process stops there. 21 C.F.R. § 314.101(d)(3).
>
> …
>
> If the FDA accepts an ANDA as being properly filed … the FDA then proceeds to the substantive review stage. During the substantive review stage, the FDA goes beyond its preliminary threshold determination and this time thoroughly reviews the sufficiency of the ANDA's information … If, after substantive review, the FDA determines that the information contained in the ANDA is in fact

> insufficient regarding any one of these criteria, the FDA will refuse to approve the ANDA. [reference omitted]
>
> If the FDA finds that the information in the ANDA is sufficient under the FDCA and FDA regulations, it will approve the ANDA …

Pfizer, Inc. v. Shalala, 1 F. Supp. 2d 38, 43 (D.D.C. 1998).

For all of these reasons, an ANDA need not be approvable when first submitted to be substantially complete. FDA conducts only a threshold review for substantial completeness; this review is distinct from the critical review of data to support approval.[6]

B. Re-Review of 2002 ANDA Submission

Although the threshold review of an ANDA assesses whether the application is sufficiently complete "on its face," there may be rare circumstances - such as are presented here - when more than a "facial" review of the ANDA as submitted will be appropriate to avoid the misuse of the 180-day exclusivity incentive. In the event that the agency has a reasonable basis to question whether data that is facially acceptable is, in fact, reliable, it may subject an ANDA to closer scrutiny. As described below, FDA has concerns about the reliability of certain Ranbaxy data; these concerns led to a reassessment of ANDA 076477 as submitted.

III. RE-EXAMINATION OF ANDA 076477

The current assessment of Ranbaxy's ANDA as it was submitted in 2002 takes place against the backdrop of the types of irregularities FDA has identified in other Ranbaxy applications. On February 25, 2009, FDA issued a letter to Ranbaxy describing why the firm's Paonta Sahib site was being placed on AIP. The observations that led to the AIP included stability testing problems and instances of employees signing documents on dates when they were not present at the facility. In addition, CDER wanted to confirm to the extent possible that the data and information reported for the Ranbaxy atorvastatin drug product for which approval was sought in 2002 was actually derived from the proposed drug product and not from other sources.

Most of the examples FDA had of unreliable data pertained to irregularities with respect to Ranbaxy's post-approval stability data. Problems in the stability program included stability samples being stored in refrigerators prior to testing and Ranbaxy's failure to document or report this storage condition. Further, corrected stability test reports were submitted to approved and pending ANDAs and revealed that in some cases stability testing was performed several months later than originally reported in the ANDA. It was

[6] It should be noted that although an ANDA may be substantially complete but not approvable without additional information, the optimum submission is an ANDA that can be approved on the basis of the information submitted or without significant amendments. It is nevertheless common for ANDA applicants - including those eligible for 180-day exclusivity - to amend applications multiple times before approval.

also observed that stability testing for several time points (e.g., 3, 6, 9, 12 months) was conducted on the same day or within a period of days. The AIP letter also noted that Ranbaxy's verification audit of stability data identified many instances of incorrect test results recorded on the stability reports (i.e., incorrectly transcribed from the raw data).

CDER is also aware that the problems with data reliability that formed the basis for putting the Paonta Sahib site on the AIP appear to date from 2003, after the 2002 submission of ANDA 076477, a factor suggesting that the specific reliability concerns may not be applicable to the atorvastatin ANDA.

A. OGD Review

Staff in OGD have recently re-reviewed Ranbaxy's original 2002 ANDA submission to verify that it contained the items required for the ANDA to be considered substantially complete. They compared the information recorded on the ANDA Checklist for Completeness and Acceptability as an Application (attached) with the contents of the ANDA. They confirmed that Ranbaxy's original submission contained all required information described in the checklist, including a signed and completed application form, a basis for submission description of the reference listed drug (RLD), patent certification, comparison between the proposed generic drug and RLD (i.e., conditions of use, active ingredient(s), route of administration, dosage form, strength), labeling, bioavailability/bioequivalence information, components and composition statements, raw materials controls, description of manufacturing facility, outside firms including contract testing laboratories, manufacturing and processing instructions, in-process controls, container information, controls for the finished dosage form, stability information for finished dosage form, samples, environmental impact analysis statement, and Generic Drug Enforcement Act information.

Further, in light of the concerns about data reliability raised by the issues that formed the basis for the AIP, OGD staff looked at documents contained in Ranbaxy's original submission in greater depth than is usual for a substantial completeness and filing assessment. They compared the lot numbers recorded on various documents to ensure consistency throughout the submission. Staff also reviewed the dates recorded on documents such as batch records, certificates of analysis, methods, method validations, and stability data to ensure that the processes were performed in the correct order.

1. Review of Stability Data

Based on the issues raised in the AIP letter regarding stability data, OGD re-reviewed the stability data submitted in the original ANDA as well as in amendments to the ANDA.

We noted that in an amendment dated October 10, 2002, Ranbaxy submitted revised accelerated stability data tables to correct a typographical error in the storage conditions. Ranbaxy revised the storage conditions from 25ºC ± 2ºC/60% ± 5% RH to 40ºC ± 2ºC/75% ± 5% RH on stability data sheets for all strengths and bottle sizes. This revision to the original stability data was typographical and no changes were made to the actual stability data.

In a chemistry amendment dated June 18, 2007, Ranbaxy submitted revised stability data that resulted from the review by its consultant, (b) (4) . Ranbaxy had retained (b) (4) as an independent consultant after Ranbaxy received a June 15, 2006 warning letter that highlighted a number of problems at the Paonta Sahib site. (b) (4) review found errors in the stability data sheets due to inconsistent dating, specification limits that were not updated, and transcription errors. Ranbaxy stated that the inconsistent dating occurred because there was no uniform practice for identifying the date of analysis. The analyst could use the date the assay test was performed, the date the sample analysis was initiated, the date the sample analysis was completed, or some other dating practice. The appropriate date of analysis was identified as the date recorded by the analyst for the final test of the stability sample. Ranbaxy further noted that incorrect test values had been reported in the stability data sheets due to transcription errors from the record of analysis (green sheet) or the Excel calculation sheets to the stability report, or from calculation errors that resulted in a misinterpretation of results. As a result of the stability data review, Ranbaxy withdrew the (b) (4) -count bottle package configuration for the 10 mg strength because a specified impurity (b) (4)) was out of specification at the 24-month time point.

In a chemistry amendment dated September 14, 2007, Ranbaxy provided additional details and information regarding the stability data review. Protocols for the stability data review, a summary of observations in which corrections were made, updated stability data sheets, and the previously submitted stability data were provided. Ranbaxy provided a chart (Details of discrepancies observed compared to filed stability data after Retrospective Verification as per Protocol No. PQA/ST/GEN-03) that summarized corrections and changes to the submitted stability data.

Our review of Ranbaxy's stability data found that, as a result of the (b) (4) review, Ranbaxy revised some of data that had been submitted in its original 2002 submission. They made changes to the date of analysis as well as to some of the test results. The test results that were changed were still within specification. We did find some evidence of testing at multiple time points on the same date or within a period of days as was noted in the AIP letter. The initial (0 month) stability testing was performed two days after the 3-month testing for all strengths of the drug product. This may have been a result of "inconsistent dating" because, as identified by (b) (4) there was no uniform practice for identifying the date of analysis. The other time

points were tested according to the stability protocol.

Our review concluded that Ranbaxy's revisions to the stability data as submitted in 2002 did not undermine our earlier conclusion that Ranbaxy's stability data in its original submission was sufficiently complete to permit review and the application was acceptable for receipt/filing.

2. Review of Dissolution Data[7]

Ranbaxy had another consultant, (b) (4) perform a product validity evaluation in which it reviewed raw data and compared them with the data that were submitted in Ranbaxy's ANDA. In a report, (b) (4) concluded that many results were verified as reported correctly, but they identified deficiencies such as analyst and documentation errors, document control issues, and lack of investigation regarding an out of specification result. Further, (b) (4) report noted that the original dissolution data from the side-by-side Ranbaxy/RLD dissolution testing could not be located.

As noted above, Ranbaxy submitted an amendment dated on April 1, 2011, that contained documents to support their view that their ANDA was substantially complete when filed. The submission consisted of documents that were previously submitted to FDA (responses to 483s, warning letters, copies of EIR letters, chemistry amendment with revised stability data), a CD with HPLC chromatograms and worksheets for the release testing and some of the stability testing, and copies of pages from equipment use logbooks.

Copies of pages from three HPLC equipment logbooks were submitted to show that Ranbaxy has a record of when they performed the dissolution testing even though they cannot locate the raw data. They also included an email chain from July 2002 discussing the dissolution testing.

3. Review of Bioequivalence Data

OGD's review paid particular attention to the in-vivo bioequivalence studies, and focused on the timing of events in the in-vivo bioequivalence studies as contained in Ranbaxy's original ANDA submission.[8] Nothing unusual was uncovered. Although Ranbaxy had not submitted long-term stability data from the frozen plasma samples in its original submission, it is not uncommon for firms to submit bioequivalence studies to OGD without long-term frozen plasma storage stability data. This has never been considered a reason to issue a Refuse to Receive letter to the ANDA

[7] Drug absorption from a solid dosage form depends on the release of the drug substance from the drug product, the dissolution or solubilization of the drug in the body, and the permeability across the gastrointestinal tract. Because of the critical nature of the first two of these steps, in vitro dissolution may be relevant to the prediction of in vivo performance.

[8] This review was prompted by the unusual fact that the first strength of Atorvastatin Calcium Tablets produced by Ranbaxy was not the 80 mg strength, i.e., the strength that is designated as the RLD in the Orange Book and thus the strength for which all in-vivo bioequivalence studies must be conducted. The RLD strength is usually the first produced by prospective applicants because this allows them to begin their in vivo studies at the earliest possible date.

sponsor. In the case of ANDA 076477, this information was requested by FDA in early 2003. The information was submitted by Ranbaxy and incorporated into the original bioequivalence review.

B. Office of Compliance Review

CDER's Office of Compliance (Compliance) also reviewed the sections of ANDA 076477 referenced below, submitted to FDA in August 2002, as well as a number of other documents including public sources of pharmacological data. The purpose of the review was to determine whether there was any evidence specific to ANDA 076477 to indicate that this application was affected by the same systemic concerns that were the basis for the AIP. Compliance provided the following information to OGD.

1. Review of Bioequivalence Data

The Bioequivalence Branch of the Division of Bioequivalence and Good Laboratory Practice Compliance in the Office of Scientific Investigation (OSI) compared information in the public domain to data submitted by Ranbaxy, to look for evidence suggesting that the sponsor had falsely used data from public sources as their own in ANDA 076477. The investigation focused on representation of pharmacokinetic (PK) data, such as plasma concentration vs. time profiles, and representative chromatograms for atorvastatin and/or metabolites that may have been duplicated in study reports submitted to the FDA by Ranbaxy.

Methods: A literature search was conducted using keywords such as: Lipitor, atorvastatin, Pfizer, original studies, and Pfizer authors. Databases including EMBASE, SciFinder, BIOSIS and Medline were searched for articles prior to 2002 using the above keywords. The article search was further narrowed down to human studies by excluding in-vitro and pre-clinical studies. Studies with clinical endpoints (e.g., LDL, VLDL and total cholesterol) were excluded.

A total of nine publications meeting the search criteria were identified. Chromatograms, PK data tables, and plasma concentration vs. time profiles (i.e., PK profiles) for atorvastatin and its metabolites (ortho-atorvastatin, para-atorvastatin) were compared to data Ranbaxy submitted in ANDA 076477.

Since multiple plasma drug concentration vs. time curves from the Ranbaxy studies were reported on the same graph, individual plots were isolated and then compared to analogous plots in the publications identified. Plots from different sources were evaluated for similarities or evidence suggesting possible data reproduction. Changes in scale and possible stretching/skewing of data were considered, as well as differences in measurement units.

The same approach was used to evaluate chromatograms submitted by Ranbaxy. Chromatograms for atorvastatin, its metabolites and internal standards in subject and quality control (QC) plasma samples were compared to those found in non-Ranbaxy publications.

Results: Comparison of PK tables and PK profiles found in Ranbaxy ANDA 076477 with data in the public domain did not identify any data that Compliance could determine to be a fraudulent duplication. Similarly, chromatograms in relevant publications did not exactly match those provided by Ranbaxy.

Conclusion: The review of currently available documentation failed to identify any improper use or falsification of data in ANDA 076477 submitted by Ranbaxy in August of 2002. It should be noted, however, that currently available tools (hardware, software) allow for duplication and falsification of data using hard to detect methods. This is a significant limitation to the above investigation.

2. Review of Chemistry Data

The Office of Manufacturing and Product Quality reviewed the chemistry data submitted in ANDA 076477 to determine if there was any evidence of fraudulent data. Compliance personnel compared chemistry information that was publically available at the time of the 2002 filing to the data in the ANDA submissions. The comparison showed that Ranbaxy's formulation was different from the innovator drug regarding some of the excipients and quantities of excipients. The drug substance synthetic sequenc (b) (4)

The dissolution data in the 2002 submission appears very similar to the Pfizer innovator product. This data did not show a high level of variability in dissolution. (b) (4)

Concern about the reliability of the 2002 dissolution arose because the dissolution data submitted in 2007 was not consistent with the dissolution data Ranbaxy had submitted in 2002. Although this difference in dissolution raised questions, it may be explained by the use of the laboratory scale batch to generate the later data. Hardness and particle size are two variables that could affect dissolution. Ranbaxy did not submit the batch production record for this batch. Ranbaxy's submission did not contain information regarding particle size. Ranbaxy did submit hardness data showing variability in hardness in the tablet. It is possible that variability in hardness led to a high degree of variability in the dissolution data. Because the differences in dissolution data have a reasonable explanation, these differences are not necessarily evidence of unreliable or fraudulent data.

The (b) (4) audit of the raw data for ANDA 076477 states that there is no raw data for dissolution testing. Ranbaxy has acknowledged that they have no electronic analytical data to support the chemistry data submitted prior to 2006. There is no requirement that a sponsor retain this data; nevertheless, the prudent manufacturer would have retained the information to support the data submitted in the application. Had Ranbaxy retained the raw data from its dissolution testing, FDA would have had additional information on which to assess the reliability of the submitted information.

3. Office of Compliance Conclusion

Compliance has not to date uncovered any evidence of falsification specific to this ANDA. The team conducting an investigation into Ranbaxy's conduct, which includes the Office of Criminal Investigations, has represented that its own review of issues related to Ranbaxy's Paonta Sahib facility has not uncovered evidence that the conduct addressed in the AIP letter was ongoing at the time ANDA 076477 was submitted in 2002.

IV. CONCLUSION

In light of the concerns raised about the reliability of data in certain Ranbaxy ANDAs, OGD (with the assistance of Compliance) has re-reviewed ANDA 076477 to assess whether it was substantially complete when it was submitted to FDA in 2002. We have concluded that, on its face, the Ranbaxy application was sufficiently complete to permit a substantive review, and that there is no evidence of fraud to support a conclusion that this determination is not justified. Ranbaxy should be notified that the 2002 determination that the application could be received for review as substantially complete remains unchanged.

Attachment: ANDA Checklist

cc: Deborah Autor, J.D., Director
Office of Compliance

ANDA CHECKLIST
FOR COMPLETENESS and ACCEPTABILITY of an APPLICATION

ANDA# 76-477 **FIRM NAME** RANBAXY LABORATORIES LTD

RELATED APPLICATION(S) ____ **FIRST GENERIC?** YES

DRUG NAME: ATORVASTATIN CALCIUM

DOSAGE FORM: TABLETS, 10 MG, 20 MG, 40 MG AND 80 MG

Electronic Submission: NA E-mail notification sent: NA Comments: NA

Random Assignment Queue: Random 2 Chem Team Leader: Smela, Mike PM: Chen, Peter

Labeling Reviewer: Payne, Angela Micro Review: NA PD study (Med Ofcr): NA

Letter Date AUGUST 19, 2002	**Received Date** August 19, 2002
Comments EC 4 YES **On Cards YES** **ALTERING AGENTS**	**Therapeutic Code 3021600 LIPID**
Methods Validation Package (3 copies) (Required for Non-USP drugs) YES	
Archival, and Review copies Field Copy Certification (Original Signature) YES	
Cover Letter YES	
Table of Contents YES	

ACCEPTABLE

Sec. I	**Signed and Completed Application Form (356h)** (Statement regarding Rx/OTC Status) RX YES, 80 mg is RLD	☒
Sec. II	**Basis for Submission** **NDA: 20-702** RLD: LIPITOR Firm: PFIZER ANDA suitability petition required? If yes, consult needed for pediatric study requirement.	☒

Sec. III	**Patent Certification** 1. Paragraph: IV 2. Expiration of Patent: JANUARY 8, 2017 3. SEPT. 24, 2009 U-161 4. MARCH 24, 2010 PED - U-161 5. DECEMBER 28, 2010 U-162 6. JUNE 28, 2011 U-162 7. NOVEMBER 11, 2014 U-213 8. MAY 11, 2015 U-213 9. JULY 8, 2016 10. Jan 8, 2017 11. JAN 19, 2013 12. JULY 19-2013 PED 13. A. Pediatric Exclusivity Submitted? B. Pediatric Exclusivity Tracking System checked? **Exclusivity Statement YES DEC 2, 2002, APRIL 22, 2005, JUNE 2, 2003 - CHECK EXCLUSIVY STATEMENT** **Exc. Statement. - doesn't list exclusivities, says exclusivity will expire on 4/22/05. Firm revised 10/09/02.**	☒
Sec. IV	**Comparison between Generic Drug and RLD-505(j)(2)(A)** 1. Conditions of use ok 2. Active ingredients ok 3. Route of administration ok 4. Dosage Form ok 5. Strength ok	☒
Sec. V	**Labeling** 1. 4 copies of draft (each strength and container) or 12 copies of FPL ok 2. 1 RLD label and 1 RLD container label ok 3. 1 side by side labeling comparison with all differences annotated and explained ok (b) (4)	☒

Sec. VI	**Bioavailability/Bioequivalence** 1. Financial certification (Form FDA 3454) and Disclosure stmt (Form 3455) (for BE studies only!) YES, Both a 3454 and 3455 were submitted. Asked firm to clarify. Clarification provided 10/09/02. 2. In Vivo Study Protocol(s): YES 3. In Vivo Study(ies): FED AND FAST 80 MG 4. Computer Disk Submitted: YES 5. Request for Waiver of In Vivo Study(ies): YES 10 MG, 20 MG, 40 MG 6. In Vitro Dissolution Data: YES 7. Formulation Data Same? (Comparison of all Strengths) (Opthalmics, Otics, Externals, Parenterals) YES 8. Paragraph IV bio study acceptable for filing YES 9. Lot numbers of products used in Bio-study 1200558 for 80 mg 10 mg 1201336 20 mg 1201334 40 mg 1201328 10.DSI inspection request needed? NA ☐ 1st Generic ☐ 1st study for site ☐ Other **E-mail notification to Bio PMs sent**	☒
Sec. VII	**Components and Composition Statements** 1. Unit composition and batch formulation ok 2. Inactive ingredients as appropriate YES	☒
Sec. VIII	**Raw Materials Controls** 1. **Active Ingredients** a. Addresses of bulk manufacturers Yes b. Type II DMF authorization letters or synthesis ok, DMF 16098 c. COA(s) specifications and test results from drug substance mfgr(s) ok d. Applicant certificate of analysis ok e. Testing specifications and data from drug product manufacturer(s) ok f. Spectra and chromatograms for reference standards and test samples ok g. CFN numbers 2. **Inactive Ingredients** a. Source of inactive ingredients identified ok b. Testing specifications (including identification and characterization) ok c. Suppliers' COA (specifications and test results) ok d. Applicant certificate of analysis ok	☒
Sec.IX	**Description of Manufacturing Facility** 1. Full Address(es)of the Facility(ies) ok 2. CGMP Certification ok 3. CFN numbers	☒
Sec. X	**Outside Firms Including Contract Testing Laboratories** 1. Full Address NA, none used 2. Functions NA 3. CGMP Certification/GLP NA 4. CFN numbers	☒

Sec. XI	**Manufacturing and Processing Instructions** 1. Description of the Manufacturing Process (including MicrobiologicalValidation, if Appropriate) ok 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified ok 10 mg - (b) (4) 20 mg - 40 mg - 80 mg - 3.If sterile product: Aseptic fill / Terminal sterilization NA 4.Filter validation (if aseptic fill) NA 5. Reprocessing Statement Yes	☒
Sec. XII	**In-Process Controls** 1. Copy of Executed Batch Record (Antibiotics/3 Batches if bulk product produced by fermentation) with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures), Batch Reconciliation and Label Reconciliation ok 10 mg - lot 1201336 (b) (4) 20 mg - lot 1201334 40 mg - lot 1201328 80 mg - lot 1200558 2. In-process Controls a. Sampling plans and test procedures ok b. Specifications and data ok	☒
Sec. XIII	**Container** 1. Summary of Container/Closure System (if new resin, provide data) ok 2. Components Specification and Test Data (Type III DMF References) ok 3. Packaging Configuration and Sizes ok 4. Container/Closure Testing ok 5. Source of supply and suppliers address ok	☒
Sec. XIV	**Controls for the Finished Dosage Form** 1. Sampling Plans and Test Procedures ok 2. Testing Specifications and Data ok 3. Certificate of Analysis for Finished Dosage Form ok 10 mg - lot 1201336 20 mg - lot 1201334 40 mg - lot 1201328 80 mg - lot 1200558	☒

Sec. XV	**Stability of Finished Dosage Form** 1. Protocol submitted ok 2. Post Approval Commitments ok 3. Expiration Dating Period 2 yr 4. Stability Data Submitted YES a. 3 month accelerated stability data YES b. Batch numbers on stability records the same as the test batch Conditions on the accelerated stability data are 25 C/60% RH - Spoke with firm, the sheets contain typographical errors. Corrected accelerated stability data sheets sent. (10/9/02) 10 mg - (b) (4) 20 mg - 40 mg - 80 mg -	☒
Sec. XVI	**Samples** - Statement of Availability and Identification of: 1. Drug Substance ok 2. Finished Dosage Form ok 3. Same lot numbers yes 10 mg - lot 1201336 Drug substance - 1197242, 1199895, 1199898 20 mg - lot 1201334 40 mg - lot 1201328 80 mg - lot 1200558	☒
Sec. XVII	**Environmental Impact Analysis Statement** orig sig.	☒
Sec. XVIII	**GDEA (Generic Drug Enforcement Act)/Other:** 1. Letter of Authorization (U.S. Agent [if needed, countersignature on 356h]) yes 2. Debarment Certification (original signature) YES 3. List of Convictions statement (original signature) yes	☒

Reviewing CSO/CST **Beth Fabian-Fritsch** **Date** **10/09/02**	**Recommendation:** ☒ **FILE** ☐ **REFUSE to RECEIVE**
Supervisory Concurrence/Date:	**Date:** 11-OCT-2002
Duplicate copy sent to bio: (Hold if RF and send when acceptable) Duplicate copy to HFD- for consult: Type:	

ADDITIONAL COMMENTS REGARDING THE ANDA:

10/09/02 - Spoke with Abha Pant and Scott Tomsky. They will fax the information to me and follow up with hard copy.

I asked for a revised exclusvity statement that acknowledges all of the exclusivities that exist for atorvastatin.
I also need clarification for the financial disclosure. Forms 3454 and 3455 were submitted for both studies.
Lastly, the accelerated stability data sheets list the conditions as 25 degrees Celsius and 60 % relative humidity.
I asked if this was a typographical error. It was confirmed. I asked the firm to revise the data sheets with the correct conditions. This will lead to less confusion with the reviewing chemist.

10/10/02 left message for Alka Pant.
I need the patent certification to be revised. The p III certification should contain the expiration dates of the patents.

OGD Form Revised 11/30/2001
MSWord Template revised: 8/7/2002

10/10/02: rec'd fax addressing the p III patent certification

Patent and Exclusivity Search Results from query on 020702 001.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Use Code	
020702	001	4681893	SEP 24,2009	U-161	
020702	001	4681893*PED	MAR 24,2010	U-161	- P III
020702	001	5273995	DEC 28,2010	U-162	
020702	001	5273995*PED	JUN 28,2011	U-162	P III
020702	001	5686104	NOV 11,2014	U-213	
020702	001	5686104*PED	MAY 11,2015	U-213	- P IV
020702	001	5969156	JUL 08,2016		
020702	001	5969156*PED	JAN 08,2017		- P IV
020702	001	6126971	JAN 19,2013		
020702	001	6126971*PED	JUL 19,2013		- P IV

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
020702	001	I-281	DEC 02,2002
020702	001	D-77	APR 22,2005
020702	001	PED	JUN 02,2003

Thank you for searching the Electronic Orange Book

Patent and Exclusivity Terms

Return to Electronic Orange Book Home Page

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE : September 4, 2002

TO : Director
Division of Bioequivalence (HFD-650)

FROM : Chief, Regulatory Support Branch
Office of Generic Drugs (HFD-615) 04-SEP-2002

SUBJECT: Examination of the bioequivalence study and request for waiver submitted with an ANDA for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg to determine if the application is substantially complete for filing and/or granting exclusivity pursuant to USC 355 (j)(5)(B)(iv).

Ranbaxy Laboratories Ltd has submitted ANDA 76-477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. The ANDA contains a certification pursuant to 21 USC 355 (j)(2)(A)(vii)(iv) stating that patent(s) for the reference listed drug will not be infringed by the manufacturing or sale of the proposed product. Also it is a first generic. In order to accept an ANDA that contains a first generic, the Agency must formally review and make a determination that the application is substantially complete. Included in this review is a determination that the bioequivalence study and request for waiver are complete, and could establish that the product is bioequivalent.

Please evaluate whether the request for study and request for waiver submitted by Ranbaxy on August 19, 2002 for its Atorvastatin Calcium product satisfies the statutory requirements of "completeness" so that the ANDA may be filed.

A "complete" bioavailability or bioequivalence study is defined as one that conforms with an appropriate FDA guidance or is reasonable in design and purports to demonstrate that the proposed drug is bioequivalent to the "listed drug".

BIOEQUIVALENCE CHECKLIST FOR APPLICATION COMPLETENESS
First Generic ANDA

ANDA# 76-477 FIRM NAME Ranbaxy Laboratories Limited

DRUG NAME ATORVASTATIN CALCIUM TABLETS, 10 MG, 20 MG, 40 MG and 80

DOSAGE FORM ORAL TABLETS

Requested by: _____
Chief, Regulatory Support Team, (HFD-615)

Summary of Findings by Division of Bioequivalence

☒ **Study meets statutory requirements**

☐ **Study does NOT meet statutory requirements**
Reason: This is the reason the study does not meet the requirements, they didn't send us anything!

☒ **Waiver meets statutory requirements**

☐ **Waiver does NOT meet statutory requirements**
Reason: This is the reason the waiver does not meet the requirements: they didn't send us anything either!!

RECOMMENDATION: ✔ COMPLETE ___ INCOMPLETE

Reviewed by:

Patrick Nwakama Date: 9/4/2002
Reviewer

Gur-Jai Pal Singh Date: 9/7/02
Team Leader

Dale P. Conner Date: 9/9/02
Director, Division of Bioequivalence

Item Verified:	Yes	No	Required Amount	Amount Sent	Comments
Protocol	X				FOR FASTING AND NON-FASTING STUDIES
Assay Methodology	X				
Procedure SOP	X				
Methods Validation	X				
Study Results Ln/Lin	X				
Adverse Events	X				
IRB Approval	X				
Dissolution Data	X				
Pre-screening of Patients	X				
Chromatograms	X				
Consent Forms	X				
Composition	X				All dosage strengths are (b) (4) (b) (4) :
Summary of Study	X				
Individual Data & Graphs, Linear & Ln	X				
PK/PD Data Disk (or Elec Subm)	X				
Randomization Schedule	X				
Protocol Deviations	X				
Clinical Site	X				
Analytical Site	X				
Study Investigators	X				
Medical Records	X				
Clinical Raw Data	X				
Test Article Inventory	X				

BIO Batch Size	X				(b) (4)
Assay of Active Content Drug	X				
Content Uniformity	X				TEST - 100% (RSD 2.3%) REF - 98.9%(RSD 1.4%)
Date of Manufacture	X				04/02
Exp. Date of RLD	X				06/03
BioStudy Lot Numbers	X				TEST - 1200558 REF. - 00371V
Statistics	X				
Summary results provided by the firm indicate studies pass BE criteria	X				
Waiver requests for other strengths / supporting data	X				10 MG, 20 MG & 40 MG

Additional Comments regarding the ANDA:

Created PDF Form:BIO CHKLST.PDF 05/15/02

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA L DOWNS
07/29/2011

MARTIN H Shimer
07/29/2011

KEITH O WEBBER
07/29/2011

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville, MD 20857

ANDA 076477

Ranbaxy, Inc.
Attention: Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited
600 College Road East
Princeton, NJ 08540

Dear Mr. Tomsky:

Ranbaxy submitted ANDA 076477 for atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg, and 80 mg to FDA on August 19, 2002. When it was submitted, the ANDA contained at least one paragraph IV certification to a patent for the listed drug.

OGD informed Ranbaxy by letter dated October 11, 2002 (attached), that the ANDA was received as acceptable for filing as of August 19, 2002. We recently reviewed the 2002 decision that ANDA 076477 was sufficiently complete to permit a substantive review. Based on this review, we currently have no basis to conclude that the 2002 decision to receive ANDA 076477 was in error. Therefore, there is no change to the determination that, as submitted in 2002, your application was sufficiently complete to permit a substantive review.

If you have questions, please contact Dave Read, Regulatory Counsel, Office of Generic Drugs, Center for Drug Evaluation and Research, at 240-276-9320.

Sincerely,

{See appended electronic signature page}

Keith O. Webber, Ph.D.
Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

Attachment

ANDA 76-477

OCT 11 2002

Ranbaxy Pharmaceuticals Inc.
U.S. Agent for: Ranbaxy Laboratories Limited
Attention: Abha Pant
600 College Road East
Princeton, NJ 08540

Dear Madam:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is made to the telephone conversation dated October 9, 2002 and your correspondences dated October 9 and 10, 2002.

NAME OF DRUG: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg

DATE OF APPLICATION: August 19, 2002

DATE (RECEIVED) ACCEPTABLE FOR FILING: August 19, 2002

You have filed a Paragraph IV patent certification, in accordance with 21 CFR 314.94(a)(12)(i)(A)(4) and Section 505(j)(2)(A)(vii)(IV) of the Act. Please be aware that you need to comply with the notice requirements, as outlined below. In order to facilitate review of this application, we suggest that you follow the outlined procedures below:

CONTENTS OF THE NOTICE

You must cite section 505(j)(2)(B)(ii) of the Act in the notice and should include, but not be limited to, the information as described in 21 CFR 314.95(c).

SENDING THE NOTICE

In accordance with 21 CFR 314.95(a):

- Send notice by U.S. registered or certified mail with return receipt requested to each of the following:

1) Each owner of the patent or the representative designated by the owner to receive the notice;

2) The holder of the approved application under section 505(b) of the Act for the listed drug claimed by the patent and for which the applicant is seeking approval.

3) An applicant may rely on another form of documentation only if FDA has agreed to such documentation in advance.

DOCUMENTATION OF NOTIFICATION/RECEIPT OF NOTICE

You must submit an amendment to this application with the following:

- In accordance with 21 CFR 314.95(b), provide a statement certifying that the notice has been provided to each person identified under 314.95(a) and that notice met the content requirements under 314.95(c).

- In accordance with 21 CFR 314.95(e), provide documentation of receipt of notice by providing a copy of the return receipt or a letter acknowledging receipt by each person provided the notice.

- A designation on the exterior of the envelope and above the body of the cover letter should clearly state "PATENT AMENDMENT". This amendment should be submitted to your application as soon as documentation of receipt by the patent owner and patent holder is received.

DOCUMENTATION OF LITIGATION/SETTLEMENT OUTCOME

You are requested to submit an amendment to this application that is plainly marked on the cover sheet "PATENT AMENDMENT" with the following:

- If litigation occurs within the 45-day period as provided for in section 505(j)(4)(B)(iii) of the Act, we ask that you provide a copy of the pertinent notification.

- Although 21 CFR 314.95(f) states that the FDA will presume the notice to be complete and sufficient, we ask that if you are not sued within the 45-day period, that you provide a letter immediately after the 45 day

period elapses, stating that no legal action was taken by each person provided notice.

- You must submit a copy of a court order or judgement or a settlement agreement between the parties, whichever is applicable, or a licensing agreement between you and the patent holder, or any other relevant information. We ask that this information be submitted promptly to the application.

If you have further questions you may contact Gregg Davis, Chief, Regulatory Support Branch, at (301) 827-5862.

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Peter Chen
Project Manager
(301) 827-5848

Sincerely yours,

Wm Peter Rickman
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KEITH O WEBBER
07/29/2011

BIOEQUIVALENCE AMENDMENT

ANDA 076477

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Pl.
Rockville, MD 20855-2810

APPLICANT: Ranbaxy Laboratories Ltd.

TEL: 609-720-5609

ATTN: Scott D. Tomsky

FAX: 609-514-9797

FROM: Nam Chun

FDA CONTACT PHONE: (240) 276-8782

Dear Sir:

This facsimile is in reference to the bioequivalence data submitted on August 19, 2002, pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg.

Reference is also made to amendments submitted on July 18, 2011.

The Division of Bioequivalence has completed its review of the submission(s) referenced above and has identified deficiencies which are presented on the attached **2** pages. This facsimile is to be regarded as an official FDA communication and unless requested, a hard-copy will not be mailed.

You should submit a response to these deficiencies in accord with 21 CFR 314.96. Your amendment should respond to all the deficiencies listed. **Facsimiles or partial replies will not be considered for review.** Your cover letter should clearly indicate:

Bioequivalence Response to Information Request

If applicable, please clearly identify any new studies (i.e., fasting, fed, multiple dose, dissolution data, waiver or dissolution waiver) that might be included for each strength. We also request that you include a copy of this **communication with your response.**
Please submit a copy of your amendment in an archival (blue) jacket and unless submitted electronically through the gateway, a review (orange) jacket. Please direct any questions concerning this communication to the project manager identified above.

Please remember that when changes are requested to your proposed dissolution methods and/or specifications by the Division of Bioequivalence, an amendment to the Division of Chemistry should also be submitted to revise the release and stability specification. We also recommend that supportive dissolution data or scientific justification be provided in the CMC submission to demonstrate that the revised dissolution specification will be met over the shelf life of the drug product.

SPECIAL INSTRUCTIONS:

*Effective **01-Aug-2010**, the new mailing address for Abbreviated New Drug Application (ANDA) Regulatory Documents is:*

Office of Generic Drugs
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855-2810

ANDAs will only be accepted at the new mailing address listed above. For further information, please refer to the following websites prior to submitting your ANDA Regulatory documents: Office of Generic Drugs (OGD): http://www.fda.gov/cder/ogd or Federal Register: http://www.gpoaccess.gov/fr/

Please submit your response in electronic format. This will improve document availability to review staff.

BIOEQUIVALENCE DEFICIENCY

ANDA:	076477
APPLICANT:	Ranbaxy Laboratories Ltd.
DRUG PRODUCT:	Atorvastatin Calcium Tablet 10, 20 , 40, and 80 mg

The Division of Bioequivalence (DBE) has completed its review of your submission(s) acknowledged on the cover sheet. The following deficiency has been identified:

The dissolution testing data as submitted in the current amendment for the test lots Nos. RI530902, RI540901, RI550901 and RI560901 (all with (b) (4) Active Pharmaceutical Ingredient (API)), using the modified dissolution method with a slower paddle speed of 50 rpm, are **incomplete**. The dissolution testing for these lots was conducted between June and July 2011, and these lots were manufactured in May 2009. Therefore, these lots were more than 24 months old at the time of testing. Unless you provide adequate additional stability data to support any expiry period beyond 24 months, these lots are considered expired and unacceptable for the testing at this time. In addition, we note that there was a discrepancy in the expiration dates reported by you for the test lots with (b) (4) API between the current amendment and previous submissions: The expiration date for each of (b) (4) API test products, 10, 20, 40, and 80 mg, Lot Nos. RI530902, RI540901, RI550901 and RI560901, was reported to be 4/2012 in the 07/18/2011 submission, whereas in the previous submission, dated 11/12/2010, the expiration date for each of these lots was correctly reported as 4/2011.

For the above reason, please repeat the dissolution testing on ***unexpired*** test batches of Atorvastatin Calcium Tablets (with (b) (4) API), 10, 20, 40, and 80 mg, using the following modified FDA method:

Medium: 0.05M Phosphate Buffer, pH 6.8 at 37^0C
Volume: 900 mL
USP Apparatus: II (Paddle) at 50 rpm

[NOTE: The method should use conventional USP II Vessels, and not (b) (4) ® Vessels.]

Sincerely yours,

{See appended electronic signature page}

Dale P. Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

DALE P CONNER
08/16/2011

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

August 26, 2011

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

ESG
BE AMENDMENT

Reference: **ANDA 076477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Bioequivalence Response to Information Request Dated August 16, 2011

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the bioequivalence deficiency letter dated August 16, 2011 and the subsequent telephonic discussion between Scott Tomsky of Ranbaxy with Nam Chun from OGD on August 24, 2011.

Ranbaxy is hereby submitting a complete **response** to the above referenced deficiency.

Ranbaxy is providing this submission in an electronic PDF format. The submission is approximately 2.0MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses with McAfee Virus Scan Enterprise 8.5., updated on August 26, 2011. Please note the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-5334 (email: pushpinder.singh@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission. Thankyou.

Sincerely,

Pushpinder

Pushpinder Singh
Regulatory Affairs Associate *(for)*
Scott D. Tomsky
US Agent for RanbaxyLaboratories Ltd.

August 19, 2011
ATORVASTATIN MEETING
9:00-10:30 am

Attendees:
Keith Webber
Dave Gill
Laxma Nagavelli
Haitao Li
Suhas Patankar
Bob West
Tim Ames
Robert Gaines
Leigh Ann Sears
Sivakumar Vaithiyalingam
Gil Kang
Cecilia Parise
Andre Raw
Robert Lionberger
Lawrence Yu

This group meeting was held to discuss the expedited Atorvastatin's current CMC status and their potential Tentative Approval status. The 5 ANDA's discussed were:

076477 (Ranbaxy)
077575 (Sandoz)
078773 (TEVA)
090548 (Apotex)
091226 (Mylan/Matrix)

As an action item, it was decided that since TEVA, Apotex, and Mylan ANDA's do not currently meet the USP Monograph; they will receive a communication next week to have the firm to petition USP for conversion of draft pending USP monograph to authorized USP monograph.

The possibility for in-use studies/simulated studies and comparing other in-use stability studies were discussed for the ANDA's.

At the conclusion of the meeting, it was decided more time to review the ANDA's were needed to have an answer to the ANDA statuses. A meeting will be held in 3 weeks to discuss the ANDA's cmc statuses.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEIGH A SEARS
08/26/2011

LAXMA R NAGAVELLI
08/26/2011

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

September 1, 2011

Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

ESG
GRATUITOUS AMENDMENT

Reference: **ANDA 076477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Gratuitous Amendment

Dear Sir/Madam:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the Amendment dated July 27, 2011 submitted in response to information request (quality deficiency) dated June 14, 2011.

In the above referenced quality deficiency, the Agency indicated that (b) (4) DMF (b) (4) had been found inadequate and that the ANDA deficiency response should be submitted only after the DMF deficiencies have been responded. However, based on a telephone conversation with Mr. Robert West, OGD on July 25, 2011, Ranbaxy submitted the ANDA deficiency response even though the DMF holder had not responded to the DMF deficiencies. Ranbaxy committed that if any changes to the API specifications or test methods are required based on the (b) (4) DMF response, all such changes will be made to the relevant documents in the ANDA, in a timely manner, prior to approval of the ANDA.

Through this Amendment, Ranbaxy would like to inform the Agency that (b) (4) responded to the DMF deficiencies on August 9, 2011. Based on the current specifications and test procedure for the API in (b) (4) DMF (b) (4), the specifications and test procedure for (b) (4) API at the drug product manufacturing site has also been revised. The revisions made to the API documentation are outlined below:

1) The following changes have been made to the API specifications:

Test	Existing Specifications	Revised Specifications
Specific Rotation	(b) (4)	
Any Other Individual Impurity (Previously Named: Individual unspecified/unknown impurity)		

2) A test for Specific Rotation has been added to the API test method.

The revised API specifications and test methods are provided in **Attachment 1** and **Attachment 2**, respectively.

At this time we would also like to confirm that the specifications for the API from both (b) (4) and Ranbaxy (Process I and Process II) proposed in the ANDA are in compliance with the current USP monograph for Atorvastatin Calcium.

Ranbaxy is providing this submission in an electronic PDF format. The submission is approximately 2.0 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses with McAfee Virus Scan Enterprise 8.5, updated on September 1, 2011. Please note the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-5362 (email: johanan.jeyaraj@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission. Thank you.

Sincerely,

Johanan Jeyaraj
Regulatory Affairs Associate *(for)*
Scott D. Tomsky
US Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

September 19, 2011

Keith Webber
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

ESG
AMENDMENT TO A PENDING
ANDA – CHEMISTRY

RE: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
AMENDMENT TO A PENDING ANDA – WITHDRAWAL OF MANUFACTURING SITE

Dear Dr. Webber:

Reference is made to our Abbreviated New Drug Application (ANDA #076477) for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

Reference is also made to the following amendments:-

- December 04, 2009 Amendment in which Ranbaxy proposed multiple changes including addition of Ohm Laboratories, Inc. as drug product manufacturing site as well as additional source of API, (b) (4) (DMF # (b) (4)).
- December 09, 2009 Amendment in which Ranbaxy submitted pilot and new pivotal bioequivalence studies on the drug product manufactured at Ohm Laboratories.
- November 12, 2010 Amendment for addition of a new source of API (Ranbaxy's Process I and Process II APIs (DMF # 24139) for the drug product manufactured at Ohm Laboratories.

By way of this amendment, Ranbaxy hereby withdraws the original drug product manufacturing facility – Ranbaxy Laboratories Limited's Paonta Sahib, India site - from this application.

Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency via the ESG. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.0.0, updated on September 19, 2011. Please note the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-8066 or Mr. Scott D. Tomsky at 609-720-5609 if you have any questions regarding this submission. Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

Date Requested: 9/19/2011

TO: Sam Haidar, Ph.D., R.Ph.
Acting Branch Chief for Bioequivalence and GLP
Division of Scientific Investigations
WO, Bldg 51, Room 5210

FROM: Dale P. Conner, Pharm D
Director, Division of Bioequivalence I, HFD-650

SUBJECT Biopharmaceutics Compliance Program 7348.001

REQUEST FOR INSPECTION:

Electronic Submission: Yes
Bio Study Status: Review complete and Inadequate
Priority: A

Due Date: 12/19/2011

ANDA No.	076477
Drug Product Name	Atorvastatin Calcium Tablets
Strength(s)	10 mg, 20 mg, 40 mg, and 80 mg
Applicant Name	Ranbaxy Laboratories Ltd., India
Address	Plot # GP-5, Sector 18, HSIDC, Old Delhi, Gurgaon Road, Gurgaon, 122015, Hariyana, India
Applicant's Point of Contact	Scott D. Tomsky, US Agent, 600 College Road East, Ranbaxy Inc., Princeton, NJ 08540
Contact's Telephone Number	609-720-5609
Contact's Fax Number	609-514-9797
Original Submission Date(s)	August 19, 2002 December 9, 2009 November 12, 2010 (additional API – Ranbaxy Process 1 and Process 2)
Submission Date(s) of Amendment(s) Under Review	**July 18, 2011** **(Additional Dissolution Data for all Strengths)**
Reviewer	S. P. Shrivastava, Ph.D.
Overall Review Result	**INADEQUATE**
Waiver Request Result	**INADEQUATE :** 10, 20 and 40 mg
Dissolution Testing Site	Ohm Laboratories, Inc.
Dissolution Testing Site Address	1385 Livingston Avenue, North Brunswick, New Jersey 08902

Reason for Inspection: For Cause
Comments: This is a for cause inspection request for the **Dissolution Testing Site**.

REASONS FOR A FOR CAUSE INSPECTION REQUEST and BACKGROUD INFORMATION

For the detailed reasons for the request, please see the draft bioequivalence review attached[1].

The For Cause inspection request reasons are mainly the following:

(1) The history of questionable dissolution data submitted for ANDA 76477 (Please see the review for more details).

(2) The fact that, based on the latest amendment dated August 26, 2011, the firm stated that it is planning to manufacture commercial batches using the Ranbaxy-Process II API as the primary source, instead of the (b) (4) API from which the biostudy test lot was manufactured, and therefore, the validity of these production batches, with respect to bioequivalence evaluation, is mainly hinged on the dissolution data comparing the biostudy test lot with (b) (4) API and the lots manufactured from the Ranbaxy Process-I API and Ranbaxy Process-II API: It is important to make certain that the dissolution testing for these lots was conducted appropriately and the latest dissolution data can be authenticated.

We recommend that an OSI inspection be requested immediately for dissolution testing conducted for the biostudy test lot as well as exhibit lots manufactured using the (b) (4) API (comparing them against the RLD product), and the test lots manufactured using the Ranbaxy Process-I and Ranbaxy Process-II APIs (comparing them against the RLD product), using both the previously FDA-recommended method as well as the modified FDA method used in the latest amendment.

[1] In order to expedite the inspection for the dissolution testing, the OSI inspection request is being made before the bioequivalence review is finalized. However, the content of the bioequivalence review is not expected to be significantly changed from the draft copy attached.

(b) (4)

35 PAGES HAVE BEEN WITHHELD IN FULL AS B4 (CCI/TS) and B5 (DRAFT) IMMEDIATELY FOLLOWING THIS PAGE

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HOAINHON N CARAMENICO
09/22/2011

HOAINHON N CARAMENICO on behalf of DALE P CONNER
09/22/2011

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

September 27, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on September 27, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

September 28, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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If there are any questions regarding this submission, please contact the undersigned at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

September 29, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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If there are any questions regarding this submission, please contact the undersigned at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

September 30, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

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If there are any questions regarding this submission, please contact the undersigned at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 03, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

TELEPHONE AMENDMENT FAX

ANDA 076477

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North II
7500 Standish Place, Room 150
Rockville, MD 20855-2773 (240-276-9327)

APPLICANT:
Ranbaxy Laboratories Limited
ATTN: Scott D. Tomsky

TEL: (609) 720-5609
FAX: (609) 514-9797

FROM: Haitao Li, PhD

FDA CONTACT PHONE: 240-276-8462

Dear Sir:

This facsimile is in reference to your abbreviated new drug application dated August 19, 2002, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Atorvastatin Calcium Tablets, 10mg, 20mg, 40 mg and 80 mg.

Reference is also made to the amendments dated July 27, 2011 and September 1, 2011.

The deficiencies presented below represent MINOR deficiencies identified during the ongoing review and the current review cycle will remain open. You should respond to these deficiencies with a "Telephone Amendment" with in ten working days. If you have questions regarding these deficiencies please contact the Project Manager, Leigh Ann Sears at 240-276-8453. Please submit documentation by fax to the attention of the Chemist at 240-276-8474. Please also submit official hard copies of any faxed documentation to the Document Room.

SPECIAL INSTRUCTIONS:

Please submit your response in electronic format.
This will improve document availability to review staff.

CHEMISTRY COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 076477 APPLICANT: Ranbaxy Laboratories Limited

DRUG PRODUCT: Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

The deficiencies presented below represent Telephone deficiencies.

A. Deficiencies:

1. Please address the following and provide a revised drug substance specification and updated certificate of analysis for the API sourced from (b) (4)

   a. The PSD specification for the API should be inline with DMF holder's specification.

2. Please revise the blend uniformity assay in-line with the drug product release assay.

3. Please revise the assay range to (b) (4) % for drug product release and stability specifications or propose range based on comparison to RLD. And also please provide revised drug product release and stability specifications and updated batch analysis data.

4. Please provide commitment that no drug product made from amorphous Atorvastatin Calcium API is marketed and all references made to this material are withdrawn.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HAITAO LI
10/03/2011

LAXMA R NAGAVELLI
10/03/2011

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 04, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 04, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 5, 2011

Keith Webber
Office of Generic Drugs, CDER, FDA
Document Control Room
Metro Park North VII
7620 Standish Place
Rockville, MD 20855

ESG
TELEPHONE AMENDMENT

Reference: **ANDA 076477**
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Response to the Telephone Deficiencies received on September 29, 2011

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 for Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg. Reference is also made to the Telephone Deficiencies received from the Agency on September 29, 2011.

At this time Ranbaxy is submitting a **complete response** to the above referenced FDA correspondence.

Ranbaxy is providing this submission in an electronic PDF format. The submission is approximately 3.5 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses with McAfee Virus Scan Enterprise 8.5, updated on October 5, 2011. Please note the non-repudiation letter for Ranbaxy employees was submitted to the Agency on March 16, 2010.

Please contact the undersigned at 609-720-8017 (email: brett.johnson@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (email: scott.tomsky@ranbaxy.com) if you have any questions regarding this submission. Thank you.

Sincerely,

Brett Johnson

Brett Johnson
Senior Manager, Regulatory Affairs *(for)*
Scott D. Tomsky
US Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 05, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
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Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 05, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8017 (e-mail: brett.johnson@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

Brett Johnson

Brett Johnson
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 06, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 07, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 10, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 10, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 11, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 12, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 12, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST. PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 13, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 13, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 14, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 14, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 17, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

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As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 17, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST. PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 18, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 18, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 19, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 19, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 20, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 20, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 21, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

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As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 21, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 24, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: October 24, 2011

FROM: Keith O. Webber, Ph.D., Deputy Director
Office of Pharmaceutical Science
Center for Drug Evaluation and Research

SUBJECT: Approvability of ANDA 076477

TO: ANDA 076477 - Atorvastatin Calcium Tablets
Ranbaxy Pharmaceuticals Ltd. (Ranbaxy)

ANDA 076477 for Ranbaxy's atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg, and 80 mg, uses an active pharmaceutical ingredient (API) that is a crystalline form of atorvastatin calcium. The reference listed drug, Lipitor of Pfizer Inc., also uses a crystalline form. (b) (4)

There is a pending citizen petition submitted by Pfizer (Docket No. FDA-2005-P-0315; formerly Docket No. 2005P-0452) that raises issues with respect to the API. We have carefully reviewed Pfizer's petition and determined that the issues it raises pertain only to amorphous forms of atorvastatin calcium API. Ranbaxy's product is therefore unaffected by the petition and FDA can approve ANDA 076477 prior to issuance of a response to the citizen petition.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PATRICIA L DOWNS
10/24/2011

KEITH O WEBBER
10/24/2011

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 25, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 26, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 26, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 27, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 28, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on October 28, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

October 31, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
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Patent Amendment– Revised Patent Certification

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 01, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on November 01, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC. 600 COLLEGE ROAD EAST PRINCETON, NJ 08540 PHONE (609) 720-9200 FAX (609) 720-1155

November 02, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

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Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 03, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 04, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

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Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 07, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 08, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 09, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 10, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 11, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 07, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 15, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 16, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 17, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 18, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 21, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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Sincerely,

S Manan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 22, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

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Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 23, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
PATENT AMENDMENT

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Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

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November 25, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
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Rockville, MD 20855

ESG
PATENT AMENDMENT

Reference: ANDA 076477
Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg
Patent Amendment– Revised Patent Certification

Dear Dr. Webber:

Reference is made to Ranbaxy Laboratories Limited's pending ANDA 076477 Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg and 80 mg.

By way of this amendment, Ranbaxy is hereby submitting a revised patent certification to include the newly listed patent, U.S. Patent No. 8,026,376, for the reference listed drug, Pfizer Inc.'s Lipitor® (Atorvastatin Calcium) Tablets (NDA 020702). The revised patent certification is located in **Attachment 1**.

As per FDA's special instructions, Ranbaxy is providing this submission in an electronic PDF format. This submission is approximately 1 MB in size and is being submitted to the Agency through the FDA's electronic submission gateway. The contents of the submission have been scanned for viruses using McAfee VirusScan Enterprise 8.5 updated on November 25, 2011.

If there are any questions regarding this submission, please contact the undersigned at 609-720-8017 (e-mail: brett.johnson@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

Brett Johnson

Brett Johnson
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 28, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
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If there are any questions regarding this submission, please contact the undersigned at 609-720-8066 (e-mail: sameer.manan@ranbaxy.com) or Scott D. Tomsky at 609-720-5609 (e-mail: scott.tomsky@ranbaxy.com). Thank you.

Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 29, 2011

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Sincerely,

SManan

Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

RANBAXY

RANBAXY INC., 600 COLLEGE ROAD EAST, PRINCETON, NJ 08540. PHONE: (609) 720-9200 FAX: (609) 720-1155

November 30, 2011

Keith Webber
Office of Generic Drugs
Center for Drug Evaluation and Research
Food and Drug Administration
MetroParkNorth-VII
7620 Standish Place,
Rockville, MD 20855

ESG
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Sincerely,

SManan
Sameer Manan
Senior Manager, Regulatory Affairs (*for*)
Scott D. Tomsky
U.S. Agent for Ranbaxy Laboratories Limited

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 30, 2011

FROM: Dave Read
Regulatory Counsel, Office of Generic Drugs (HFD-600)

TO: ANDA 076477

SUBJECT: Telecon

At the request of Rick Blumberg (OCC) and Elizabeth Dickinson (OCC), at about 2 pm on Nov. 29, Dave Read and Keith Webber, Ph.D. (Acting Director, Office of Generic Drugs) called Carmen Shepard and Kate Beardsley, attorneys for the applicant Ranbaxy.

We discussed the recently completed inspection at the Toansa API facility in India. They were well aware of it and had read the Form 483. Keith explained that the review of the ANDA was complete, and but for resolution of the Toansa inspection results, the ANDA was satisfactory. They said that Ranbaxy would be submitting a response to the 483 today.

We acknowledged the significance of tomorrow, which is the widely anticipated launch date of generic atorvastatin. We said that it did not appear that resolution of the Toansa inspection results could be reached by tomorrow because multiple parties are involved, and we did not venture to guess when resolution would be reached.

Carmen and Kate raised the matter of using only the (b) (4) API site. We explained that we don't approve parts of ANDAs, and if Ranbaxy elected to use only the (b) (4) site, Ranbaxy would have to submit an amendment withdrawing the Toansa site. (We said Ranbaxy could later supplement to add the Toansa site, although they raised the question of whether such a supplement would be reviewed under the terms of the AIP.) They said that it would likely result in the loss of (b) (4) to Ranbaxy if the Toansa material was not available.

They asked whether, if they were to submit such an amendment immediately, the ANDA could be approved tomorrow. We said it was possible, but we could not guarantee it.

The conversation concluded with them saying they would immediately contact Ranbaxy management and get back to us later today. By e-mail later that day, they said they would not be calling us back on the 29th.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

LEIGH A SEARS
11/30/2011

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: November 30, 2011

FROM: Keith O. Webber, Ph.D., Deputy Director, Office of Pharmaceutical Science, CDER

TO: ANDA 076477

SUBJECT: Concerns that Gave Rise to the Application Integrity Policy; OGD's Review of ANDA 076477

The purpose of this memorandum is to document an important aspect of the Office of Generic Drug's (OGD's) review of Ranbaxy Laboratories Limited's (Ranbaxy's) abbreviated new drug application for atorvastatin calcium tablets, 10 mg, 20 mg, 40 mg, and 80 mg (ANDA 076477). OGD's review concludes not only that ANDA 076477 meets the approval requirements, but also that the data and information submitted do not reveal irregularities that would cause OGD to question the ANDA's reliability. This memorandum focuses on the latter and has been prepared in consultation with Vilayat A. Sayeed, Ph.D. (OGD's Director, Chemistry Division III), Dale Conner, Pharm. D. (Director, Division of Bioequivalence, OGD), and William P. Rickman, Director, Division of Labeling and Program Support, OGD).

In a letter dated February 25, 2009, CDER invoked the Application Integrity Policy (AIP) against Ranbaxy's applications containing data developed at Ranbaxy's Paonta Sahib facility. Ranbaxy's ANDA 076477 (atorvastatin calcium, 10, 20, 40, and 80 mg) is among the (b) (4) ANDAs listed in an attachment to the February 25, 2009 AIP letter; however, it was not among the examples of specific applications with data irregularities cited in the AIP letter. In a letter sent to Ranbaxy on May 16, 2011, CDER's Director, Dr. Woodcock, informed Ranbaxy that CDER would review ANDA 076477 under an exception to the AIP. This letter was preceded by a May 11, 2011, memorandum from Deborah Autor (Director, CDER's Office of Compliance) to Dr. Woodcock, addressing the question of whether OGD should proceed with review of Ranbaxy's ANDA 076477 (May 11, 2011, memorandum). The May 11, 2011 memorandum sets forth the complicated circumstances related to the ANDA and the reasons supporting its review.

Factors suggesting that Ranbaxy's originally-filed 2002 ANDA 076477 may not be implicated by the specific reliability concerns associated with other Ranbaxy ANDAs containing data developed at Paonta Sahib are documented elsewhere and not duplicated here.[1]

[1] See e.g., May 11, 2011 memorandum and July 29, 2011 memorandum from Martin Shimer, Branch Chief, Regulatory Support Branch, OGD, to ANDA 076477 -- Ranbaxy Laboratories Limited, Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg, Subject: Re-examination of ANDA 076477 for Substantial/Sufficient Completeness (July 29, 2011, memorandum).

As noted in the May 11, 2011 memorandum, Ranbaxy submitted, in December 2009, a major amendment to ANDA 076477. This amendment proposed a substantially modified product from that proposed in Ranbaxy's original 2002 ANDA. Most significantly, Ranbaxy proposed a product that would be manufactured in Ranbaxy's Ohm Laboratories (New Brunswick, New Jersey) facility, as opposed to the Paonta Sahib facility in India. The active pharmaceutical ingredient (API) would be obtained from (b) (4) This API is the crystalline form of atorvastatin calcium, as opposed to the amorphous form of the API from Ranbaxy's Toansa (India) facility proposed in the 2002 submission. FDA inspected (b) (4), at which the API for this ANDA is manufactured, from (b) (4) and on (b) (4) the Office of Compliance entered into the Establishment Evaluation Systems (EES) an overall recommendation of "Acceptable" for this facility. An "Acceptable" recommendation indicates that the Office of Compliance does not have significant cGMP concerns. Qualitative and quantitative changes to the formulation were proposed that: (a) differed from the original 2002 ANDA; and (b) were nearly identical to that of Lipitor. As appropriate with such a significant reformulation, this amendment included new bioequivalence studies. In November 2010, Ranbaxy submitted another major amendment proposing to include its Toansa (India) facility as an additional source of API (crystalline atorvastatin calcium).[2] FDA conducted a pre-approval inspection for this ANDA at Ranbaxy's Toansa (India) facility from November 21-25, 2011, and on November 30, 2011, the Office of Compliance entered into EES an overall recommendation of "Acceptable" for this facility.

The May 11, 2011 memorandum stated that:

> "[T]o ensure data reliability of the new Ranbaxy submissions from Ohm Laboratories, we need to determine that they are free of the concerns which gave rise to the AIP. Among the factors to be assessed are the following:
>
> - Have data from Paonta Sahib or other facilities with significant [current good manufacturing practices] cGMP or data reliability concerns been included in the Ohm Laboratories submission?
> - Have data "migrated" from earlier submissions into the amendments?
> - Does the application adequately address known areas of concern, including dissolution, stability, other analytical data, and exhibit batch production records?"

Below, this memorandum summarizes OGD's assessment of the Ohm Laboratories submissions in light of each of the above concerns.

- Have data from Paonta Sahib or other facilities with significant cGMP or data reliability concerns been included in the Ohm Laboratories submission?

[2] OGD initially, and even upon re-examination, determined that Ranbaxy's ANDA 076477 was substantially complete when it was submitted in 2002. See July 29, 2011 memorandum. As noted in the July 29, 2011 memorandum, it is "common for ANDA applicants - including those eligible for 180-day exclusivity - to amend applications multiple times before approval." Id. at 6.

Ranbaxy's ANDA does not include data generated at facilities with significant cGMP concerns. Ranbaxy "withdrew" the Paonta Sahib manufacturing site from the ANDA. See November 4, 2011 Chemistry Review at 14. Based on a pre-approval inspection conducted from September 28-30 and October 3, 2011, at Ohm Laboratories's New Brunswick, NJ, facility, CDER's Office of Compliance entered into EES on October 25, 2011, an overall recommendation of "Acceptable" for such facility, which is the manufacturing site of Ranbaxy's proposed product. This product will be packaged at Ohm Laboratories's North Brunswick, NJ, site. FDA most recently inspected Ohm Laboratories's North Brunswick, NJ, site in July 2010, and following that inspection, the Office of Compliance entered an "Acceptable" recommendation for that facility into EES.

OGD's review did not reveal that data from the Paonta Sahib manufacturing site has been included in the Ohm Laboratories submissions for the reasons noted under the bullet below. OGD's review confirms, to the extent possible, that the data and information in the Ohm Laboratories submissions comes from Ranbaxy's proposed atorvastatin calcium product and not from other sources.

As evidence of the scrutiny applied to this ANDA, the bioequivalence reviews document a few instances where reviewers noted certain discrepancies and followed up with the applicant appropriately. See e.g., October 5, 2011 Bioequivalence Review at 7-8 (discrepancy regarding expiration dating) and May 4, 2011 Bioequivalence Review (unexpected bioequivalence values). OGD carefully evaluated the applicant's responses and considered them to be reliable and to adequately address the concerns raised. Consistent with the normal review process, the reviewers were able to either independently evaluate the data or obtain additional data from Ranbaxy as needed. The information submitted is consistent with the type of information that would be expected for ANDAs generally, and does not reveal or suggest the type of irregularities that would lead OGD to question the reliability of the ANDA.

As a precautionary measure, the agency reviewed the previous inspections conducted of the following sites that had been used by Ranbaxy in generating data submitted to meet the bioequivalence requirement for Ranbaxy's atorvastatin ANDA: Cetero Research (clinical site), (b) (4) (analytical site), as well as an inspection of Ohm Labs (dissolution testing site) requested and conducted specifically as part of the review of ANDA 076477. See e.g., Bioequivalence Reviews dated May 4, 2011, and October 25, 2011. These additional steps were taken to evaluate the reliability of data and information submitted and the inspection results were evaluated. See e.g., Bioequivalence Review dated May 4, 2011. Nothing from these inspections led OGD to question the reliability of the data and information in the ANDA.

- Have data "migrated" from earlier submissions into the amendments?

Based on OGD's review of ANDA 076477, there is no indication that data have "migrated" from earlier submissions into the amendments. In the case of bioequivalence data, the old and new studies were compared and the respective data sets are very different. Precautionary measures such as clear verification of the source of data and information have been taken to ensure that Ranbaxy is not relying on the original Paonta Sahib manufacturing site or the information related to the original amorphous form of the API.

First, the documents plainly state the source of the data in the submissions as being Ohm Laboratories. In addition, there are Drug Master Files (DMFs) for the APIs that have been incorporated by reference into the ANDA, i.e., (b) (4) API (DMF (b) (4) and Ranbaxy's Toansa Process I and Process II APIs (DMF 24139). The technical data on the acceptability of the APIs are available in the respective DMFs. See November 4, 2011 Chemistry Review at 14.

Second, in the communication dated December 4, 2009, Ranbaxy: (1) changed the API from amorphous form to crystalline form ((b) (4) API, DMF (b) (4)); (2) changed the site of manufacture from Paonta Sahib, India, to Ohm Laboratories, New Brunswick, New Jersey; and (3) provided new chemistry, manufacturing, and controls (CMC) data and bioavailability/ bioequivalence (BA/BE) study to support this change. In the amendment dated November 12, 2010, Ranbaxy added an alternate source of crystalline API (Ranbaxy Toansa site, DMF 24139) and provided all the relevant CMC and dissolution data to support the new API supplier. A close inspection of these data does not call into question Ranbaxy's representation that the data provided to the application originated from Ohm Laboratories. There is no evidence to suggest that data has "migrated" from earlier submissions. We also note that, as a scientific matter, the data and information originally submitted would not be useful to support the changes corresponding to the new amendments, making it unlikely that the applicant would attempt to "migrate" the data.

Third, in the communication dated September 19, 2011, Ranbaxy "withdrew" the Paonta Sahib site from the application and, in the amendment dated October 5, 2011, Ranbaxy "withdrew" all data and references for product using the amorphous form of the API atorvastatin calcium and made a commitment that drug product made using the amorphous form of the API would not be introduced in the market.

- Does the application adequately address known areas of concern, including dissolution, stability, other analytical data, and exhibit batch production records?"

OGD reviews "dissolution, stability, other analytical data, and exhibit batch production records" as a standard part of the ANDA review process. OGD expects ANDA applicants to address these areas adequately before approval. The reviewers were acutely aware of the sensitivity of this ANDA, not only because of the AIP concern, but also because this is the first generic product for what most regard as the largest blockbuster drug ever. This ANDA received three levels of review in the Chemistry division and no irregularities were noted. Based on the review of the data submitted to the application and on the clean inspectional records, the Director of Chemistry Division III is fully satisfied that these areas of concern have been adequately addressed in the ANDA. The approval recommendation is based on the data provided from the batches made at Ohm Laboratories, New Brunswick, NJ.

In sum, OGD's review of Ranbaxy's ANDA 076477 (including the December 2009 and November 2010 amendments) and inspection of facilities referenced in the ANDA does not reveal irregularities that would cause OGD to question the reliability of the ANDA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

CECELIA M PARISE
11/30/2011

KEITH O WEBBER
11/30/2011

ROUTING SHEET

☒ **APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)** ☐ **CGMP**

Division: III	**Team:** 34	**PM:** Leigh Ann Sears

Electronic ANDA: Yes ☒ No ☒

ANDA #:076477
Firm Name:Ranbaxy Laboratories Limited
ANDA Name:Atorvastatin Calxium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg
RLD Name:Lipitor Tablets (NDA #20702 by Pfizer)

Electronic AP Routing Summary Located:

V:\Chemistry Division III\Team 34\Electronic AP Summary\ 76477 AP-TA APRV ROUT SUMRY.doc

AP/TA Letter Located:

V:\Chemistry Division III\Team 34\Final Version For DARRTS Folder\APPROVAL LETTERS\76477_AP.doc

Project Manager Evaluation: **Date: 10/25/2011 Initials:** LS

☐ Previously reviewed and tentatively approved --- Date _____
☐ Previously reviewed and CGMP Complete Response issued -- Date _____

Original Rec'd date 8/19/2002	Date of Application 8/19/2002	Date Acceptable for Filing 8/19/2002
Patent Certification (type) PIV	Date Patent/Excl. expires '104, '156, and '971 '104-MOU- expires 2015, 2017, and 2013	Citizens' Petition/Legal Case? Yes☐ No ☒ (If YES, attach email from PM to CP coord)
First Generic Yes ☒ No ☐ **DMF#:** _____ (provide MF Jackets)	Priority Approval (Top 100, PEPFAR, etc.)? Yes ☒ No ☐ Comment: Prepared Draft Press Release sent to Cecelia Parise Yes ☐ No ☒ Date: Cec prepared press release	
☐ Suitability Petition/Pediatric Waiver	Pediatric Waiver Request: Accepted ☐ Rejected ☐ Pending ☐	

EER Status: ☐ Pending ☒ Acceptable ☐ OAI *EES Date Acceptable: 11/30/2011* ☐ Warning Letter Issued; Date:
Has there been an amendment providing for a Major change in formulation since filling? Yes ☐ No ☐ Comment:
Date of Acceptable Quality (Chemistry) 10/21/2011 Addendum Needed: Yes ☐ No ☐ Comment:
Date of Acceptable Bio 10/25/2011 Bio reviews in DARRTS: Yes ☐ No ☐ (Volume location:)
Date of Acceptable Labeling 7/29/2011 Attached labeling to Letter: Yes ☐ No ☐ Comment:
Date of Acceptable Sterility Assurance (Micro) n/a

Methods Val. Samples Pending: Yes ☐ No ☒**;** Commitment Rcvd. from Firm: Yes ☐ No ☐

Post Marketing Agreement (PMA): Yes ☐ No ☒ (If yes, email PM Coordinator) Comment:

Modified-release dosage form: Yes ☐ No ☒ (If yes, enter dissolution information in Letter)

Routing:

☒ Labeling Endorsement, Date emailed: 10/31/2011 REMS Required: Yes ☐ No ☒ REMS Acceptable: Yes ☐ No ☐

☒ Regulatory Support

☒ Paragraph 4 Review (Dave Read, Susan Levine), Date emailed: 10/31/2011

☒ Division

☐ 1st Generic Review

☒ Bob West / Peter Rickman
☐ Keith Webber

☒Filed AP Routing Summary in DARRTs	☒Notified Firm and Faxed Copy of Approval Letter	☒ Sent Email to "CDER-OGDAPPROVALS" distribution list

OGD APPROVAL ROUTING SUMMARY

1. ***Regulatory Support Branch Evaluation***

Martin Shimer **Date: 10/28/2011**

Chief, Reg. Support Branch **Initials:** MHS

Contains GDEA certification: Yes ☒ No ☐	Determ. of Involvement? Yes ☐ No ☒
(required if sub after 6/1/92)	Pediatric Exclusivity System
	RLD = Lipitor NDA# 20-702 Date Checked Granted Nothing Submitted ☐ Written request issued ☐ Study Submitted ☐
Patent/Exclusivity Certification: Yes ☒ No ☐ If Para. IV Certification- did applicant: Notify patent holder/NDA holder Yes ☒ No ☐ Was applicant sued w/in 45 days:Yes ☒ No ☐ Has case been settled: Yes ☒ No ☐ Date settled: Is applicant eligible for 180 day	
Generic Drugs Exclusivity for each strength: Yes ☒ No ☐	
Date of latest Labeling Review/Approval Summary _____	
Any filing status changes requiring addition Labeling Review Yes ☐ No ☒	

Type of Letter:
☒ APPROVAL ☐ TENTATIVE APPROVAL ☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH) ☐ CGMP
☐ OTHER:

Comments:ANDA submitted on 8/19/2002, BOS=Lipitor NDA 20-702, PIII to '893 and '995, PIV to '104, '156 and '971 patents. ANDA ack for filing with PIV for the 10 mg, 20 mg, 40 mg and 80 mg strengths on 8/19/2002 (LO dated 10/11/2002). Patent Amendment rec'd on 10/11/12-PIII to '893 and '995, PIV to '104, '156 and '971. Patent Amendment rec'd on 1/9/2003-change cert on the '893 patent from PIII to PIV. Patent Amendment rec'd on 2/11/2003-RR from Pfizer in NY, NY signed and dated 1/27/2003. Patent Amendment rec'd on 2/20/2003-change from PIII to PIV on the '995. Patent Amendment rec'd on 9/16/2003-PIV to the '729. Patent Amendment rec'd on 3/3/2003-CA 03-209 filed in the D of DE on 2/21/2003 for infringement of the '893. Patent Amendment rec'd on 3/10/2003-RR from Pfizer in NY, NY signed and dated 3/3/2003. Patent Amendment rec'd on 3/10/2003-RR from Pfizer Inc. in NY, NY signed and dated 1/15/2003-this is documentation of notice for the '893. Patent Amendment rec'd on 3/21/2003-not sued within 45 days on the '104, '156 and '971 patents. Patent Amendment received on 4/18/2003-CA 03-374 filed in the D of DE on 4/11/2003 for infringement of the '995 and CA 03-375 filed in the D of DE on 4/11/2003 for infringement of the '893. Patent Amendment rec'd on 6/18/2003-Letter from Connolly Bove…CA 03-209 JJF filed in the D of DE on 2/21/2003 for infringement of the '893 patent. Patent Amendment rec'd on 3/12/2003-RR from Pfizer Inc. in NY, NY signed and dated 3/6/2003-this notice was for the '995 patent.
Patent Amendment rec'd on 8/19/2003-PIV to the '729 again 8/20/2003, 8/21, 8/22, 8/25(X2), 8/26, 8/27, 8/28, 8/29, 9/2, 9/3, 9/4, 9/5, 9/8, 9/9, 9/10, 9/11, 9/12, 9/15, 9/17, patent amendment rec'd on 10/23-w/d certs to the '729.
Patent Amendment rec'd on 1/19/2006-Final Judgment Order in CA 03-209 JJF finding that Ranbaxy has infringed claims 1-4 and 8-9 of the '893 patent and also claim 6 of the '995 patent.
Patent Amendment rec'd on 4/5/2006-PIV to the '893, '995, '104, '156 and '971 patents
Patent Amendment rec'd on 3/17/2009-PIV to the '893, '995, '104, '156, '971 and '667, submitted again on 3/18, again 3/19.
Patent Amendment rec'd on 5/15/2009-notice sent to Pfizer in NY, NY on 3/18/2009, this is notice for the '667, RR from Pfizer in NY, NY signed and dated 3/20/2009
Patent Amendment rec'd on 2/15/2011-Letter from Zuckerman Spaeder on behalf of Ranbaxy requesting that Ranbaxy remain eligible for 180 day exclusivity.
Patent Amendment rec'd on 3/22/2011-Letter from Hyman Phelps on behalf of Mylan responding to Ranbaxy's 2/14/2011 letter.
Patent Amendment rec'd on 4/4/2011-
Patent Amendment rec'd on 6/3/2011-cover letter indicates that D of DE decision for CA 03-209 was appealed to the CAFC in December of 2006 (06-1179). This appeal was settled on 6/17/2008 with the settlement indicating that Ranbaxy could launch on 11/30/2011. This amendment also contained patent certs: PIV to '995, '104, '156, '971 and '667-not certifications had changed from previous cert.
Patent Amendment rec'd on 6/14/2011-RR from Pfizer in NY, NY with notice delivered on 6/8/2011.
Patent Amendment rec'd on 7/29/2011-sponsor states that they were not sued within 45 day in relation to their 6/14/2011 certs.
Patent Amendment rec'd on 9/28/11-PIV to '376(unlisted), again 9/29, 9/30, 10/3, 10/4, 10/5, 10/6, 10/7, 10/11, 10/12, 10/13, 10/14, 10/17, 10/18, 10/19, 10/20, 10/21, 10/24, 10/25, 10/26, 10/27

Memo dated 10/24/11-OGD may approve the Ranbaxy ANDA without responding to CP 2005P-0315.

Summary-Over the long course of the review for this ANDA Ranbaxy has consistently challenged all listed patents with PIV certifications. Initially Ranbaxy provided PIII certs to the '893 and '995 but changed these certifications within 6 months of the submission date of their ANDA to PIV certs. Ranbaxy was sued on the '893 and '995 patents, lost their litigation in the D of DE and then appealed this decision. During the pending appeal, Ranbaxy and Pfizer entered into a settlement agreement for these drug products. At this point, the only remaining patents which are unexpired are the '104, '156 and '971 patents. Ranbaxy provided PIV certs to each of these three patents in their original ANDA submission and was not sued by Pfizer. These are also the patents as to which Ranbaxy's continued eligibility are associated since exclusivity for these four drug products are governed by our pre-MMA rules. It is not necessary for OGD to obtain a copy of the dismissal order for the CAFC appeal (the case would have been closed upon entry of the settlement agreement) since the appeal addressed the '893 and '995 patents which are now expired.

ANDA is eligible for immediate Full Approval with an award of pre-MMA 180 day exclusivity. The approval letter must grant Ranbaxy 180 day exclusivity related to PIV certs on the '104, '156 and '971 patents.

2. ***Labeling Endorsement***

Reviewer, T. Vu:
Date10/31/2011
InitialsLS for TV

Labeling Team Leader, John Grace:
Date10/31/2011
InitialsLS for JG

REMS required?
☐Yes ☒No

REMS acceptable?
☐Yes ☐No ☒n/a

Comments:
From: Grace, John F
Sent: Monday, October 31, 2011 12:47 PM
To: Vu, Thuyanh (Ann); Sears, Leigh Ann
Subject: RE: Labeling sign-off for ANDA 076477 (Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg by Ranbaxy)
concur.

John F. Grace
Team Leader, Labeling Review Team 1 (HFD-613)
FDA/CDER/OPS/OGD/DLPS/LRB/LRT1
7520 Standish Place, MPN1
Rockville, MD 20855
(240)276-8985
john.grace@fda.hhs.gov

From: Vu, Thuyanh (Ann)
Sent: Monday, October 31, 2011 12:47 PM
To: Sears, Leigh Ann; Grace, John F
Subject: RE: Labeling sign-off for ANDA 076477 (Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg by Ranbaxy)
Please sign off for me. I checked OB, Drugs@FDA and DAARTS.

As an FYI, OND has a labeling supplement for the RLD they are working on. I'm hoping that OND will approve the labeling supplement after the November 7 goal date.

Ann

From: Sears, Leigh Ann
Sent: Monday, October 31, 2011 11:18 AM
To: Grace, John F; Vu, Thuyanh (Ann)
Subject: Labeling sign-off for ANDA 076477 (Atorvastatin Calcium Tablets, 10 mg, 20 mg, 40 mg, and 80 mg by Ranbaxy)
Importance: High
Hello Ann and John,

Please perform labeling sign-off for this first generic ANDA. It is ready for full approval set for goal date, November 7, 2011.

Thanks,
Leigh Ann

3. ***Paragraph IV Evaluation*** **PIV's Only**
David Read **Date 31Oct2011**
OGD Regulatory Counsel **InitialsDTR**
Pre-MMA Language included ☐
Post-MMA Language Included ☐
Comments:Changes to AP letter saved to V drive.

4. ***Quality Division Director /Deputy Director Evaluation*** **Date 11/4/11**
Chemistry Div. **III (Sayeed)** **InitialsVAS**
Comments:cmc satisfactory.

5. ***First Generic Evaluation*** **First Generics Only**
Frank Holcombe **Date 11/7/11**
Assoc. Dir. For Chemistry **Initials rlw/for**
Comments: (First generic drug review)
N/A. By endorsing this approval package, the CMC division director has confirmed that there are no precident setting issues associated with the CMC review of this ANDA. Thus, no further CMC review is necessary.

OGD Office Management Evaluation

6. Peter Rickman **Date 11/7/11**
Director, DLPS **Initials rlw/for**
Para.IV Patent Cert: Yes☐ No☐
Pending Legal Action: Yes ☐ No ☐
Petition: Yes☐ No☐
Comments: In December 2009, Ranbaxy submitted a major amendment to their ANDA to provide for the addition of Ranbaxy's Ohm Laboratories in New Brunswick, NJ as an alternate manufacturer of the drug product. In addition, the source of the active ingredient (API) was changed to (b) (4) New CMC data and bioequivalence studies to support approval of the drug product manufactured at the Ohm site were also submitted at that time. In addition, Ranbaxy submitted an amendment in November 2010 to add its Toansa, India site as an alternate manufacturer of the API. Finally, in September 2011, Ranbaxy submitted an amendment to the ANDA to provide for the withdrawal of the Ranbaxy manufacturing site located in Paonta Sahib, India. Thus, at present Ranbaxy's ANDA provides for the manufacture, testing and packaging of the drug product at the Ohm Laboratories site in New Brunswick, NJ. The API will be obtained either from (b) (4) or from Ranbaxy's site in Toansa, India.

Bioequivalence studies (fasting and non-fasting) on the 80 mg tablet strength found acceptable (Ohm site). In-vitro dissolution testing found acceptable for all 4 tablet strengths. Waivers granted under 21 CFR 320.22(d)(2) for the 10 mg, 20 mg and 40 mg tablet strengths. Waiver also granted for the addition of API obtained from Toanda site. Bio study sites have acceptable DSI inspection histories. Office-level bio endorsed 5/4/11, 5/12/11, 8/8/11, 10/25/11.

Final-printed labeling found acceptable for approval 7/29/11, as endorsed 10/31/11. No REMS is required.

CMC found acceptable for the manufacture of the drug product at the Ohm Laboratories site and for API supplied by (b) (4) and Ranbaxy's Toansa site (Chemistry Review #7) 11/4/11.

Addendum to final BE review endorsed 11/21/11.

AND/OR

7. Robert L. West
Deputy Director, OGD
Date 11/7/11
Initials RLWest

Para.IV Patent Cert: Yes☒ No☐
Pending Legal Action: Yes☐ No☒
Petition: Yes☒ No☐
Press Release Acceptable ☐
Date PETS checked for first generic drug _____

Comments: Acceptable EES dated 10/25/11 (Verified 11/7/11). No "OAI" Alerts noted.

Ranbaxy submitted paragraph IV certifications to the '995, '104, '156, '971 and '667 patents. Ranbaxy was sued within the 45-day period on the '995 and the unlisted '893 patents. Ranbaxy was not sued on the '104, '156, '971 or '667 patents. (Note: the '995 and '667 patents expired on June 28, 2011). There are no additional patents or exclusivity listed in the current "Orange Book" for this drug product.

This ANDA is recommended for final approval based upon a settlement agreement entered into between Ranbaxy and Pfizer as noted above by M.Shimer. Although the agreement provides for Ranbaxy to be able to market the drug product on November 30, 2011, there is no block to the agency's approval at this time.

The ANDA was allowed to be reviewed as an exception to the agency's AIP policy in a notification to Ranbaxy signed by Center Director, Janet Woodcock, M.D. on 5/16/11. The exception was granted in order to permit OGD and OC to assess the reliability of the data (Memorandum dated 5/11/11 from D. Autor/OCC). To permit this determination to be made prior to the effective date of the settlement agreement, Expedited Review status was granted to Ranbaxy's ANDA and also to several other ANDAs that could potentially be approved if it were determined that Ranbaxy's application could not.

A Citizen Petition submitted by Pfizer is currently under agency review. It has been concluded that the issues raised in the C.P. are not pertinent to the Ranbaxy ANDA, as amended, and that this petition need not be responded to prior to the approval of Ranbaxy's ANDA (memorandum in DARRTS 10/24/11).

With this approval, Ranbaxy is eligible for 180-day generic drug exclusivity for all strengths of this drug product.

8. ***OGD Director Evaluation***
Keith Webber
Deputy Director, OPS

Comments: RLWest for Keith Webber, Ph.D. 11/7/11.
First Generic Approval ☒
PD or Clinical for BE ☐
Special Scientific or Reg.Issue ☐
Press Release Acceptable ☐

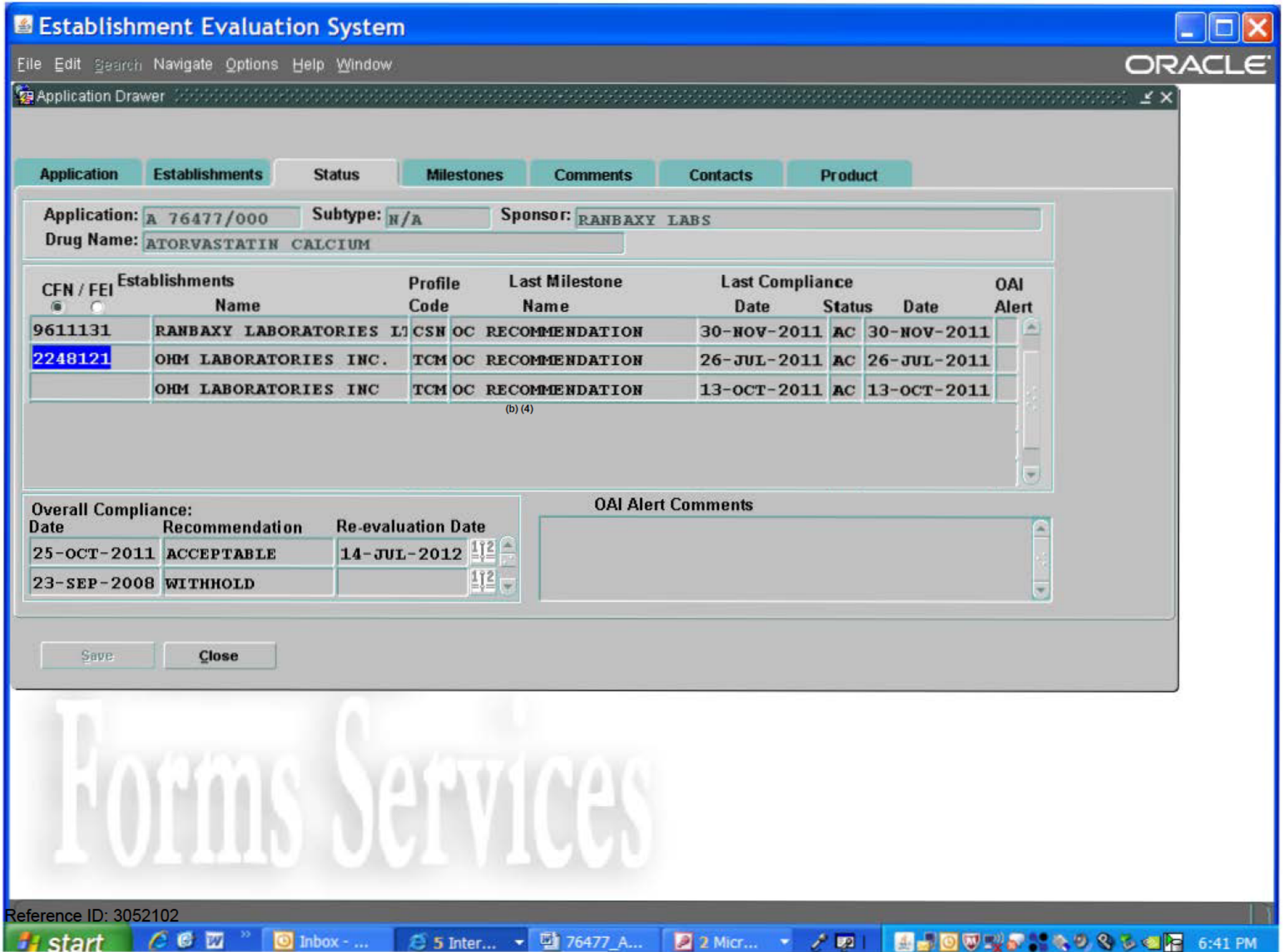
Comments:First-generic approval for this drug proeuct.

9. Project Manager
Date 11/30/2011
Initials LS

Check Communication and Routing Summary into DARRTS

EER DATA:

APPEARS THIS WAY ON THE ORIGINAL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ORACLE
Application Drawer
Application
Establishments
Status
Milestones
Comments
Contacts
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Subtype: N/A
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Last Compliance Date
Status
Date
OAI Alert
9611131 RANBAXY LABORATORIES LT CSN OC RECOMMENDATION 30-NOV-2011 AC 30-NOV-2011
2248121 OHM LABORATORIES INC. TCM OC RECOMMENDATION 26-JUL-2011 AC 26-JUL-2011
OHM LABORATORIES INC TCM OC RECOMMENDATION 13-OCT-2011 AC 13-OCT-2011
(b) (4)
Overall Compliance:
Date
Recommendation
Re-evaluation Date
25-OCT-2011 ACCEPTABLE 14-JUL-2012
23-SEP-2008 WITHHOLD
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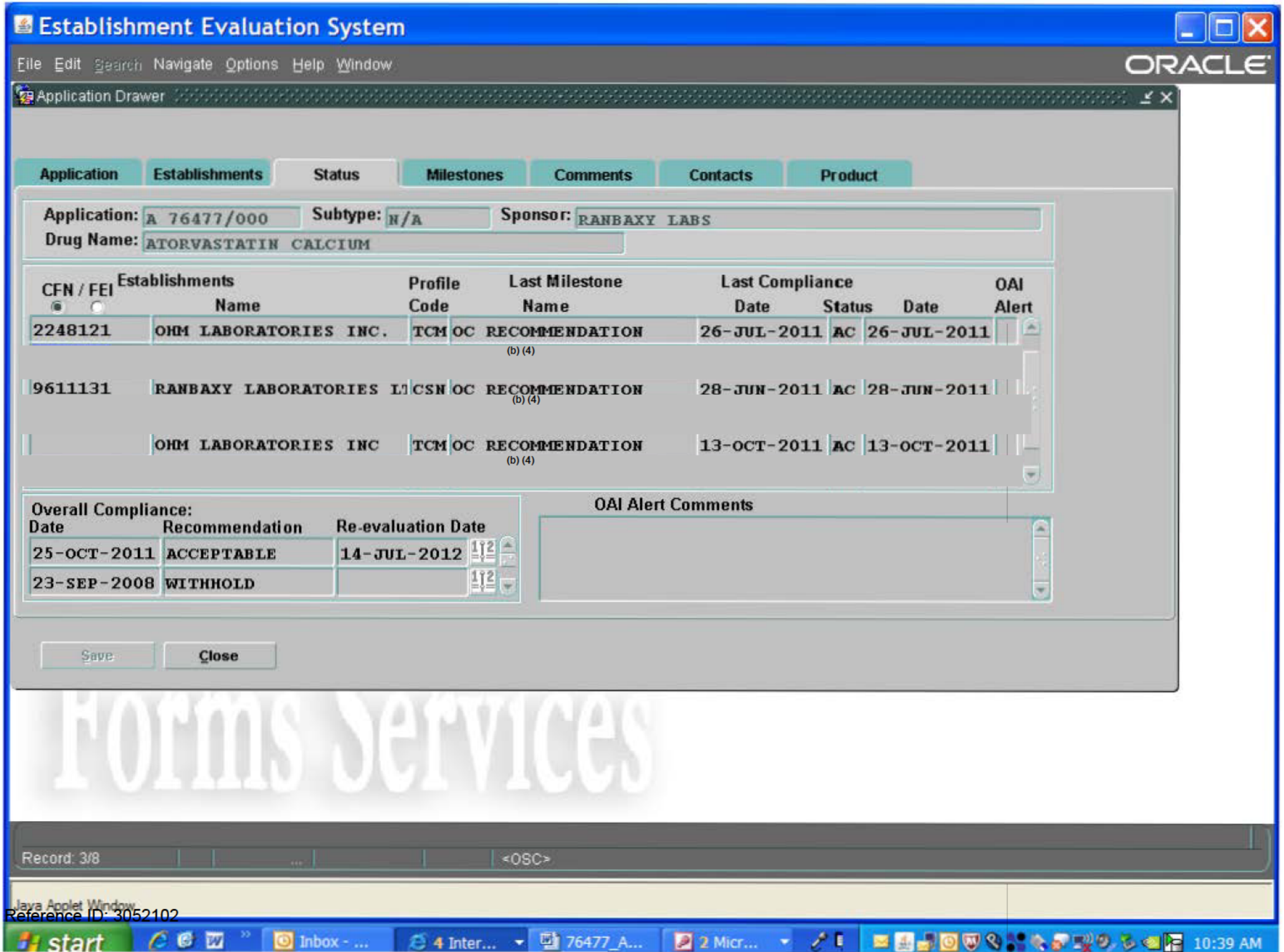

Reference ID: 3052102

DARRTS Application History:

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DARRTS Home > Application Search > Application Search Results > View Application >

Application Type/Number:	ANDA-076477	**Product Name:**	ATORVASTATIN CALCIUM	**Dosage Form:**	TABLET (IMMED./COMP. RELEASE), FILM COATED	**Applicant:**	RANBAXY LABORATORIES LTD	**Responsible Organization:**	CDER/OG

Application History

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	Supp. Document Number/Communication Author	Received / Communication Date	Sent Via	Submit / Final Date	Supporting Document Category/Subcategory / Communication Function	Submission Type-Number (Classification)	Cop
View	LI, HAITAO	11/04/2011	N/A	11/04/2011	REV-QUALITY-03(General Review)	Original-1	Archiv
View	103	11/04/2011		11/04/2011	Patent & Exclusivity/Patent Certification	Original-1	View EDR
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View	2	02/20/2003		02/18/2003	Correspondence	Original-1
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View	1	08/19/2002		08/19/2002	New/ANDA	Original-1

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Orange Book Report:

Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations

Patent and Exclusivity Search Results from query on Appl No 020702 Product 004 in the OB_Rx list.

<>

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N020702	004	5273995	Dec 28, 2010	Y	Y	U - 162	
N020702	004	5273995*PED	Jun 28, 2011			U - 162	
N020702	004	5686104	Nov 11, 2014		Y	U - 213	
N020702	004	5686104*PED	May 11, 2015			U - 213	
N020702	004	5969156	Jul 8, 2016	Y			
N020702	004	5969156*PED	Jan 8, 2017				
N020702	004	6126971	Jan 19, 2013		Y		
N020702	004	6126971*PED	Jul 19, 2013				
N020702	004	RE40667	Dec 28, 2010	Y	Y	U - 162	
N020702	004	RE40667*PED	Jun 28, 2011				

<>

There is no unexpired exclusivity for this product.

Additional information:

1. **Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).**
2. **Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.**
3. ****** The expiration date for U.S. Patent No. 5,608,075 is March 4, 2009.**

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View a list of all exclusivity codes

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Office of Generic Drugs
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Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through September, 2011
Patent and Generic Drug Product Data Last Updated: November 04, 2011

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