CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

21-468 / S-004, S-005

Trade Name: Fosrenol

Generic Name: Lanthanum Carbonate

Sponsor: Shire US, Inc.

Approval Date: March 3, 2006 (for both supplements)

Purpose:

S-004
Provides for FPL for the new formulation of the product

S-005
Provides for revisions to the labeling to include a precautionary statement regarding abdominal opacity in x-rays for patients receiving concurrent lanthanum carbonate treatment

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APPLICATION NUMBER:

21-468 / S-004, S-005

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APPLICATION NUMBER:

21-468 / S-004, S-005

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

NDA 21-468/S-004
NDA 21-468/S-005

Dennis Ahern, M.S.
Associate Director, Regulatory Affairs
Shire US, Inc.
725 Chesterbrook Blvd.
Wayne, PA 19087-5637

Dear Mr. Ahern:

Please refer to your supplemental new drug application (S-005) dated September 29, 2005, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for FOSRENOL® (Lanthanum Carbonate) Chewable Tablets, 250 and 500mg.

Please also refer to the approval letter for S-004 dated November 23, 2005 for the new formulation of FOSRENOL® (Lanthanum Carbonate) Chewable Tablets, 250, 500, 750, and 1000 mg.

We acknowledge receipt of your submissions dated November 29, 2005 (NDA 21-468/S-005) and December 9, 2005 (NDA 21-468/S-004).

NDA 21-468/S-005 "Changes Being Effected" supplemental new drug application provides for revisions to the labeling to include a precautionary statement regarding a safety surveillance analysis that reported a radio-opaque appearance on abdominal x-rays in patients receiving concurrent lanthanum carbonate treatment.

NDA 21-468/S-004 provides for final printed labeling for the new formulation of FOSRENOL®.

We have reviewed the final printed labeling (NDA 21-468/S-004) that you submitted in accordance with our November 23, 2005 letter, and we find it acceptable.

We have completed our review of NDA 21-468/S-005, as amended, and it is approved, effective on the date of this letter, for use as recommended in the agreed-upon labeling text and with the minor editorial revisions listed below.

NDA 21-468/S-004
NDA 21-468/S-005

1. Under the **PRECAUTIONS** section,

a. a new subsection, **Diagnostic Tests** was added after the **General**, but before the **Long-term Effects** subsections to read:

Diagnostic Tests:
Abdominal x-rays of patients taking lanthanum carbonate may have a radio-opaque appearance typical of an imaging agent.

b. in the **Information for the Patient** subsection, a new paragraph was added:

Notify your physician that you are taking FOSRENOL® prior to an abdominal x-ray (see **PRECAUTIONS, Diagnostic Tests**).

NDA 21-468/S-004

1. In the **HOW SUPPLIED** section, the replacement of the 250 and 500 mg, old formulation, which is being depleted for the new formulation and addition of the newly approved 750 and 1000 mg formulations were added to read:

250 mg supplied in bottles of 90 tablets
NDC 54092-251-90

500 mg Patient Pack (2 bottles of 45 tablets, NDC 54092-252-45, per each patient pack)
NDC 54092-252-90

750 mg Patient Pack (6 bottles of 15 tablets, NDC 54092-253-15, per each patient pack)
NDC 54092-253-90

1000 mg Patient Pack (9 bottles of 10 tablets, NDA 54092-254-10, per each patient pack)
NDC 54092-254-90

NDA 21-468/S-005

1. In the **HOW SUPPLIED** section, the revision of the 500 mg tablet and addition of the 750 mg and 1000 mg formulations were added to read:

250 mg supplied in bottles of 400 tablets
NDC 54092-251-04

500 mg Patient Pack (2 bottles of 45 tablets, NDC 54092-252-45, per each patient pack)
NDC 54092-252-90

750 mg Patient Pack (6 bottles of 15 tablets, NDC 54092-253-15, per each patient pack)
NDC 54092-253-90

1000 mg Patient Pack (9 bottles of 10 tablets, NDA 54092-254-10, per each patient pack)
NDC 54092-254-90

As reflected in your December 9, 2005 submission, you acknowledge that for the 250 mg strength, you will be replacing the commercial bottle from a 625 cc/400 count to a 200 cc/ 90 count configuration and that you intend, once the old formulation of the 250 mg strength is depleted to manufacture only

the new formulations of FOSRENOL®. In accordance with the FDA guidance "Changes to an Approved NDA or ANDA—April 2004," the above change to the labeling (NDA 21-468/S-005) regarding the 250 mg bottle may be reported to the FDA as an annual report. You should provide stability data from the first production batch for this change in the 2005-2006 NDA annual report and annual batches thereafter on long-term stability studies.

The final printed labeling (FPL) for NDA 21-468/S-005 must be identical to the package insert submitted for NDA 21-468/S-004 that reflects all approved strengths of the new formulation. These revisions are terms for the approval of this application.

Please submit an electronic version of the FPL according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA*. Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Individually mount 15 of the copies on heavy-weight paper or similar material. For administrative purposes, designate this submission "**FPL for approved supplement NDA 21-468/S-005**." Approval of this submission by FDA is not required before the labeling is used.

In addition, submit three copies of the introductory promotional materials that you propose to use for this product. Submit all proposed materials in draft or mock-up form, not final print. Send one copy to this division and two copies of both the promotional materials and the package insert directly to:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Drug Marketing, Advertising, and Communications
Food and Drug Administration
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you issue a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter), we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH
Food and Drug Administration
WO 22, Room 4447
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

We remind you that you must comply with reporting requirements for an approved NDA (21 CFR 314.80 and 314.81).

If you have any questions, please call:

Dianne Paraoan
Regulatory Health Project Manager
(301) 796-1129

Sincerely,

{See appended electronic signature page}

Norman Stockbridge
Director
Division of Cardiovascular and Renal Products
Office of Drug Evaluation 1
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/

Norman Stockbridge
3/3/2006 03:46:54 PM

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-468 / S-004, S-005

LABELING

FOSRENOL® (foss-wren-all)

(Lanthanum Carbonate) 250 mg and 500 mg Chewable Tablets.

DESCRIPTION

FOSRENOL® contains lanthanum carbonate (2:3) hydrate with molecular formula $La_2(CO_3)_3\ xH_2O$ (on average x=4-5 moles of water) and molecular weight 457.8 (anhydrous mass). Lanthanum (La) is a naturally occurring rare earth element. Lanthanum carbonate is practically insoluble in water.

Each FOSRENOL®, white to off-white, chewable tablet contains lanthanum carbonate hydrate equivalent to 250 or 500 mg of elemental lanthanum and the following inactive ingredients: dextrates (hydrated) NF, colloidal silicon dioxide NF, magnesium stearate NF, and talc USP.

CLINICAL PHARMACOLOGY

Patients with end stage renal disease (ESRD) can develop hyperphosphatemia that may be associated with secondary hyperparathyroidism and elevated calcium phosphate product. Elevated calcium phosphate product increases the risk of ectopic calcification. Treatment of hyperphosphatemia usually includes all of the following: reduction in dietary intake of phosphate, removal of phosphate by dialysis and inhibition of intestinal phosphate absorption with phosphate binders. FOSRENOL® does not contain calcium or aluminum.

Pharmacodynamics:

Lanthanum carbonate dissociates in the acid environment of the upper GI tract to release lanthanum ions that bind dietary phosphate released from food during digestion. FOSRENOL® inhibits absorption of phosphate by forming highly insoluble lanthanum phosphate complexes, consequently reducing both serum phosphate and calcium phosphate product.

In vitro studies have shown that in the physiologically relevant pH range of 3 to 5 in gastric fluid, lanthanum binds approximately 97% of the available phosphate when lanthanum is present in a two-fold molar excess to phosphate. In order to bind dietary phosphate efficiently, lanthanum should be administered with or immediately after a meal.

Pharmacokinetics:

Absorption/Distribution:

Following single or multiple dose oral administration of FOSRENOL® to healthy subjects, the concentration of lanthanum in plasma was very low (bioavailability <0.002%). Following oral administration in ESRD patients, the mean lanthanum C_{max} was 1.0 ng/mL. During long-term administration (52 weeks) in ESRD patients, the mean lanthanum concentration in plasma was approximately 0.6 ng/mL. There was minimal increase in plasma lanthanum concentrations with increasing doses within the therapeutic dose range. The effect of food on the bioavailability of FOSRENOL® has not been evaluated, but the timing of food intake relative to lanthanum administration (during and 30 minutes after food intake) has a negligible effect on the systemic level of lanthanum.

In vitro, lanthanum is highly bound (>99%) to human plasma proteins, including human serum albumin, α1-acid glycoprotein, and transferrin. Binding to erythrocytes *in vivo* is negligible in rats.

In 105 bone biopsies from patients treated with FOSRENOL® for up to 4.5 years, rising levels of lanthanum were noted over time. Estimates of elimination half-life from bone ranged from 2.0 to 3.6 years. Steady state bone concentrations were not reached during the period studied.

In studies in mice, rats and dogs, lanthanum concentrations in many tissues increased over time and were several orders of magnitude higher than plasma concentrations (particularly in the GI tract, bone and liver). Steady state tissue concentrations in bone and liver were achieved in dogs between 4 and 26 weeks. Relatively high levels of lanthanum remained in these tissues for longer than 6 months after cessation of dosing in dogs. There is no evidence from animal studies that lanthanum crosses the blood-brain barrier.

Metabolism/Elimination:

Lanthanum is not metabolized and is not a substrate of CYP450. *In vitro* metabolic inhibition studies showed that lanthanum at concentrations of 10 and 40 μg/ml does not have relevant inhibitory effects on any of the CYP450 isoenzymes tested (1A2, 2C9/10, 2C19, 2D6, and 3A4/5). Lanthanum was cleared from plasma following discontinuation of therapy with an elimination half-life of 53 hours.

No information is available regarding the mass balance of lanthanum in humans after oral administration. In rats and dogs, the mean recovery of lanthanum after an oral dose was about 99% and 94% respectively and was essentially all from feces. Biliary excretion is the predominant route of elimination for circulating lanthanum in rats. In healthy volunteers administered intravenous lanthanum as the soluble chloride salt (120 μg), renal clearance was less than 2% of total plasma clearance. Quantifiable amounts of lanthanum were not measured in the dialysate of treated ESRD patients.

In Vitro- Drug Interactions:

Gastric Fluid: The potential for a physico-chemical interaction (precipitation) between lanthanum and six commonly used medications (warfarin, digoxin, furosemide, phenytoin, metoprolol, and enalapril) was investigated in simulated gastric fluid. The results suggest that precipitation in the stomach of insoluble complexes of these drugs with lanthanum is unlikely.

In Vivo- Drug Interactions:

Lanthanum carbonate is neither a substrate nor an inhibitor of CYP450 enzymes.

The absorption of a single dose of 1000 mg of FOSRENOL® is unaffected by co-administration of citrate. No effects of lanthanum were found on the absorption of digoxin (0.5-mg), metoprolol (100-mg), or warfarin (10-mg) in healthy subjects co-administered lanthanum carbonate (three doses of 1000 mg on the day prior to exposure and one dose of 1000 mg on the day of coadministration). Potential pharmacodynamic interactions between lanthanum and these drugs (e.g., bleeding time or prothrombin time) were not evaluated. None of the drug interaction studies was done with the maximum recommended therapeutic dose of lanthanum carbonate. No drug interaction studies assessed the effects of drugs on phosphate binding by lanthanum carbonate.

Clinical Trials:

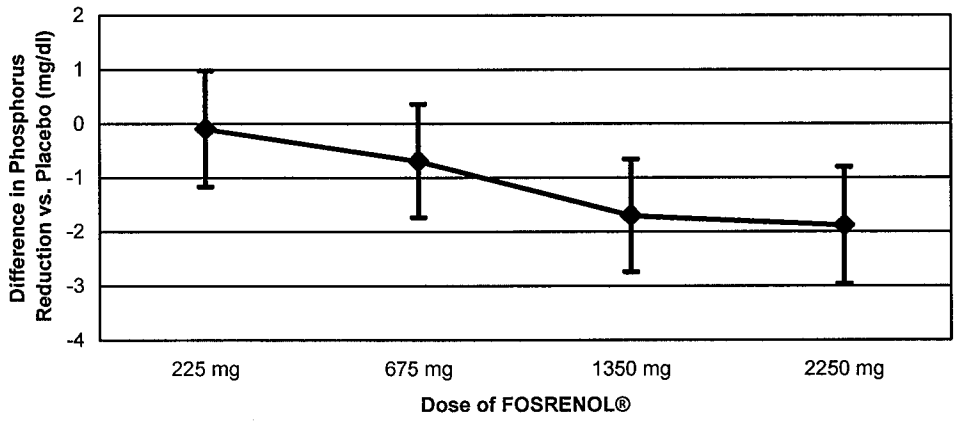
The effectiveness of FOSRENOL® in reducing serum phosphorus in ESRD patients was demonstrated in one short-term, placebo-controlled, double-blind dose-ranging study, two placebo-controlled randomized withdrawal studies and two long-term, active-controlled, open-label studies in both hemodialysis and peritoneal dialysis (PD) patients.

Double-Blind Placebo-Controlled Studies:

One hundred forty-four patients with chronic renal failure undergoing hemodialysis and with elevated phosphate levels were randomized to double-blind treatment at a fixed dose of lanthanum carbonate of 225 mg (n=27), 675 mg (n=29), 1350 mg (n=30) or 2250 mg (n=26) or placebo (n=32) in divided doses with meals. Fifty-five percent of subjects were male, 71% black, 25% white and 4% of other races. The mean age was 56 years and the

duration of dialysis ranged from 0.5 to 15.3 years. Steady-state effects were achieved after two weeks. The effect after six weeks of treatment is shown in Figure 1.

Figure 1. Difference in Phosphate Reduction in the FOSRENOL® and Placebo Group in a 6-Week, Dose-Ranging, Double-Blind Study in ESRD Patients (with 95% Confidence Intervals)



One-hundred eighty five patients with end-stage renal disease undergoing either hemodialysis (n=146) or peritoneal dialysis (n=39) were enrolled in two placebo-controlled, randomized withdrawal studies. Sixty-four percent of subjects were male, 28% black, 62% white and 10% of other races. The mean age was 58.4 years and the duration of dialysis ranged from 0.2 to 21.4 years. After titration of lanthanum carbonate to achieve a phosphate level between 4.2 and 5.6 mg/dl in one study (doses up to 2250 mg/day) or $\leq$ 5.9 mg/dl in the second study (doses up to 3000 mg/day) and maintenance through 6 weeks, patients were randomized to lanthanum or placebo. During the placebo-controlled, randomized withdrawal phase (four weeks), the phosphorus concentration rose in the placebo group by 1.9 mg/dl in both studies relative to patients who remained on lanthanum carbonate therapy.

Open-Label Active-Controlled Studies:

Two long-term open-label studies were conducted, involving a total of 2028 patients with ESRD undergoing hemodialysis. Patients were randomized to receive FOSRENOL® or alternative phosphate binders for up to six months in one study and two years in the other. The daily FOSRENOL® doses, divided and taken with meals, ranged from 375 mg to 3000 mg. Doses were titrated to reduce serum phosphate levels to a target level. The daily doses of the alternative therapy were based on current prescribing information or those commonly utilized. Both treatment groups had similar reductions in serum phosphate of about 1.8 mg/dL. Maintenance of reduction was observed for up to three years in patients treated with FOSRENOL® in long-term, open label extensions.

No effects of FOSRENOL® on serum levels of 25-dihydroxy vitamin D3, vitamin A, vitamin B12, vitamin E and vitamin K were observed in patients who were monitored for 6 months.

Paired bone biopsies (at baseline and at one or two years) in 69 patients randomized to either FOSRENOL® or calcium carbonate in one study and 71 patients randomized to either FOSRENOL® or alternative therapy in a second study showed no differences in the development of mineralization defects between the groups.

Vital Status was known for over 2000 patients, 97% of those participating in the clinical program during and after receiving treatment. The adjusted yearly mortality rate (rate/years of observation) for patients treated with FOSRENOL® or alternative therapy was 6.6%.

INDICATIONS AND USAGE

FOSRENOL® is indicated to reduce serum phosphate in patients with end stage renal disease.

CONTRAINDICATIONS

None known.

PRECAUTIONS

General:

Patients with acute peptic ulcer, ulcerative colitis, Crohn's disease or bowel obstruction were not included in FOSRENOL® clinical studies. Caution should be used in patients with these conditions.

Long-term Effects:

There were no differences in the rates of fracture or mortality in patients treated with FOSRENOL® compared to alternative therapy for up to 3 years. The duration of treatment exposure and time of observation in the clinical program are too short to conclude that FOSRENOL® does not affect the risk of fracture or mortality beyond 3 years.

Information for the Patient:

FOSRENOL® tablets should be taken with or immediately after meals. Tablets should be chewed completely before swallowing. Intact tablets should not be swallowed.

Drug Interactions:

FOSRENOL® is not metabolized.

Studies in healthy subjects have shown that FOSRENOL® does not adversely affect the pharmacokinetics of warfarin, digoxin or metoprolol. The absorption and pharmacokinetics of FOSRENOL® are unaffected by co-administration with citrate-containing compounds (see **CLINICAL PHARMACOLOGY: In Vitro/In Vivo Drug Interactions**).

An *in vitro* study showed no evidence that FOSRENOL® forms insoluble complexes with warfarin, digoxin, furosemide, phenytoin, metoprolol and enalapril in simulated gastric fluid. However, it is recommended that compounds known to interact with antacids should not be taken within 2 hours of dosing with FOSRENOL®.

Carcinogenesis, Mutagenesis, Impairment of Fertility:

Oral administration of lanthanum carbonate to rats for up to 104 weeks, at doses up to 1500 mg of the salt per kg/day [2.5 times the maximum recommended daily human dose (MRHD) of 5725 mg, on a mg/m^2 basis, assuming a 60-kg patient] revealed no evidence of carcinogenic potential. In the mouse, oral administration of lanthanum carbonate for up to 99 weeks, at a dose of 1500 mg/kg/day (1.3 times the MRHD) was associated with an increased incidence of glandular stomach adenomas in male mice.

Lanthanum carbonate tested negative for mutagenic activity in an *in vitro* Ames assay using *Salmonella typhimurium* and *Escherichia coli* strains and *in vitro* HGPRT gene mutation and chromosomal aberration assays in Chinese hamster ovary cells. Lanthanum carbonate also tested negative in an oral mouse micronucleus assay at doses up to 2000 mg/kg (1.7 times the MRHD), and in micronucleus and unscheduled DNA synthesis assays in rats given IV lanthanum chloride at doses up to 0.1 mg/kg, a dose that produced plasma lanthanum concentrations >2000 times the peak human plasma concentration.

Lanthanum carbonate, at doses up to 2000 mg/kg/day (3.4 times the MRHD), did not affect fertility or mating performance of male or female rats.

Pregnancy:

Pregnancy Category C. No adequate and well-controlled studies have been conducted in pregnant women. The effect of FOSRENOL® on the absorption of vitamins and other nutrients has not been studied in pregnant women. FOSRENOL® is not recommended for use during pregnancy.

In pregnant rats, oral administration of lanthanum carbonate at doses as high as 2000 mg/kg/day (3.4 times the MRHD) resulted in no evidence of harm to the fetus. In pregnant rabbits, oral administration of lanthanum carbonate at 1500 mg/kg/day (5 times the MRHD) was associated with a reduction in maternal body weight gain and food consumption, increased post-implantation loss, reduced fetal weights, and delayed fetal ossification. Lanthanum carbonate administered to rats from implantation through lactation at 2000 mg/kg/day (3.4 times the MRHD) caused delayed eye opening, reduction in body weight gain, and delayed sexual development (preputial separation and vaginal opening) of the offspring.

Labor and Delivery

No lanthanum carbonate treatment-related effects on labor and delivery were seen in animal studies. The effects of lanthanum carbonate on labor and delivery in humans is unknown.

Nursing Mothers:

It is not known whether lanthanum carbonate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when FOSRENOL® is administered to a nursing woman.

Geriatric Use:

Of the total number of patients in clinical studies of FOSRENOL®, 32% (538) were ≥ 65, while 9.3% (159) were ≥ 75. No overall differences in safety or effectiveness were observed between patients ≥ 65 years of age and younger patients.

Pediatric Use:

While growth abnormalities were not identified in long-term animal studies, lanthanum was deposited into developing bone including growth plate. The consequences of such deposition in developing bone in pediatric patients are unknown. Therefore, the use of FOSRENOL® in this population is not recommended.

ADVERSE REACTIONS

The most common adverse events for FOSRENOL® were gastrointestinal events, such as nausea and vomiting and they generally abated over time with continued dosing.

In double-blind, placebo-controlled studies where a total of 180 and 95 ESRD patients were randomized to FOSRENOL® and placebo, respectively, for 4-6 weeks of treatment, the most common events that were more frequent (≥5% difference) in the FOSRENOL® group were nausea, vomiting, dialysis graft occlusion, and abdominal pain (Table 1).

Table 1. Adverse Events That Were More Common on FOSRENOL® in Placebo-Controlled, Double-Blind Studies with Treatment Periods of 4-6 Weeks.

	FOSRENOL® % (N=180)	Placebo % (N=95)
Nausea	11	5
Vomiting	9	4
Dialysis graft occlusion	8	1
Abdominal pain	5	0

The safety of FOSRENOL® was studied in two long-term clinical trials that included 1215 patients treated with FOSRENOL® and 943 with alternative therapy. Fourteen percent (14%) of patients in these comparative, open-label studies discontinued in the FOSRENOL®-treated group due to adverse events. Gastrointestinal adverse events, such as nausea, diarrhea and vomiting, were the most common type of event leading to discontinuation.

The most common adverse events (≥5% in either treatment group) in both the long-term (2 year), open-label, active controlled, study of FOSRENOL® vs. alternative therapy (Study A) and the 6-month, comparative study of FOSRENOL® vs. calcium carbonate (Study B) are shown in Table 2. In Table 2, Study A events have been adjusted for mean exposure differences between treatment groups (with a mean exposure of 0.9 years on lanthanum and 1.3 years on alternative therapy). The adjustment for mean exposure was achieved by multiplying the observed adverse event rates in the alternative therapy group by 0.71.

Table 2. Incidence of Treatment-Emergent Adverse Events that Occurred in ≥ 5% of Patients (in Either Treatment Group) and in Both Comparative Studies A and B

	Study A %	Study B %

	FOSRENOL® (N = 682)	Alternative Therapy Adjusted Rates (N=676)	**FOSRENOL®** (N=533)	Calcium Carbonate (N=267)
Nausea	36	28	16	13
Vomiting	26	21	18	11
Dialysis graft complication	26	25	3	5
Diarrhea	23	22	13	10
Headache	21	20	5	6
Dialysis graft occlusion	21	20	4	6
Abdominal pain	17	17	5	3
Hypotension	16	17	8	9
Constipation	14	13	6	7
Bronchitis	5	6	5	6
Rhinitis	5	7	7	6
Hypercalcemia	4	8	0	20

OVERDOSAGE

There is no experience with FOSRENOL® overdosage. Lanthanum carbonate was not acutely toxic in animals by the oral route. No deaths and no adverse effects occurred in mice, rats or dogs after single oral doses of 2000 mg/kg. In clinical trials, daily doses up to 4718 mg/day of lanthanum were well tolerated in healthy adults when administered with food, with the exception of GI symptoms. Given the topical activity of lanthanum in the gut, and the excretion in feces of the majority of the dose, supportive therapy is recommended for overdosage.

DOSAGE AND ADMINISTRATION

The total daily dose of FOSRENOL® should be divided and taken with meals. The recommended initial total daily dose of FOSRENOL® is 750-1500 mg. The dose should be titrated every 2-3 weeks until an acceptable serum phosphate level is reached. Serum phosphate levels should be monitored as needed during dose titration and on a regular basis thereafter.

In clinical studies of ESRD patients, FOSRENOL® doses up to 3750 mg were evaluated. Most patients required a total daily dose between 1500 mg and 3000 mg to reduce plasma phosphate levels to less than 6.0 mg/dL. Doses were generally titrated in increments of 750 mg/day.

Tablets should be chewed completely before swallowing. Intact tablets should not be swallowed.

HOW SUPPLIED

FOSRENOL® is supplied as a chewable tablet in two dosage strengths for oral administration: 250 mg tablets and 500 mg tablets. Each chewable tablet is white to off-white and embossed on one side with 'S405' and the dosage strength corresponding to the content of elemental lanthanum. The 250 mg tablets are round/convex and the 500 mg tablets are flat with a beveled edge.

250 mg supplied in bottles of 100	NDC 54092-247-01
500 mg supplied in bottles of 100	NDC 54092-249-01

Storage

Store at 25°C (77°F): excursions permitted to 15-30°C (59-86°F)

[See USP controlled room temperature]

Protect from moisture

Rx only

Manufactured for Shire US Inc.

Wayne, PA 19087-2088, USA

1-800-828-2088

Revision Date: 10/2004

247 0107 001

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-468 / S-004, S-005

CHEMISTRY REVIEW(S)

CHEMIST'S REVIEW	1. ORGANIZATION: HFD-110	2. NDA Number 21-468
3. Name and Address of Applicant (City & State) Shire Development Inc. 725 Chesterbrook Blvd. Wayne, PA 19087		4. Supplement(s) Number(s) Date(s) SCF-004 3/15/05
5. Drug Name Fosrenol®	6. Nonproprietary Name	7. Amendments - Dates SCF-004 (BC) 7/14/05
6. Supplement Provides For: This Prior Approval Supplement provides for optimized formulation of Fosrenol chewable tablets of 250 mg, 500 mg, 750 mg, and 1000 mg strengths.		
9. Pharmacological Category	10. How Dispensed Rx	11. Related NDAs
12. Dosage Form(s) Chewable Tablets	13. Potencies 250 mg and 500 mg	
Chemical Name and Structure: Lanthanum carbonate (2:3) hydrate Molecular formula: $La_2(CO_3)_3.xH_2O$ (on average x=4-5 moles of water) Molecular weight: 457.8 (anhydrous)		15. Records/Reports Current Yes X No Reviewed Yes No X

16. Comments:

The NDA supplement is submitted under the consideration of the Guidance for Industry on 'Changes to an Approved NDA/ANDA'. This is a "*Prior Approval*" supplement, which provides for reformulated Fosrenol chewable tablets of 250 mg, 500 mg, 750 mg, and 1000 mg strengths. These four new tablets are known as the 'optimized' formulations. These formulations were previously submitted in the January 24, 2004 NDA 21-468 resubmission. In November 16, 2004 meeting, the agency requested Shire to submit dissolution data for optimized formulations at different testing condition 5, 10, 15, and 20 dpm. Shire had agreed in the meeting that additional bioequivalence were needed to support the approval of the 'optimized' formulations. Subsequently, both FDA and Shire agreed in February 28, 2005 meeting that the current formulation dissolution specification for S-003 will be set at 10 dpm with a Q value of ——— ———. This was based on limited data presented by the applicant. In this submission, the applicant has presented the dissolution data mainly focused on ——— rate in Apparatus 3 but very limited data at 10 dpm rate, as agreed in the November 2004 meeting. Based on the data presented, the bioequivalence study is acceptable to the OCPB. However, the proposed dissolution specification by the applicant in USP Apparatus 3, ——— rate with Q value of ——————— is not acceptable to the OCPB; instead the following currently used dissolution methodology for the approved formulation is recommended: USP Apparatus 3, 10 dpm in 0.25N HCl, and a Q value of ———————. If additional stability testing for the optimized formulation produces results that indicate substantial failures at 10 dpm, then the agency will reconsider increasing the dip rate, and/or changing the Q value (March 4, 2005 document, 2/28/05 T-con minutes).

b(4)

17. Conclusions and Recommendations: The supplement is 'approvable' from the standpoint of chemistry, manufacturing and controls, pending satisfactory responses to the deficiencies on page **27** and **28**.

18. Reviewer:

Name	Signature	Date Completed
Kris Raman, Ph.D.		7/14/05

33 Page(s) Withheld

√ § 552(b)(4) Trade Secret / Confidential

____ § 552(b)(4) Draft Labeling

____ § 552(b)(5) Deliberative Process

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

/s/

Kris Raman
7/14/05 07:43:28 PM
CHEMIST

Kasturi Srinivasachar
7/14/05 07:52:46 PM
CHEMIST

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-468 / S-004, S-005

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA #	21-468 SCF 004
Submission Dates	03/15/05 and 05/17/05 and 08/01/05
Drug	lanthanum carbonate
Formulation	chewable tablets (optimized)
Dosage strength	250, 500, 750 and 1000 mg
OCPB Division	DPE 1
OND Division	Cardio-Renal Drug Products
Reviewer	Robert O. Kumi, Ph.D.
Team Leader	Patrick Marroum, Ph.D.

REVIEW ADDENDUM: NDA 21-468 SCF 004

Background and Introduction

On March 15, 2005 Shire Pharmaceuticals submitted NDA 21-468 SCF 004 to seek approval of **a new "optimized" chewable lanthanum carbonate** tablet formulation (1000, 750, 500 and 250 mg strengths) and to set a dissolution method and specification for this new formulation. The Agency issued Shire an approvable letter on July 15, 2005 citing three deficiencies:

1. Inadequate dissolution data to support the proposed changes to the currently approved dissolution methodology (USP Apparatus 3, 900 mL of 0.25 N HCl, 37° C) and specification (Q = ———————. The sponsor was asked to provide complete dissolution data for all relevant batches and dosage strengths using the following experimental conditions: b(4)
   - USP Apparatus 3
   - 0.25 N HCl
   - Dip rates including 10, 15 and 20 dpm
   - Six or more tablets for each experiment
2. The biowaivers for the 250, 500 and 750 mg tablets could not be granted due to the use of an inadequate dissolution method as outlined in deficiency 1. b(4)
3. The ——— expiration period for the drug product was not acceptable due to the use of an inadequate dissolution method.

The current submission, an Amendment to SCF 004, was submitted on August 1, 2005 in response to the deficiencies cited in the July 15, 2005 action letter.

Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics has reviewed the information in NDA 21-468 SCF 004, August 1, 2005 submission. The information provided in this submission adequately addresses deficiencies 1 and 2 cited in the July 15, 2005 action letter, thus,

1) The proposed dissolution method (USP Apparatus 3 at 10 dpm in 0.25 N HCl, 900 mL, 37 °C) and specification (Q = ——————— are acceptable b(4)
2) Biowaivers should be granted for the 750, 500 and 250 mg optimized formulations

The following review assesses the adequacy of the current submission (August 1, 2005) with respect to deficiencies 1 and 2; deficiency #3 will be addressed by the Chemistry Reviewer.

Deficiency 1

During the July 19, 2005 teleconference, Shire indicated that they would withdraw the proposed change in dissolution qualification (method and specification) and adopt that for the currently approved formulation. Subsequently, the applicant provided the requested dissolution data at the

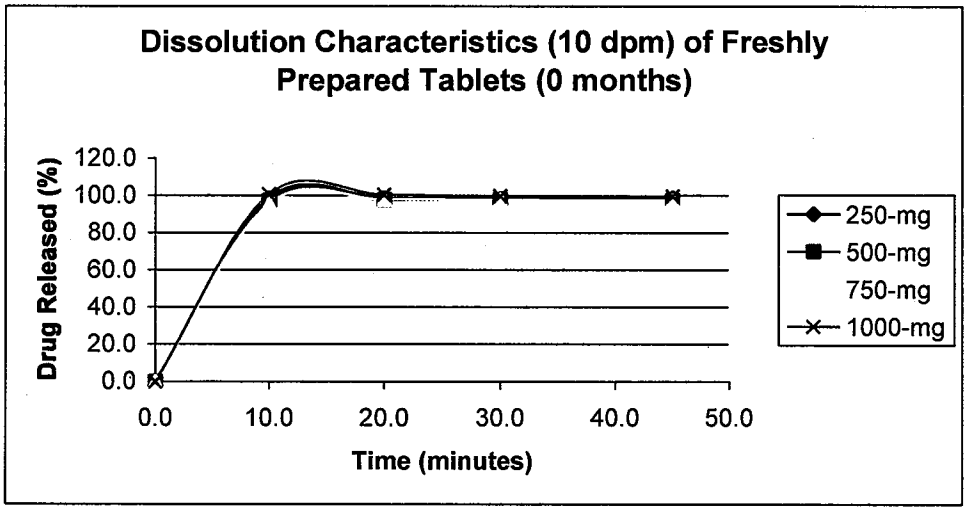
10 and 20 dpm dissolution rates; however 15 dpm data were not provided. Exclusion of the 15 dpm data is acceptable because this dip rate is bracketed by the 10 and 20 dpm data. The currently approved dissolution qualification is:

- **Method** USP Apparatus 3, at 10 dpm in 0.25 N HCl (900 mL, 37 °C) b(4)
- **Specification** Q = ————————

This review focuses on the 10 dpm data because these data are the most relevant for setting the dissolution method and specification; most of the 20 dpm data ———————— b(4)
————————n. In brief, the 20 dpm data offered some degree of discrimination among various formulations (differing manufacturing process, moisture content and age), but it was not clear if 20 dpm was an optimal dip rate for setting the dissolution qualification.

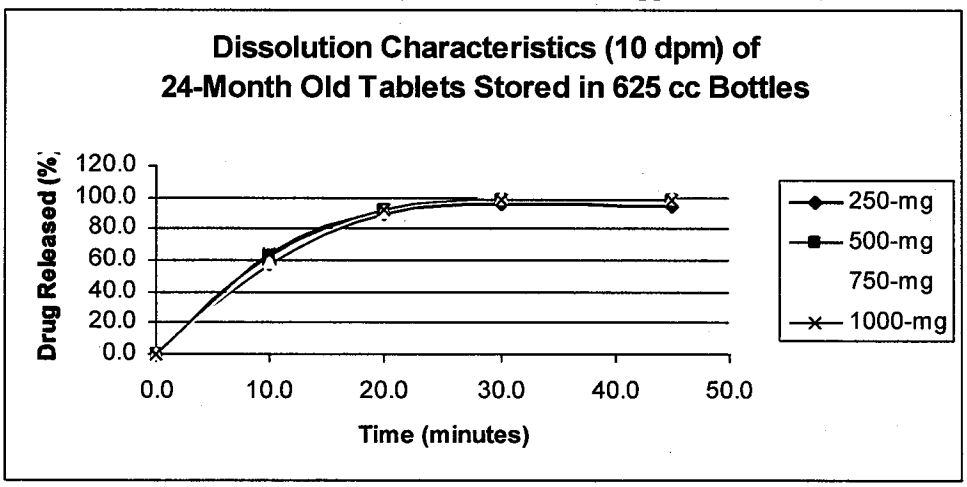
Figures 1 and 2 demonstrate the utility of the proposed method; additional supportive data are included in the Appendix (Tables A and B).

Figure 1: Dissolution Profiles for Optimized Formulation* (Appendix Table 1)



* CV for each dissolution time point was < 5 %

Figure 2: Dissolution Profiles for Optimized Tablets^ (Appendix Table 2)



^ CV for each dissolution time point < 10 %

The tabulated data (Appendix Tables A and B) indicate that tablets stored for 6 to 24 months at 25 °C with 60% RH in 625 cc or ——bottles (commercial package) generally satisfy the proposed ——dissolution specification (Q = ——; at the S1 stage. It is noted that dissolution data were also generated for tablets stored under accelerated storage conditions (30 °C with 60-65% RH and 40°C with 75% RH); these data are supportive but not considered critical in evaluating the dissolution methodology and specification. Therefore, data generated from accelerated conditions will not be discussed in this review. Generally, 10 dpm data were comparable to those at 20 dpm; batches that failed (Q = ——) at the various testing stages (particularly S1) at 10 dpm also failed at 20 dpm. Consequently, the use of 10 dpm, the lower dip rate, is preferable because it may allow for greater discrimination relative to the faster dip rate (20 dpm). Overall, the data support selection of the 10 dpm rate. b(4)

Reviewer Comment on Data Adequacy/Robustness

Data provided in the current submission (August) are more robust than those previously (March) submitted as they include information obtained at 10 and 20 dpm rates for: 1) all tablet strengths, 2) bulk substance and 3) different storage periods (0- 24 months).

Conclusion and Recommendation for Deficiency 1

The data indicate that the following dissolution method and specification are suitable for the new optimized 250, 500, 750 and 1000 mg lanthanum carbonate (Fosrenol) formulations:

Method USP Apparatus 3, at 10 dpm in 0.25 N HCl (900 mL, 37 °C) b(4)

Specification Q = ——

Deficiency 2

The granting of the biowaiver is dependent on the use of an adequate dissolution method. As noted previously, the dissolution characteristics of the optimized formulations are adequately determined under the currently proposed dissolution conditions (see Deficiency 1 Conclusion).

Dissolution Profile Comparisons

Dissolution profiles for the 250, 500 and 750 mg tablets compared to the 1000 mg tablets are shown in Figure 3 (per applicant). The plots show that the dissolution profiles for each of the lower strength tablets are similar to that of the 1000 mg tablet, except for the initial time point (10 minutes). Numerically, the 1000 mg formulation had more drug released at the 10-minute time point than the lower strength tablets; the reason for this finding is unclear.

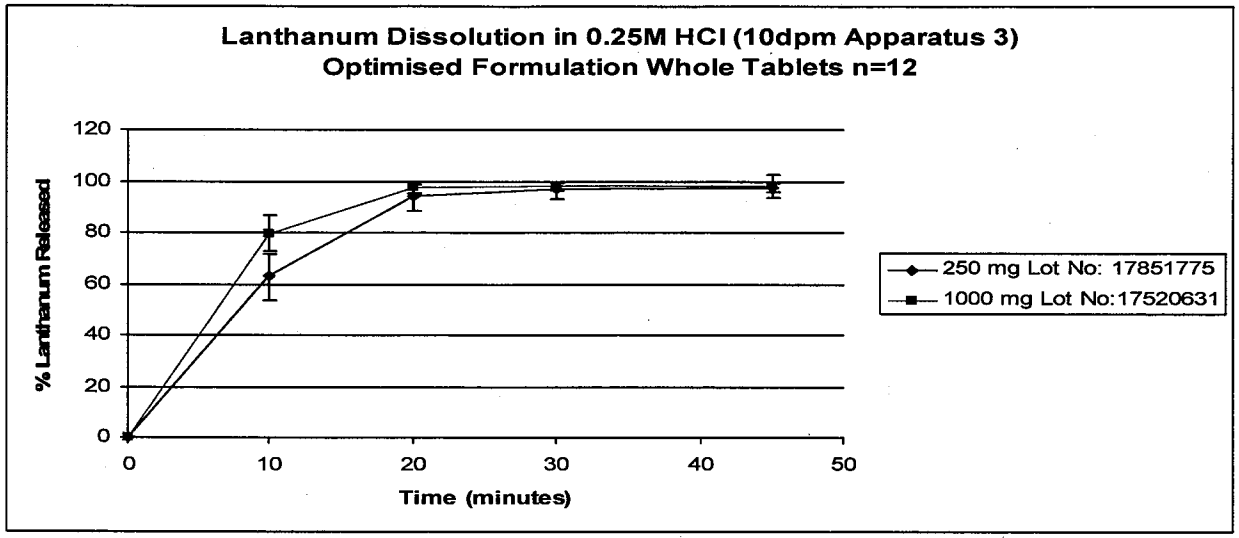
The applicant calculated f_2 (Table 1) to demonstrate that the dissolution of each of the lower strength tablets was similar to the reference 1000 mg tablets.

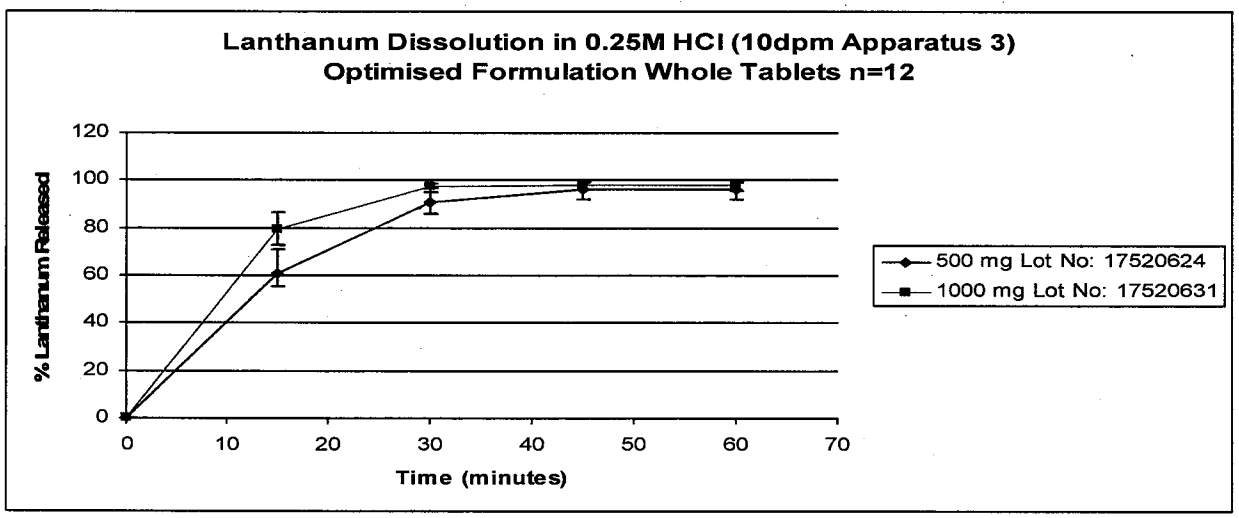
Table 1: f_2 Calculations for Optimized Formulations

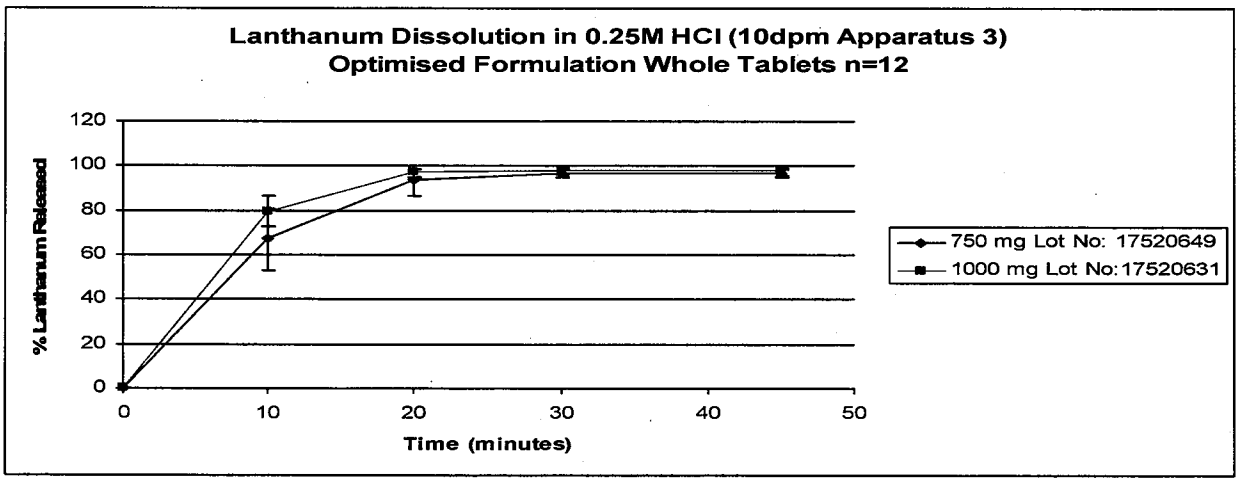
Strength	Batch Number	f_2 (similarity factor vs. 1000 mg tablet)
250	17851775	54
500	17520624	50
750	17520649	59

The f_2 values for the 250, 500 and 750 mg tablets were all $\geq$ 50 indicating similarity of dissolution to the 1000 mg tablet. However, as shown in Figure 3, > 85 % of the drug is released within 20 minutes (second sampling point) for all formulations.

Figure 3: Dissolution Profiles for Biowaivers







This rapid drug release diminishes the reliability and significance of the f_2 calculations. According to the Dissolution Guidance for Immediate Release Products, for f_2 calculations only one measurement should be used in the f_2 calculation after 85 % of drug is released from both formulations. Thus, there was no need to calculate f_2 becasuse > 85 % of drug was dissolved

within 20 minutes. Accordingly, the calculated f_2 values are not reliable. Irrespective of the limitations associated with the f_2 calculations, overall the provided data demonstrate that the dissolution of all of the lower strength formulations is comparable to that of the reference 1000 mg formulation. Consequently, the dissolution data support approval of the biowaiver request.

Conclusion and Recommendation for Deficiency 2

Overall, the dissolution characteristics of the 250, 500 and 750 mg tablets are similar to that of the 1000 mg tablets. This finding suggests that the biowaivers for the lower strength tablets should be granted. The f_2 values also support the similar dissolution behavior of the lower strength tablets relative to the 1000 mg tablet although the f_2 estimation is not be reliable.

APPENDIX
Dissolution Method and Specification Data

Table 1: Data Used in Plots for Freshly Prepared Tablets

Batch Number	Store Time (months)	Store Temp (°C)	Whole Tablet Dissolution Apparatus 3 (10dpm) Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
	0	Initial release				
17851775						
99188384	0	Initial release				
250mg	0	Initial release				
Boots	0	Initial release				
	0	Initial release				
	0	Initial release				
		MEAN (n=6)	98.4	98.5	98.4	98.6
		SD (n=6)	2.3	1.4	1.4	1.6
	0	Initial release				
17520624						
2052094	0	Initial release				
500mg	0	Initial release				
Boots	0	Initial release				
	0	Initial release				
	0	Initial release				
		MEAN (n=6)	97.2	97.7	97.9	97.7
		SD (n=6)	1.2	0.5	0.6	0.6
17520649	0	**Initial release**				
2052124	0	**Initial release**				
750mg	0	**Initial release**				
Boots	0	**Initial release**				
	0	**Initial release**				
	0	**Initial release**				
		MEAN (n=6)	97.3	100.0	99.9	99.7
		SD (n=6)	2.4	1.2	1.3	1.3

Batch Number	Store Time	Store Temp	Whole Tablet Dissolution Apparatus 3 (10dpm) Individual Drug Release (Mean in Brackets)			
	0	Initial release				
17520649						
2052124	0	Initial release				
750mg	0	Initial release				
Boots	0	Initial release				
	0	Initial release				
	0	Initial release				
		MEAN (n=6)	97.3	100.0	99.9	99.7
		SD (n=6)	2.4	1.2	1.3	1.3

b(4)

b(4)

b(4)

Table 2: Data Used in Plots for 24 –Month Old Tablets

Batch Number	Store Time (months)	Store Temp (°C)	Whole Tablet Dissolution Apparatus 3 (10dpm) Individual Drug Release (Mean in Brackets)			
			10 mins	20 mins	30 mins	45 mins
7209960	24	25°C/ 60%RH				
8851379	24	25°C/ 60%RH				
220002324	24	25°C/ 60%RH				
250 mg	24	25°C/ 60%RH				
625 cc, HDPE	24	25°C/ 60%RH				
Boots	24	25°C/ 60%RH				
		MEAN (n=6)	61.9	95.1	99.2	99.2
		SD (n=6)	8.3	3.5	2.1	2.3
7209999	24	**25°C/ 60%RH**				
8851424	24	**25°C/ 60%RH**				
220002326	24	**25°C/ 60%RH**				
500 mg	24	**25°C/ 60%RH**				
625 cc, HDPE	24	**25°C/ 60%RH**				
Boots	24	**25°C/ 60%RH**				
		MEAN (n=6)	62.3	92.1	97.8	98.2
		SD (n=6)	5.0	4.8	1.7	1.6
7265723	24	**25°C/ 60%RH**				
8851381	24	**25°C/ 60%RH**				
220002330	24	**25°C/ 60%RH**				
750 mg	24	**25°C/ 60%RH**				
625 cc, HDPE	24	**25°C/ 60%RH**				
Boots	24	**25°C/ 60%RH**				
		MEAN (n=6)	58.9	91.1	99.1	100.0
		SD (n=6)	5.6	7.9	1.1	0.9
7209986	24	**25°C/ 60%RH**				
8851422	24	**25°C/ 60%RH**				
220002331	24	**25°C/ 60%RH**				
1000 mg	24	**25°C/ 60%RH**				
625 cc HDPE	24	**25°C/ 60%RH**				
Boots	24	**25°C/ 60%RH**				
		MEAN (n=6)	64.0	91.3	98.7	98.9
		SD (n=6)	4.3	4.0	1.8	1.5

b(4)

b(4)

Table A: 25°C/60%RH Dissolution data summary 10 and 20dpm (samples stored for longest periods shown at the tope of the table)

Batch Number	Strength	Pack	Store time (months)	10dpm		20dpm	
				30mins	45mins	30mins	45mins
7209963 8851380 220002325	250 mg	625cc	18 24 32	X (3) - X FAIL S3	X (3) - X FAIL S3	X (3) X PASS S2 X FAIL S3	Y Y Y
7210002 8851426 220002327	500 mg	625cc	24 32	- X FAIL S3	- X FAIL S3	X PASS S2 X PASS S2	Y Y
7210002 8851431 220002329	500 mg		18 24 32	- - X FAIL S3	- - X FAIL S3	X X FAIL S2 X FAIL S3	Y X PASS S2 X FAIL S3
7209999 8851429 220002328	500 mg		24	Y	Y	Y	Y
7209960 8851379 220002324	250 mg	625cc	18 24	- Y	- Y	Y Y	Y Y
7209999 8851424 220002326	500 mg	625cc	18 24	- Y	- Y	Y Y	Y Y
7265723 8851381 220002330	750 mg	625cc	18 24	- Y	- Y	Y Y	Y Y
7209986 8851422 220002331	1000 mg	625cc	24	Y	Y	Y	Y
7209989 8851423 220002332	1000 mg	625cc	18 24	- Y	- Y	Y Y	Y Y
3G2745 D-$-2003-85	500 mg		18	Y	Y	Y	Y
3G2746 D-$-2003-86	500 mg		18	X PASS S2	Y	Y	Y
3G2747 D-$-2003-87	500 mg		18	Y	Y	Y	Y
3G2742A D-$-2003-73	250 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2743A D-$-2003-74	250 mg	625cc	6 18	- X PASS S2	- X PASS S2	Y X PASS S2	Y Y
3G2744A D-$-2003-75	250 mg	625cc	18	Y	Y	Y	Y
3G2745A D-$-2003-77	500 mg	625cc	18	Y	Y	Y	Y
3G2746A D-$-2003-76	500 mg	625cc	6 18	- X PASS S2	- Y	Y Y	Y Y
3G2747A D-$-2003-78	500 mg	625cc	18	Y	Y	Y	Y
3G2748A D-$-2003-79	750 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2749A D-$-2003-80	750 mg	625cc	18	Y	Y	Y	Y
3G2750A D-$-2003-81	750 mg	625cc	18	Y	Y	Y	Y
3G2751A D-$-2003-82	1000 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2752A D-$-2003-83	1000 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2753A D-$-2003-84	1000 mg	625cc	6 18	- Y	- Y	Y Y	Y Y

b(4)

b(4)

Table A: Continued 25°C/60%RH Dissolution data summary 10 and 20dpm

Batch Number	Strength	Pack	Store time (months)	10dpm		20dpm	
				30mins	45mins	30mins	45mins
10409389 230000193	250mg	625cc	18	-	-	Y	Y
10410686 230000194	500mg	625cc	18	-	-	Y	Y
10410693 230000195	750mg	625cc	18	-	-	Y	Y
10410690 230000196	1000mg	625cc	18	-	-	Y	Y
12945021 240000069	1000 mg		6 9 12	- - Y	- - Y	Y Y Y	Y Y Y
13528608 240000073	1000 mg		6 9 12	- - Y	- - Y	Y Y Y	Y Y Y
12945003 240000067	500 mg		6 9 12	- - Y	- - Y	Y Y Y	Y Y Y
13528603 240000068	500 mg		6 9 12	- - Y	- - Y	Y Y Y	Y Y Y
4A6742 SN00003	1000 mg		9 12	- Y	- Y	Y Y	Y Y
10409389 230000217	250 mg	Bulk	12	-	-	Y (12)	Y (12)
10410686 230000218	500 mg	Bulk	12	-		Y (12)	Y (12)
10410693 230000220	750 mg	Bulk	12	-	-	Y (12)	Y (12)
10410690 230000221	1000 mg	Bulk	12	-	-	Y (12)	Y (12)
14219595 240000302	250 mg		1 3 6 9	- - Y X PASS S2	- - Y Y	Y Y Y Y	Y Y Y Y
17851775 99188384	250mg	Bulk	Release	Y	Y	Y	Y
17520624 02052094	500mg	Bulk	Release	Y	Y	Y	Y
17520625 02052095	500mg	Bulk	Release	Y	Y	Y	Y
17520649 02052124	750mg	Bulk	Release	Y	Y	Y	Y
17520650 02052125	750mg	Bulk	Release	Y	Y	Y	Y
17520631 02052101	1000mg	Bulk	Release	Y	Y	Y	Y

b(4)

b(4)

Table B: 30°C/60-65%RH Dissolution data summary 10 and 20dpm

Batch Number	Strength	Pack	Store time (months)	10dpm		20dpm	
				30mins	45mins	30mins	45mins
7209960 8851379 220002324	250 mg	625cc	18 24	- Y	- Y	Y Y	Y Y
7209963 8851380 220002325	250 mg	625cc	18 24	X (1) -	X (1) -	X (1) X FAIL S3	Y (1) X PASS S3
7209999 8851424 220002326	500 mg	625cc	18 24	- -	- -	Y Y	Y Y
7209999 8851429 220002328	500 mg	[redacted]	24	Y	Y	Y	Y
7210002 8851431 220002329	500 mg	[redacted]	18 24	- -	- -	X X FAIL S3	X X PASS S3
7265723 8851381 220002330	750 mg	625cc	18 24	- -	- -	Y Y	Y Y
7209986 8851422 220002331	1000 mg	625cc	18 24	- Y	- Y	Y Y	Y Y
7209989 8851423 220002332	1000 mg	625cc	18 24	- X FAIL S3	- Y	Y(3) Y	Y(3) Y
7210002 8851426 220002327	500 mg	625cc	24	-	-	X FAIL S2 *	Y
3G2745 D-$-2003-85	500 mg	[redacted]	18	Y	Y	Y	Y
3G2746 D-$-2003-86	500 mg	[redacted]	18	Y	Y	Y	Y
3G2747 D-$-2003-87	500 mg	[redacted]	18	Y	Y	Y	Y
3G2742A D-$-2003-73	250 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2743A D-$-2003-74	250 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2744A D-$-2003-75	250 mg	625cc	18	Y	Y	Y	Y
3G2745A D-$-2003-77	500 mg	625cc	18	Y	Y	Y	Y
3G2746A D-$-2003-76	500 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2747A D-$-2003-78	500 mg	625cc	18	Y	Y	Y	Y
3G2748A D-$-2003-79	750 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2749A D-$-2003-80	750 mg	625cc	18	X PASS S2	Y	Y	Y
3G2750A D-$-2003-81	750 mg	625cc	18	Y	Y	Y	Y
3G2751A D-$-2003-82	1000 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2752A D-$-2003-83	1000 mg	625cc	6 18	- Y	- Y	Y Y	Y Y
3G2753A D-$-2003-84	1000 mg	625cc	6	- Y	- Y	Y Y	Y Y
10409389 230000193	250mg	625cc	18	-	-	Y	Y

*insufficient sample available for S3 (2) testing

b(4)

b(4)

Table B: Continued 30°C/60-65%RH Dissolution data summary 10 and 20dpm

Batch Number	Strength	Pack	Store time months	10dpm		20dpm	
				30mins	45mins	30mins	45mins
10410686 230000194	500mg	625cc	18	-	-	Y	Y
10410693 230000195	750mg	625cc	18	-	-	Y	Y
10410690 230000196	1000mg	625cc	18	-	-	Y	Y
12945021 240000069	1000 mg		6	-	-	Y	Y
			9	-	-	Y	Y
			12	Y	Y	Y	Y
13528608 240000073	1000 mg		6	-	-	Y	Y
			9	-	-	Y	Y
			12	Y	Y	Y	Y
4A6742 SN00003	1000mg		9	-	-	Y	Y
			12	X PASS S2	Y	Y	Y
12945003 240000067	500 mg		6	-	-	Y	Y
			9	-	-	Y	Y
			12	Y	Y	Y	Y
13528603 240000068	500 mg		6	-	-	Y	Y
			9	-	-	Y	Y
			12	Y	Y	Y	Y
14219595 240000302	250 mg		1	-	-	Y	Y
			3	-	-	Y	Y
			6	Y	Y	Y	Y

b(4)

Biowaiver Data

Table 1 Raw data for Optimised formulation Dissolution 0.25N HCl, Apparatus 3 at 10dpm

Strength	Batch Number	Dissolution results				
		10 Minutes	20 Minutes	30 Minutes	45 Minutes	f2 Similarity Factor Compared to 1000mg tablet
250mg	17851775				(mean 97.6)	54
500mg	17520624				(mean 95.9)	50
750mg	17520649				(mean 96.8)	59
1000mg	17520631				(mean 97.9)	NA

b(4)

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Robert Kumi
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Patrick Marroum
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BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA #	21,468 SCF 004
Submission Dates	03/15/05 and 05/17/05
Drug	lanthanum carbonate
Formulation	chewable tablets (optimized)
Dosage strength	250, 500, 750 and 1000 mg
OCPB Division	DPE 1
ORM Division	Cardio-Renal Drug Products
Reviewer	Robert O. Kumi, Ph.D.
Team Leader	Patrick Marroum, Ph.D.

Table of Contents

1. Executive Summary

In NDA 21,468 SCF 004, Shire Pharmaceuticals is seeking approval of a new **"optimized" chewable lanthanum carbonate** formulation. Currently, Fosrenol®, lanthanum carbonate, is approved for the treatment of hyperphosphatemia. The sponsor conducted one pharmacodynamic bioequivalence (BE) study (SPD405-121) with the 1000 mg optimized formulation and provided dissolution data in support of this application. The dissolution data were provided in support of a biowaiver request for the optimized lower strength tablets (250, 500 and 750 mg) and to establish a dissolution method and specification for the new optimized tablet.

Recommendations

1. The BE study is acceptable. The pharmacodynamic (PD) and pharmacokinetic (PK) information indicate that the new optimized 1000 mg lanthanum carbonate formulation is bioequivalent (PK and PD) to the 250 mg existing lanthanum carbonate formulation at the 1000 mg dose level. This bioequivalence determination is based on urinary phosphorus excretion, which is assumed to be an acceptable surrogate for the effectiveness of phosphate binding capacity. The data provided in the study report support approval of the new lanthanum carbonate formulation from a PK/PD perspective.

2. **The applicant's proposed dissolution** methodology and specification are not supported by the information provided. Based on the provided dissolution information, OCPB recommends the following interim dissolution methodology and specification:
   - Dissolution Method USP Apparatus 3, 10 dpm in 0.25 N HCl
   - Dissolution Specification Q = ————————

b(4)

The applicant proposed the same medium, but a ——— dip rate; **the applicant's** specification was Q = ———————— .

3. The applicant should provide complete dissolution data for all freshly prepared and relevant stability (as available) batches for all dosage strengths; these data should be obtained at different dip rates including, 10, 15 and 30 dpm. Six or more tablets should be evaluated in each experiment. These data will aid in finalizing the dissolution methodology and specification.

4. The biowaiver cannot be granted due to the use of an inadequate dissolution method (see Recommendations 2 and 3).

Comment to Chemistry Reviewer
The dissolution information provided by the applicant is incomplete; therefore it is not possible to set a final dissolution specification currently. It appears that the dissolution specifications will be determined largely from the stability batches (long-term storage) because there appear to be dissolution differences between freshly prepared batches and batches stored for over 18 months. One other factor that may impact arriving at a satisfactory dissolution methodology is the proposed storage container.

This review includes the following four sections:

1. Background and Introduction
2. Bioequivalence Review
3. Dissolution Method and Dissolution Specification
4. Biowaiver Request (Dissolution Information)

Background and Introduction

Regulatory History

- In January 2004, NDA 21-468 SCF 003 was resubmitted with CMC, preclinical and clinical data on the currently approved Fosrenol and optimized formulation
- In the November 2004 meeting held between the applicant (Shire) and FDA it was decided that further dissolution and stability data were required for substantial evaluation of the optimized formulation of Fosrenol
- In March 2005 (current submission), Shire submitted the current application to provide updated information on the optimized formulation

Clinical Pharmacology Information
The clinical pharmacology information was reviewed previously in NDA 21-468. The maximal daily dosage is 3000 mg lanthanum carbonate (Fosrenol) which is given in divided doses.

Formulation History

- The current formulation (Fosrenol) is a chewable tablet, available as 250 and 500 mg tablets weighing ———— mg, respectively. The 250 mg current formulation has been used in all clinical studies to date. b(4)
- The current formulation was reformulated into smaller tablets (optimized formulations) weighing—— (250 mg tablet) and—— (500 mg tablet) mg,

respectively. Subsequently, higher strength optimized tablets, 750 mg and 1000 mg, were formulated.

According to the applicant, the currently approved tablets are similar to the optimized tablets with minor modifications:

1) same excipients at ————————
2) same manufacturing process ———————— and equipment
3) both are chewable tablets.

b(4)

The amount of ————————————————————————————————————
———— from the new optimized formulation.

The applicant highlights the following two limitations of the currently approved product:

- Need to take more than 10 tablets per day to receive an effective dose
- Existing formulation tablets are large

2. Bioequivalence (BE) Review

Sponsor	Shire
Investigator	Ulrike Lorch, MD, Richmond Pharmacology Ltd., London, UK
Study	SPD405-121
Study Period	09/2004 – 10/2004

Title: Phase I pharmacodynamic equivalence study comparing urinary phosphate excretion for two formulations of lanthanum carbonate chewable tablets in healthy subjects

Study Objectives (Applicant cited)

Primary

- To compare the average of daily urinary phosphorus excretion over three consecutive 24-hour periods in volunteers receiving a diet with standardized phosphate intake following dosing with two formulations of lanthanum carbonate (1000 mg lanthanum) given three times daily immediately after meals

Secondary

- To compare urinary phosphorus excretion on Day 3, the absolute daily urinary phosphorus excretion during the 3-day lanthanum treatment adjusted for baseline, and the absolute urinary phosphorus excretion on Day 3 of the 3-day lanthanum treatment period adjusted for baseline, in volunteers receiving a diet with standardized phosphate intake following dosing with two formulations of lanthanum carbonate (1000 mg lanthanum) given three times daily immediately after meals for 3 days
- To compare the lanthanum pharmacokinetic profiles of two formulations of lanthanum carbonate following 3 days of 1000 mg lanthanum dosed 3 times daily immediately after meals
- To assess the safety and tolerability of the two formulations of lanthanum carbonate chewable tablets

Study Design (Methodology)

An open-label, randomized, crossover study design was employed. Healthy subjects were enrolled in the trial. Each subject received one of two treatments on two separate occasions. There was a 14-day washout period between treatment periods. Treatments were given immediately after standardized meals.

Subjects received the following two treatments:

1) Existing 1000 mg lanthanum carbonate chewable tablets three times daily for three days and once in the morning on Day 4.
2) Optimal 1000 mg lanthanum carbonate chewable tablets three times daily for three days and once in the morning on Day 4.

Subject Disposition

Fifty-two healthy subjects were enrolled (Table 1: Subject Characteristics at ScreeningTable 1) in the study and 51 subjects completed both study panels. PK

information was available for 50 subjects and PD information was available for 48 subjects.

Table 1: Subject Characteristics at Screening

Parameter	Value
Gender	
Male	25
Female	27
Ethnicity	
Caucasian	46
Black	3
Other	3
Age (years)	
Mean ± SD	23.3 ± 3.2
Range	18 - 31
Height (cm)	
Mean ± SD	172.2 ± 9.36
Range	156 – 194
Weight (kg)	
Mean ± SD	67.2 ± 8.95
Range	47 – 95

Blood Sampling

On Day 4, blood samples were collected at -0.5 hours and 0 hours (predose) and at 3, 4, 5, 6, 8, 12, 18, 24, 30, 36 and 48 hours post dose. Additionally, trough blood samples were collected on Days 1, 2, and 3.

Urine Sampling

Urine samples were collected for 24 hour periods starting on Days -2, -1, 1, 2, and 3.

Assay

Phosphorus (Pharmacodynamics)

A commercially available Phosphorus Reagent Kit developed by Roche was used to determine the amount of inorganic phosphorus in urine samples. Phosphorus levels were quantified by colorimetry. The assay performed acceptably as summarized in Table 2.

Table 2: Inorganic Phosphorus Assay Characteristics

Parameter	Measure	Reviewer Comment
Linearity	Linear range from 1.6 to 90 mmol; R > 0.9978	Satisfactory
CV (Between run Precision)	Between 0.3 and 4.9 %	Satisfactory
Relative Bias (Between run Accuracy)	Between -6.8 and +8.5 % of actual value	Satisfactory

Lanthanum (Pharmacokinetics)

Inductively coupled plasma (ICP)-MS was used to determine lanthanum concentrations in plasma. Assay performance was acceptable; the applicant provided assay data in tabular format but did not calculate relative bias or CV %. Based on inspection of the data, the CV % (measure of within day precision) and relative bias (measure of within day accuracy) were both less than 15 %: relative bias for all samples ranged from -11 %

to +9 % of reference values. The assay was linear from 0.03 to 2.00 ng/mL and R^2 was greater than 0.999 for all runs.

Formulation

- lanthanum carbonate chewable tablets, 1000 mg (test: optimized formulation); batch number 10410690
- lanthanum carbonate chewable tablets, 250 mg (reference: existing formulation); batch number 9493152

Pharmacokinetic Analyses

The following lanthanum PK measures were estimated using standard noncompartmental techniques: $AUC_{(0-\infty)}$, Cmax, and Tmax. Standard pharmaco-statistical approaches were used to evaluate bioequivalence (BE); the existing formulation served as the reference.

Pharmacodynamic Analyses

ANOVA was used to compare the average of daily urinary phosphorus excretion (Peu) during the 3-day lanthanum treatment period (primary pharmacodynamic endpoint). The two formulations were considered pharmacodynamically equivalent if the 90 % confidence interval of the difference (test- reference) in average daily urinary phosphorus excretion during the 3-day lanthanum was within ± 20 % limit of the reference.

Other PD endpoints included the following:

- Peu on Day 3
- baseline corrected average Peu
- baseline corrected Peu on Day 3

The baseline was defined as Peu on Day -1 of each treatment period

Reviewer's Note

PK/PD analyses frequently utilize the 90 % confidence interval associated with the geometric mean ratio (of log transformed measures), rather than difference in means, to determine if two treatments are PK/PD equivalent. This approach accounts for the log-normal distribution of PK/PD measures; it is unclear if the PD measure (urinary phosphorus excretion) is log-normally or normally distributed. Phosphorus excretion amounts had a relatively narrow distribution in this study; therefore it is unlikely that log transformation would have a significant impact on the distribution or ensuing BE analyses. Based on this observation, this reviewer deemed the applicant's BE analyses acceptable, but conducted an additional analyses to further evaluate the conclusions (See *Reviewer's Note: Peu = 0 for some samples and Geometric Means for the treatments*)

RESULTS

Pharmacodynamics (PD)

PD measures before and after treatment with the lanthanum carbonate formulations are presented in Table 3.

Table 3: Mean ± SD PD parameters by treatment (n = 48*)

Phosphorus excretion amount in mmol	Formulation	
	4 x 250 mg Existing	1 X 1000 mg Optimized
Urine Phosphorus Excretion at Baseline (Day -1)	20.56 ± 6.30	20.83 ± 5.39
Average daily urinary phosphorus excretion during the 3-day lanthanum treatment period	12.68 ± 4.20	13.22 ± 4.59
Urinary phosphorus excretion on Day 3 of the 3-day lanthanum treatment period	9.87 ± 4.99	10.72 ± 4.68
Average daily urinary phosphorus excretion during the 3-day lanthanum treatment period adjusted for baseline	- 7.88 ± 5.30	-7.62 ± 5.40
Urinary phosphorus excretion on Day 3 of the 3-day lanthanum treatment period adjusted for baseline	-10.69 ± 5.98	-10.11 ± 5.18

* Four subjects were excluded (Subjects 29, 32, 47, and 49) from the analyses due to vomiting, use of concomitant medication or incomplete urine collection

The extent of phosphorus excretion was comparable (< 1 mmol difference) for both formulations during the study. Additionally, the amount of phosphorus excreted after administration of lanthanum carbonate decreased by more than 40 % relative to baseline (Day -1), indicating that both lanthanum carbonate formulations effectively bound phosphorus. The change in phosphorus excretion upon lanthanum carbonate administration was comparable to that obtained in a previous study in healthy volunteers: following 1000 mg lanthanum TID with food (Study LAM-IV-110), baseline Peu was 12.41 mmol reducing to 6.55 mmol on the first day and 5.05 mmol on the third day. From the two study findings it is not clear if Peu steady-state is achieved within 3 days. However, there is a clear difference between baseline and Day 3 Peu without a significant difference between Day 1 vs. Day 3 Peu. Therefore the 3-day dosing period appears suitable to assess PD BE.

Bioequivalence Assessment

The sponsor's analyses indicated that there was less than 0.9 mmol difference between the test and reference and the corresponding 90 % confidence interval ranged from -0.33 to 1.92 for all treatment comparisons (Table 4). Per the applicant's analyses, this finding indicates that the two formulations are pharmacodynamically equivalent.

Table 4: Bioequivalence Assessment Using Pharmacodynamics (Urinary Phosphorus Excretion)

Phosphorus Excretion (mmol)	Test- Reference Difference	90 % CI	± 20 % Limit
Average daily urinary phosphorus excretion during the 3-day lanthanum treatment period	0.5361	-0.1870 – 1.2591	± 2.5358
Urinary phosphorus excretion on Day 3 of the 3-day lanthanum treatment period	0.8522	-0.2094 - 1.9139	± 1.9736
Average daily urinary phosphorus excretion during the 3-day lanthanum treatment period adjusted for baseline	0.4770	-0.3076 – 1.2615	± 1.5975
Urinary phosphorus excretion on Day 3 of the 3-day lanthanum treatment period adjusted for baseline	0.7405	-0.3343 – 1.8153	± 2.1544

Reviewer's Note: Impact of Peu = 0 for some samples and Geometric Means for the treatments

In a limited number of samples (n < 15) from five subjects included in the analyses, Peu was reported as = 0.00 mmol. These Peu values occurred in both treatments, but were more prevalent in Treatment A than in Treatment B. It is unclear how Peu over a 24-hour period can be equal to zero; this finding suggests that the assay performance or sample processing was suboptimal on some occasions. The overall impact of including the Peu values = 0 is lowering of the mean for Treatment A. This reviewer reanalyzed the data excluding Peu values = 0 [Day 3 means]: existing formulation Peu = 11.0 ± 3.9 (n = 43) vs. optimized formulation Peu = 11.4 ± 3.0 (n = 45). This reanalysis reduces the treatment difference from ~ 0.85 to 0.40 mmol. Overall, inclusion or exclusion of the Peu values = 0 did not appear to significantly alter the BE conclusions.

The geometric means for the treatments (excluding Peu = 0) were similar: Treatment A Peu = 10.63 and Treatment B Peu = 10.66. The resulting point estimate (Geometric Mean Ratio: Treatment B vs. A) is ~ 1.00 . When only subjects with paired samples (both treatments) are used, the point estimate ~ 1.03 and the associated 90 % confidence interval is ~ 0.97 to 1.09 (Appendix: Table A). The point estimates and resulting 90 % confidence interval indicate that the two treatments are BE with respect to their PD activity.

Pharmacokinetics

Lanthanum pharmacokinetics were similar for both treatments as shown in Table 5.

Table 5: Mean ± SD Pharmacokinetic measures following 1000 mg lanthanum carbonate administration on Day 4 (n = 50)

PK Measure	4 x 250 mg existing formulation	1 x 1000 mg optimal formulation
AUC_{0-48} (h.ng/mL)	11.99 ±4.41	12.25 ± 4.18
Cmax (ng/mL)	0.52 ± 0.18	0.54 ± 0.19
Tmax (h)	4.08 ± 1.40	3.84 ± 1.36

The two lanthanum formulations have similar PK and may be considered BE, based on PK measures (Table 6). These PK data support the PD findings, however, it should be noted that the PK measures are not the primary BE determinants as the drug is not intended for systemic availability.

Table 6: Bioequivalence Results for PK Measures

PK Measures	Ratio Between 1 x 1000 mg optimal formulation and 4 x 250 mg existing formulation	90 % Confidence Interval
AUC_{0-48} (h.ng/mL)	1.0274	0.9827 – 1.0742
Cmax (ng/mL)	1.0257	0.9763 – 1.0775

Applicant's Safety Summary

Both formulations were safe and well-tolerated with no obvious concerns associated with either treatment. The most common adverse event was headache.

Conclusion/Recommendation

The PD and PK information indicate that the new optimized 1000 mg lanthanum carbonate formulation is bioequivalent (PK and PD) to the 250 mg existing lanthanum carbonate formulation at the 1000 mg dose level. This bioequivalence determination is based on urinary phosphorus excretion, which is assumed to be an acceptable surrogate for the effectiveness of phosphate binding capacity. The data provided in the study report support approval of the new lanthanum carbonate formulation from a PK/PD perspective.

3. Dissolution Methodology and Specification

Summary of Recommendations

The Dissolution Methodology and Specification Proposed by the applicant are unacceptable because the data provided are incomplete. OCPB recommendations and comments regarding the dissolution method and specification for the new optimized chewable tablets follow:

1. The submitted dissolution data indicate that the following recommendation for an interim dissolution method and specification are appropriate:

Dissolution Medium	0.25 N HCl, 900 mL
Apparatus	Dissolution apparatus 3 at 10 dpm
Specification	Q = ———

b(4)

- The applicant should provide relevant dissolution data using the interim dissolution method and specification. This interim procedure can be amended when the applicant provides adequate evidence that dip rates ——— are not as discriminating as dip rates ———.
- In general, dissolution testing should be conducted on all tablet strengths, as appropriate

2. Dissolution data obtained between 6 and 18 months should be provided, if available. These data may be useful for determining if formulations change release characteristics during storage. Furthermore these data may be helpful in establishing the product shelf-life. The applicant should provide complete dissolution information on stability batches including the following:
   - dissolution data on all intended dosage strengths in the final container
   - dissolution data at various relevant dip rates, such as 5, 10, 15, 20, and 30 dpm

3. The use of visual disintegration time (VDT) to predict dissolution properties does not appear appropriate. VDT does not appear to be the only factor influencing dissolution behavior; VDT appears to be an inherent property of the formulation and is not entirely determined by dip rate.

4. Overall, dissolution testing appears appropriate to discriminate among various types of optimized chewable formulations: differing ———, differing ———, and differing ——— stored under accelerated conditions (temperature above 25 C, relative humidity > 60 %).

b(4)

Overview of Proposed Dissolution Method Development and Dissolution Specification

Parameter	Applicant's Proposal	Reviewer's Recommendation
Dissolution Medium	0.25 N HCl, 900 mL	0.25 N HCl, 900 mL
Apparatus	Dissolution Apparatus 3 at ———	Dissolution Apparatus 3 at 10 dpm
Specification	Q = ———	Q = ———

b(4)

Dissolution Medium

The proposed dissolution medium is acceptable. The FDA and applicant agreed previously to the selection of the 0.25 N HCl medium; this medium is used for the approved drug product (Fosrenol chewable tablets).

Apparatus (Degree of Agitation and Impact on Disintegration Time)

Apparatus 3 is used at 10 dpm in the dissolution method for the currently approved chewable tablet formulation. Apparatus 3 was proposed by the applicant and accepted by the FDA because both agreed that chewable tablets may require more severe agitation than is typically generated in dissolution Apparatus 2. The new optimized formulation is also a chewable tablet; thus Apparatus 3 appears to be an appropriate device to assess dissolution. It should be noted that the applicant and FDA have held extensive discussions regarding the appropriate dip rate (dips per minute or dpm) for dissolution.

The applicant's main argument regarding disintegration time and its relationship with dissolution is predicated on the principle that the dip rate affects the visual disintegration time (VDT). However, the applicant has not provided sufficient objective evidence (data) showing the effect of visual disintegration time on dissolution. Such evidence may include disintegration results from standard disintegration apparatus, comparing these results to observed disintegration during dissolution testing and correlating these disintegration data to dissolution data. This evidence is needed because:

1) In some experiments, the link between VDT and dissolution was not clear as some formulations with prolonged VDT (VDT > 45 minutes) had comparable dissolution with formulations with shorter VDT (VDT ≤ 30 minutes).
2) Some batches tested at the same dpm had different VDT (e.g. prolonged vs. short).

These observations suggest that VDT may not only be a function of dip rate but may be **related to a formulation's inherent characteristics.**

As shown in some of the stability batches, **the disintegration "limitation" can be** overcome by increasing the time for Q. However, this approach may not be suitable if this time extension allows unacceptable batches to pass the dissolution specification, without preserving the ability to discriminate among formulations.

Reviewer Note on Dip Rate Selection

The use of Apparatus 3 is acceptable, but the basis for choosing the ——— rate is not clear from the data provided; the 15 dpm dip rate was as discriminating (per Applicant) as the ——— for non-long-term stability batches (< 1 month old). The applicant has not provided sufficient data to exclude the use of a dip rate ———. Until the applicant provides conclusive evidence that dip rates ——— are inappropriate for dissolution

b(4)

testing of the optimized formulations, the 10 **dpm rate should be used. The applicant's and reviewer's comments related to the selection** of dip rate are summarized in Table 7. It should be noted that the statements regarding the effect of dip rates in Table 7 are based primarily on freshly prepared batches.

Table 7: Applicant's Main Findings Regarding Dissolution and dpm Rate

Parameter	Applicant's Comment	Reviewer's Comment
Discriminatory Ability		
Potential Prolongation of Dissolution Testing Time		
Differing Disintegration Rates Between Formulations		
Disintegration Limitation		

b(4)

Applicant's Rationale for Selection of Dissolution Specification

According to the applicant, the proposed specification, Q = ——— represents an appropriate compromise between the time required to obtain sufficient product dissolution to qualify the product and choosing conditions that limit the influence of disintegration (allows time for optimized formulation to disintegrate).

b(4)

Reviewer's Note

Based on the data provided for——— Q = ——— rather than ——— appears reasonable; however, as noted previously, the applicant has to provide sufficient evidence that dip rates ——— are not as equally discriminating as the ——— rate.

Dissolution Information Provided in Support of Method Development
The applicant provided the following two sets of data:

1) Dissolution data generated from freshly prepared batches using different dip rates (dpm) and optimized tablets prepared with different characteristics:
- Significant and modest changes in [redacted] (magnesium stearate [redacted] proposed content)
- Different manufacturing processes such as [redacted] b(4)
- Exposure of formulations to different stress conditions
- Estimation of disintegration time via visual observation (VDT); the tablet has not disintegrated if there is a mass of material on [redacted] at sampling time point

2) Dissolution data generated from available stability batches

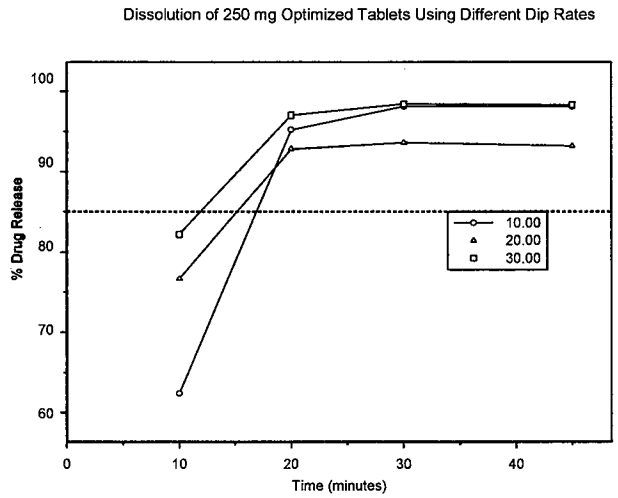
Data provided in support of the method development are in the Appendix [Tables 1-17].

Results
In the following section results are presented for various dissolution conditions. Only key points from each study will be highlighted.

Dissolution Information from Freshly Prepared Batches or Non-stability Batches

Experiment 1: Effect of amount of magnesium stearate* [redacted] and dip rate (10, 20 or 30 dpm) on dissolution and visual disintegration time (VDT) [Appendix Table 1] b(4)

Figure 1: Dissolution Rate as a Function of Dip Rate for Typical Formulation (n=2 tablets per dip rate)



*Increasing magnesium stearate increases the [redacted] content of the formulation b(4)

- ——— amount of magnesium stearate decreased dissolution rate
- The 10, 20 and 30 dpm rates were able to distinguish among the different formulations with varying magnesium stearate amounts
- VDTs for typical formulation (1x magnesium stearate) were 45, 30 and 20 minutes for the 10, 20 and 30 dpm rates respectively. However, VDT did not appear to be directly correlated to extent of dissolution. VDTs for ——— magnesium stearate formulations ≥ 45 minutes at all dip rates. b(4)
- VDT appears to be inversely proportional to dip rate; however, this relationship is based on only three data pairs.
- Greater than 90 % of optimized 1x formulation dissolved within 20 minutes for all dip rates, despite differing VDTs.

Reviewer Notes

- Only two tablets were tested, thus the values obtained may not be reliable with respect to demonstrating variability or typical distribution of drug release
- Data are presented for 250 mg tablets and may not be reflective of what may occur with all tablet strengths.
- Utility of VDT assessment is unclear. Clearly, VDT may not be the only determinant of dissolution because although dip rates and VDT varied, all dip rates released drug at similar rates.

Conclusion/Recommendation

- Data indicate that 10 dpm rate with Q = ——— is acceptable b(4)
- Applicant should provide data for all tablet strengths using appropriate dip rates, and these data should be obtained from at least six tablets

Experiment 2*

a) Effect of amount of magnesium stearate ——— b(4)

and dip rate (10, 15 or 20 dpm) on dissolution of freshly prepared 500 mg tablets (n=3, per condition) [Appendix Tables 2 and 3]

*Experiment 2 evaluated 7 day-old tablets and 14 day-old tablets.

- Drug release rate was comparable for all formulations tested
- Drug release was comparable at 10, 15 and 20 dpm rates; within 10 minutes the percent of drug release ≥ 90 % for all formulations
- VDTs were 20, 30 and 10 minutes for the 10, 15 and 20 minute dpm rates, respectively.

Reviewer Note

VDT data were not directly correlated to dpm rate; it is unclear if this is a function of inherent tablet variability.

Conclusion

Based on the data provided, the 10 dpm rate is acceptable, with Q = ——— b(4)
Additionally, VDT may not be a suitable measure to predict dissolution behavior

b) Effect of amount of magnesium stearate [redacted] b(4)

differing humidity and temperature (45°C/75 % RH) and dip rate (10, 15 or 20 dpm) on dissolution of 7 day-old 500 mg tablets [Appendix Tables 2 and 3]

- Tablets that were 7-days old had initially lower drug release than freshly prepared tablets, particularly at the 10 and 20 minute time points, but at the 30-minute time point all formulations (fresh and 7-day old) had > 90 % drug release
- All 7-day old formulations had similar dissolution profiles under the three different dpm rates, although the 10 dpm rate tended to have lower initial drug release than the 15 and 20 dpm rates
- VDTs ranged from 30 to 45 minutes for all formulations: in most case VDT was comparable for all dip rates, and other times VDT was 15 minutes longer for 10 dpm rate.

Reviewer Notes

- VDT data were not directly correlated to dpm rate and VDT did not appear to be related to dissolution rate.
- All dip rates appeared to offer comparable discriminatory ability among formulations at the 10 and 20 minute time point; however, at the 30 and 45 minute time points, there was no discrimination among formulations. It is noted that the 10 dpm rate offers the greatest discrimination among batches formulations (freshly prepared relative to other batches)

Conclusion/Recommendation

Setting Q at a time point > 30 minutes may not allow for discrimination between formulations stored under ambient conditions and formulations exposed to high relative humidity and accelerated temperature. However, if formulations exposed to these non-standard conditions remain viable over an extended period of time (shelf life), setting Q at time points ≥ 30 minutes is acceptable. If this is not the case, the more conservative Q value with respect to time is appropriate to assure product quality.

c) Effect of amount of magnesium stearate [redacted] b(4)

humidity and temperature (45°C/75 % RH) and dip rate (10, 15 or 20 dpm) on dissolution of 14 day-old tablets [Appendix: Tables 4 and 5]

The findings from this experiment are similar to those for the 7 day-old tablets (Please see section 2 b).

Experiment 3: Effect of amount of magnesium stearate [redacted]

humidity and temperature (45°C/75 % RH) and days (1, 3 or 7 days) on dissolution of tablets* [Appendix: Table 6] b(4)

* Different combinations of parameters were evaluated: [redacted] compared

- For the same day, humidity and temperature conditions, the 20 dpm rate was able to discriminate between the [redacted] tablets (lower dissolution rates) and the [redacted] tablets
- For the same humidity and temperature conditions, one day-old tablets could be distinguished from 3 day old tablets (less dissolution) at the 20 dpm rate; similarly formulations with [redacted] magnesium stearate exhibited less dissolution b(4)
- Increasing humidity and exposure to humidity decreased overall dissolution relative to freshly prepared tablets

Reviewer Note

The experiment demonstrates that the method was able to discriminate among various formulations under extreme (accelerated stability) conditions: Q will not be achieved under high temperature and humidity. However, the experiment should have included an evaluation of different dip rates to determine if one dip rate is more appropriate than another.

Conclusion/Recommendation

- The method appears adequate to discriminate high humidity (100 % RH) and temperature conditions (60 C)
- Experiment should be repeated at different dip rates and on all tablet strengths

Experiment 4: Effect of amount of magnesium stearate [redacted] b(4)

[redacted] humidity and temperature (40°C/75 % RH) and days (fresh, 7 or 8 days) on dissolution of tablets* [Appendix Tables 7]

Similar trends with respect to the effects of magnesium stearate content, humidity and temperature were observed as in previous experiment (please see preceding sections):

- Discrimination seen at all dip rates for the [redacted] formulation
- Increasing humidity decreased initial dissolution b(4)

Reviewer's Note

The applicant acknowledged that the 10 dpm rate had greater discriminatory ability for one sample, but thinks that the VDT [redacted] is inappropriately long for a dissolution test b(4)

OVERALL RECOMMENDATIONS FOR FRESHLY PREPARED FORMULATIONS AND NON-STABILITY BATCHES

- The 10 dpm rate with Q = [redacted] is suitable for quality evaluations. b(4)
- The described experiments should be repeated using all proposed formulations (n = 6 tablets, per study) at different dip rates, as appropriate.

Dissolution Information from Long-Term Stability Batches

Six-month stability Data [Appendix Tables 9, 10, 11, 12, and 13]

Dissolution data were provided for six month-old batches: these data were generated at the [redacted] rate. The tablets were stored in various containers under the following conditions: 25 °C/60% RH, 30 °C/65% RH, 40°C/75% RH. It should be noted that the majority of the data were obtained from 500 mg and 1000 mg tablets (only one 250 mg batch). b(4)

Reviewer Note

At most time points, apart from the 10-minute time point, >90 % drug was released. Over 95 % drug was released at the 30 minute time for all formulations and test conditions. VDT was 20 or 30 minutes for all conditions and formulations, apart from four instances.

Conclusion/Recommendation

- Based on the six-month stability data, Q = [redacted] is adequate. However, it should be noted that data for other dpm rates were not provided; thus, it is unclear if a lower dpm would provide sufficient or better discrimination than the [redacted] dpm rate. b(4)
- The described experiment should be repeated using all proposed formulations at different dip rates, as appropriate.

Eighteen-month stability Data (n =3 tablets per batch) [Appendix Tables 8, 14, 15, 16 and 17]

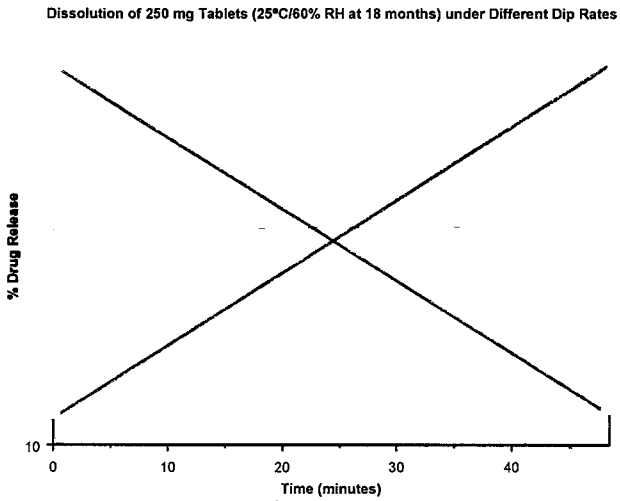
Dissolution data were provided for eighteen month-old batches (250 mg tablets): these data were generated at the [redacted] rate. The tablets were stored in 625 cc containers at 25 or 30 °C with 60% RH. Data were limited (n = 1) for all the 30 °C samples and may not be representative of the actual or mean distribution of drug release, therefore these data are not considered for this discussion. It is noted that the 30 dpm, 25°C with 60% RH data were considered for comparative purposes, although n=1 for this condition. The dissolution data were obtained from batch number 7209963 at the 5, 10, 20 and 30 dpm rates. b(4)

Reviewer Notes

- As shown in Figure 2, increasing dip rate increases the drug release rate. Clearly as presented, the 5 and 10 dpm rates would probably not achieve Q = [redacted] However, subsequent information showed that this batch had reduced drug release (rate and extent) relative to other batches. Consequently, this batch may not be suitable to evaluate the effect of dip rate on dissolution. b(4)

- The 30 dpm (n=1) data overlapped the 20 dpm data, which suggests a plateau in dip rate effect may have been reached. If the plateau has been reached, then the utility of dip rates ≥ 20 dpm is unclear because these high dip rates may mask inherent drug release characteristics or prevent discrimination among acceptable and non-acceptable batches.

Figure 2: Dissolution Rate as a Function of dip rate for Typical Formulation (18 month-old)



b(4)

Conclusions/Recommendations

- Based on the data provided, dip rates ≤10 dpm will not be feasible to assess routine dissolution. It should be noted that for freshly prepared batches, the Q value was readily reached at 10 dpm within 30 minutes. The difference in dissolution for stability batches and freshly prepared batches suggests that there may be some changes in the interaction between excipients and drug product, or potentially the container system may not provide an adequate storage environment.
- VDTs were not assessed in this experiment thus it is not possible to determine if dip rate affected disintegration and dissolution subsequently.
- The applicant should repeat the experiments to explore the effect of dip rates that are ——— (e.g. 15 dpm) on dissolution; these tests should be done on different batches of all tablet strengths with at least n = 6 tablets, per test condition. b(4)
- Stability data obtained between 6 and 18 months, for example at 12 months, should be provided, if available. These data may be useful for determining if formulations change release characteristics during storage. Furthermore these data may be helpful in establishing the product shelf-life.

——————— stability Data [Appendix Tables 15, 16 and 17] b(4)

1) ———Bottles

Data were provided for two batches of 500 mg tablets, 7210002 and 7209999. Dissolution data were generated at 25° and 30° C with 60 % RH.

Reviewer's Notes

Effect of Temperature

Typically, 25° and 30° C data are expected to have comparable drug release, since the temperature difference is relatively small. Formulation 7209999 exhibited similar dissolution characteristics at both temperatures, whereas, Formulation 7210002 had a slower drug release rate at 30° C than at 25° C.

Batch 7210002 vs. 7209999 (Apparent VDT Effect)

The two batches exhibited different dissolution profiles, especially at time points < 45 minutes. Formulation 7209999 achieved ~ 100 % dissolution within 30 minutes whereas Formulation 7210002 had achieved < 70 % dissolution within 30 minutes. The applicant attributes the difference in dissolution to the difference in VDT (> 45 minutes for slow release batch); however, the applicant's argument is weakened by the absence of VDT data for the faster drug-releasing formulation. Assuming that VDT is an acceptable measure to predict drug release, formulations with prolonged VDT may not be suitable for clinical use. The findings from this experiment impact the dissolution method and specification as follows:

- VDT may be an inherent property of the formulation, rather than a function of dip rate (both formulations were tested at ———)
- The dissolution specification should be restrictive enough to eliminate formulations with prolonged VDT and subsequent slow drug release, as necessary.

Currently, it is unknown if prolonged VDT (VDT > 45 minutes) with relatively slow dissolution will affect *in vivo* performance. The applicant proposed a specification of Q = ——————. Based on this proposal, Formulation 7210002 would pass with S3 testing and Formulation 7209999 would pass with S1 testing. It should be noted that Formulation 7209999 would also pass Q = ——————— b(4)

Conclusion/Recommendation

- It appears the —— was able to distinguish between two 500 mg formulations with differing VDT; however, it is unclear if a lower dip rate would have been effective as well. If possible, the applicant should repeat the study at 10 dpm and 15 dpm to determine if these lower dip rates are adequate.
- The data provided suggest that the Q should be set for a shorter time, such as —— minutes, to ensure that formulations with very different dissolution profiles (quality) do not meet the batch release acceptance criteria. It is not obvious why two identical formulations should have such disparate dissolution profiles, yet be considered of the same quality. b(4)
- The applicant should consider evaluating the impact of different *in vitro* drug release characteristics on *in vivo* performance.

2) 625 CC bottles

Data were provided for seven batches (14 profiles obtained) including 250 (two), 500 (two), 750 (one) and 1000 (two) mg strength tablets at 25 and 30 C with 60 % RH. For ease of review, dissolution data were considered on different levels: tablet strength and temperature (focus on 25° C data)

Reviewer's Notes

Dissolution Data for Different Dosage Strengths

Dissolution of one **250 mg** batch, 7209960, was almost complete within 30 minutes (VDT = 30 minutes) whereas the rate of drug release was decreased in batch 7209963 (VDT > 45 minutes). In the slower-releasing batch at 30 minutes (25° C) dissolution was variable to some extent (range 78 to 95 %: two tablets with less than 85 % released and four tablets with more than 85 % released) and dissolution was complete at 45 minutes. At 30° C, drug release was lower than at 25° C and required S3 testing before meeting Q criteria at ————. According to the applicant the difference in the drug release rate is attributed to the prolonged VDT. b(4)

Dissolution of one **500 mg batch**, 720999 was essentially complete within 20 minutes under all conditions tested (VDT 30 minutes). In contrast, batch 7210002 had relatively reduced drug release (VDT > 45 minutes) and required S2 and S3 testing to meet the proposed specification (Q = ————————). At the 30 minute time point < 80 % of the drug was released and at the 45 minute time point < 90 % of the drug was released. It should be noted that these 500 mg batches were also tested in the ——bottles and had similar dissolution characteristics. b(4)

Dissolution of **750 mg tablet** was effectively complete (100 % drug release) within 30 minutes; the recorded VDTs were 30 and 45 minutes

Dissolution of **1000 mg tablet** was > 90 % complete within 30 minutes; recorded VDT were 30 and 45 minutes. It is noted that the drug release rate in one batch appeared slower than in the other batch at time points < 30 minutes.

Conclusion/Recommendation

From the data provided, it is not clear if dose strength influences dissolution: the 750 and 1000 mg batches appeared to have slower initial release than the 250 and 500 mg batches that required only S1 testing. Dose strength is not expected to impact dissolution because sink conditions are supposed to be maintained for all tablet strengths in these experiments. Ideally all profiles (all tablet strengths) should have been superimposed upon one another.

Effect of Storage Time on Dissolution [Appendix: Table B]

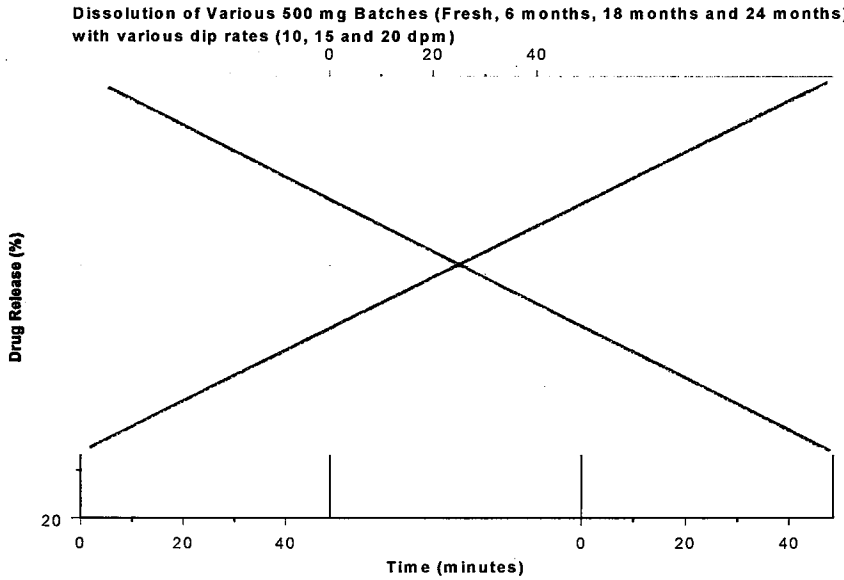
There appears to be a marked effect of storage time on dissolution behavior as shown by a comparison of freshly prepared batches to stability batches. Figure 3 and Figure 4 support this observation; however the observation is limited by the fact that

- data were pooled from different lots stored in different containers
- data were insufficient in some cases (n = 1, 2, or 3 tablets)
- batches of different strength were not evaluated under the same conditions, thereby making dosage-strength comparisons difficult

The finding of different dissolution characteristics between freshly prepared batches and stability batches suggest that there may be formulation changes as time progresses; this may be due to unanticipated drug-excipient interaction that may impact shelf-life.

Plot Note
In the following two plots, increasing symbol size indicates increasing VDT (values recorded as > 45 were given a value of 90 minutes and batches without VDT data were assigned N/A and have the smallest size on the plots). Storage conditions are delineated in each panel and varying symbols indicate different dip rates.

Figure 3: Drug Release from 500 mg Batches Highlighting Effect of Storage Time



b(4)

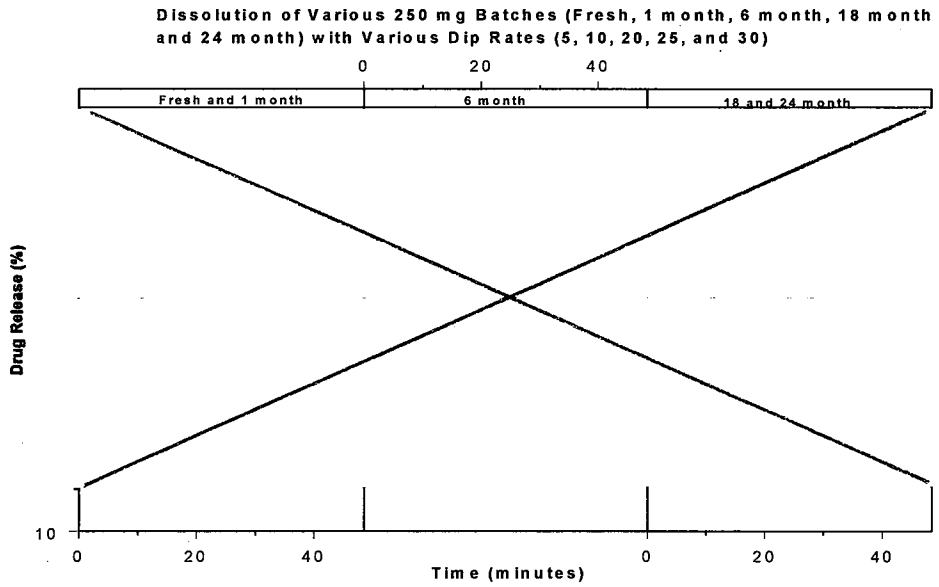
In brief Figure 3 depicts the following:

- lack of effect of dip rate or VDT on dissolution characteristics of freshly prepared batches (panel 1)
- the effect of dip rate, if any, on batches ≥ 6 months old could not be determined because data were only available at the ——— rate b(4)
- the effect of VDT on dissolution of the 24-month old batches (panel 3) could not be determined because VDT was determined for only one of the batches tested; this tested batch had VDT > 45 minutes and was assigned a value of 90 minutes

In brief Figure 4 depicts the following:

- decreasing dip rate may decrease drug release rate (Panels 1 and 3) but effect of VDT on drug release is unclear
- drug release may be decreased as storage time increases (Panels 1 and 2 vs. Panel 3); however, this conclusion is weakened by the fact that different batches are used in arriving at this conclusion
- VDT appears to be an inherent property of the batch, rather than a function of dip rate. Different drug batches evaluated at the same dip rate had differential drug release characteristics in some cases.

Figure 4: Dissolution of 250 mg Batches Highlighting Effect of Storage Time



b(4)

Discussion and Recommendations Based on Dissolution Data from Stability Batches (Stored in 625 cc bottles)

It appears the 20 dpm rate was able to discriminate among stability batches. The batches could be roughly divided into two subsets: batches that had more than 90 % release within 30 minutes (n ~ 10) and those with < 90 % release (n ~ 4) in 30 minutes. Using the applicant-proposed Q = ——————— only—— batches required testing beyond S1; ultimately, all batches ultimately passed the proposed dissolution specification. For Q= ——————— these —— batches may have failed the specification, but all remaining batches would have passed. These findings suggest that the specification proposed is too liberal because batches of inadequate quality may pass batch release requirements when they should not. It is unclear if a dip rate ——— would be acceptable. If possible, the applicant should repeat the study at 10 dpm and 15 dpm.

b(4)

The data provided suggest that the Q should be set for a shorter time, such as ——— to ensure that batches with significantly different dissolution profiles do not meet the release specification.

OVERALL RECOMMENDATIONS ON DISSOLUTION METHOD AND SPECIFICATION BASED ON DISSOLUTION DATA FROM STABILITY BATCHES AND FRESHLY PREPARED BATCHES

The dissolution medium and apparatus are acceptable; however, the applicant has not satisfactorily determined the optimal dip rate for dissolution testing. Additionally, the specification proposed, Q =——————— appears rather liberal in light of the provided data.

b(4)

Based on freshly prepared batches, a 10 or 15 dpm dip rate is acceptable because these dip rates each have as much discriminatory ability as the 20 dpm rate. On the other hand, the limited stability data (one 250 mg batch with n = 3 tablets) suggest that the 5 and 10

dpm rates were too low to achieve disintegration and subsequent dissolution of stability batches. It is noted that the 250 mg batch (# 7209963) used to conduct this dip rate evaluation had poor drug release characteristics, requiring S3 testing before passing the proposed specification. This finding suggests that batch 7209963 had inherently slow drug release and may not accurately reflect the effect of dip rates < 20 dpm on dissolution. No data were provided at the 15 dpm rate for stability batches. The majority of batches tested using the 20 dpm rate met Q = ———— at the S1 level and these batches would also meet Q = ————. b(4)

In sum, the data provided suggest that the following recommendation for an interim dissolution method and specification are adequate:

Parameter	**Reviewer's Recommendation**
Dissolution Medium	0.25 N HCl, 900 mL
Apparatus	Dissolution apparatus 3 at 10 dpm
Specification	Q = ————

b(4)

The applicant should provide the following information on all (stability and freshly prepared) batches:

- relevant dissolution data using the interim methodology and specification
- dissolution data on all intended dosage strengths in the final container
- dissolution data at various relevant dip rates, such as 5, 10, 15, 20, and 30 dpm

This information will help in establishing a final dissolution methodology and specification.

Biowaiver Request

The applicant requests a biowaiver for the 250, 500 and 750 mg optimized tablet formulations. Each of these strengths is made form a common ——. Information submitted in support of this biowaiver request included the BE study, SPD405-121, and dissolution data comparing lower strength optimized tablets to the 1000 mg optimized tablet. b(4)

Table 8: Composition of Chewable Tablet Formulation

Ingredients	Function	Amount (mg)

b(4)

As shown in Table 8, the tablets are proportionally similar. Four strengths have been proposed: 250, 500, 750 and 100 mg.

Reviewer Note on Biowaiver Requirements: Dissolution Conditions (Approved Formulation vs. Optimized Formulation)

The biowaiver evaluation is based primarily on dissolution comparisons. The applicant proposed the following dissolution method for the new optimized formulations: USP Apparatus 3 at ——— in 0.25 N HCl. The current dissolution method for the approved tablet is Apparatus 3 at 10 dpm using 0.25 N HCl. Previously, the applicant was asked to provide additional data at the 5, 10, 15 and 20 dpm rates to support approval of the dissolution method for the optimized formulation. The studies provided for the biowaiver were conducted only at ———, because the applicant considered the ——— rate appropriate. As indicated in the Dissolution section of this review, the applicant has not provided sufficient evidence to exclude the use of dip rates < ———. Based on the information provided, dissolution testing at ——— does not appear appropriate. b(4)

Methodology

Various dissolution studies were used in support of the biowaivers:

- Apparatus 2 at 50 rpm on whole tablets in three different media
- Apparatus 3 at ———

Both crushed and intact tablets were used for some of these studies. b(4)

Results

The dissolution comparisons, f2 (relative to 1000 mg tablets) for the various studies are presented in Table 9. Data for individual tablets are included in the appendix. This review focuses on the Apparatus 3 data as Apparatus 2 is not considered appropriate for dissolution testing of chewable tablets, per previous FDA-applicant discussions. It is noted that all formulations had > 90 % dissolved at the 20 minute time point, suggesting

that f2 values may not be relevant (per *Guidance for Industry: In vivo dissolution testing of Immediate Release Products)*. Dissolution comparisons are summarized in Table 9.

Table 9: Comparison of Optimized Formulations for Biowaiver Request

Similarity factor f2 figures for each formulation and strength in each dissolution test. Tablets were tested WHOLE unless otherwise indicated

Formulation	Batch Numbers	Medium *(whole tablets except where indicated)*	Apparatus (Rate)	f2 Similarity Factor %
'Optimised' 1000 mg vs. 'Optimised' 250 mg	10410690 vs. 10409389	0.25N HCl	3 ———	72 (n=12)
		0.25N HCl	2 (50rpm)	65 (n=12)
		0.1N HCl	2 (50rpm)	42 (n=12)
		PH 4.5 Buffer	2 (50rpm)	83 (n=12)
		(crushed tablets)		
'Optimised' 1000 mg vs. 'Optimised' 500 mg	10410690 vs. 10410686	0.25N HCl	3 ———	74 (n=12)
		0.25N HCl	2 (50rpm)	70 (n=12)
		0.1N HCl	2 (50rpm)	76 (n=12)
		PH 4.5 Buffer	2 (50rpm)	96 (n=12)
		(crushed tablets)		
'Optimised' 1000 mg vs. 'Optimised' 750 mg	10410690 vs. 10410693	0.25N HCl	3 ———	87 (n=12)
		0.25N HCl	2 (50rpm)	75 (n=12)
		0.1N HCl	2 (50rpm)	40 (n=12)
		PH 4.5 Buffer	2 (50rpm)	100 (n=12)
		(crushed tablets)		

b(4)

b(4)

Discussion

The suitability of the biowaiver request with respect to dissolution data is predicated on the acceptability of the dissolution method provided to support the biowaiver request. Data were provided using dissolution Apparatus 2 and Dissolution Apparatus 3.

Apparatus 2 data are supportive (please refer to Appendix for a brief discussion on the Apparatus 2 results), but the main emphasis of this review is on the Apparatus 3 results. Apparatus 3 data were provided for only one dip rate, ——— which does not appear to be an appropriate dip rate (see Dissolution Section, Page 8). Consequently, the presented f2 calculations are not acceptable. The sponsor should have conducted a more robust analysis focused on Apparatus 3 data: this analysis should have compared all strengths at different dip rates. In sum, the data provided are not adequate to support the biowaiver request. b(4)

Recommendation

The applicant has not provided adequate evidence to support the biowaiver requests on the basis of dissolution information; particularly the use of ——— rate, alone, is not supported by the dissolution data. Therefore, the biowaiver should not be granted. The sponsor should provide additional dissolution data at dip rates < ———and > ——— to support the selection of the——— rate. The acceptability of the——— data will depend on the comparative dissolution data obtained with other dip rates. Currently a 10 dpm rate is considered appropriate for dissolution evaluation of the approved formulation and appears appropriate for the new optimized formulation. b(4)

APPENDIX

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Table A: Pharmacodynamic Data Used to Estimate Point Estimate and 90 % Confidence Interval for Patients with Paired Data (Undergoing Both Treatments)

	SUBNO	LPDA	SUBNO	LPD		Ratio		
	01		01			0.905853		
	02		02			1.111787		
	03		03			1.015588		
	04		04			1.056698		
	05		05			0.627548		
	06		06			0.970656		
	07		07			1.060113		
	09		09			1.045534		
	10		10			1.063992		
	11		11			1.074744		
	12		12			0.935688		
	14		14			0.913986		
	15		15			1.118264		
	16		16			0.931195		
	17		17			1.064547		
	18		18			0.917975		
	19		19			1.044876		
	20		20			1.019379		
	21		21			1.033004		
	22		22			1.142454		b(4)
	23		23			1.035548		
	24		24			1.009051		
	25		25			1.034918		
	26		26			1.030007		
	27		27			0.767223		
	28		28			1.041969		
	30		30			0.426742		
	31		31			1.214235		
	33		33			0.744595		
	34		34			1.534996		
	38		38			1.266983		
	40		40			1.117118		
	41		41			1.232449		
	43		43			0.881131		
	44		44			0.891061		
	45		45			1.119273		
	46		46			0.981548		
	48		48			1.495066		
	50		50			1.096104		
	51		51			1.032242		
Scale	52		52			1.138845	*90 % Confidence Interval*	
Log	**Mean**	**2.360511**	**Mean**	**2.397818**		**1.027927**	**0.970299**	**1.085554**
Normal		**10.59637**	**Mean**	**10.99915**	**STD**	**0.190548**		
					CI	**0.057627**		

Appendix Table B: Reviewer-Complied Dissolution Data to show influence of storage duration on dissolution

Strength	Batch	Dip Rate	Time	Release	VDT	Storage	Temp	Humid	Contain		n	Table
250	Normal	10	10	62.4	45	0	Room	60	NA		2	1
250	Normal	10	20	95.2	45	0	Room	60	NA		2	1
250	Normal	10	30	98.1	45	0	Room	60	NA		2	1
250	Normal	10	45	98.1	45	0	Room	60	NA		2	1
250	Normal	20	10	76.7	30	0	Room	60	NA		2	1
250	Normal	20	20	92.8	30	0	Room	60	NA		2	1
250	Normal	20	30	93.6	30	0	Room	60	NA		2	1
250	Normal	20	45	93.2	30	0	Room	60	NA		2	1
250	Normal	30	10	82.2	20	0	Room	60	NA		2	1
250	Normal	30	20	97	20	0	Room	60	NA		2	1
250	Normal	30	30	98.4	20	0	Room	60	NA		2	1
250	Normal	30	45	97.7	20	0	Room	60	NA		2	1
250	3G2743A	20	10	90	30	6	25	60			6	9
250	3G2743A	20	20	101.8	30	6	25	60			6	9
250	3G2743A	20	30	101.2	30	6	25	60			6	9
250	3G2743A	20	45	101.3	30	6	25	60			6	9
250	14219595	20	10	96	20	0	25	60			6	12
250	14219595	20	20	97.8	20	0	25	60			6	12
250	14219595	20	30	97.7	20	0	25	60			6	12
250	14219595	20	45	97.4	20	0	25	60			6	12
250	14219595	20	10	94.4	20	1	25	60			6	12
250	14219595	20	20	97.3	20	1	25	60			6	12
250	14219595	20	30	96.1	20	1	25	60			6	12
250	14219595	20	45	96.7	20	1	25	60			6	12
250	7209963	25	10	61.1	#N/A	18	25	60		625	6	14
250	7209963	25	20	93.3	#N/A	18	25	60		625	6	14
250	7209963	25	30	99.8	#N/A	18	25	60		625	6	14
250	7209963	25	45	100.4	#N/A	18	25	60		625	6	14
250	7209963	30	10	67.6	#N/A	18	25	60		625	6	14
250	7209963	30	20	97.4	#N/A	18	25	60		625	6	14
250	7209963	30	30	101.1	#N/A	18	25	60		625	6	14
250	7209963	30	45	101.9	#N/A	18	25	60		625	6	14
250	7209963	5	10	25.6	#N/A	18	25	#N/A		625	3	8
250	7209963	5	20	37.2	#N/A	18	25	#N/A		625	3	8
250	7209963	5	30	43.8	#N/A	18	25	#N/A		625	3	8
250	7209963	5	45	55.3	#N/A	18	25	#N/A		625	3	8
250	7209963	10	10	34.4	#N/A	18	25	#N/A		625	3	8
250	7209963	10	20	48.1	#N/A	18	25	#N/A		625	3	8
250	7209963	10	30	69.8	#N/A	18	25	#N/A		625	3	8
250	7209963	10	45	74.8	#N/A	18	25	#N/A		625	3	8
250	7209963	20	10	45	#N/A	18	25	#N/A		625	3	8
250	7209963	20	20	69.1	#N/A	18	25	#N/A		625	3	8
250	7209963	20	30	89.4	#N/A	18	25	#N/A		625	3	8
250	7209963	20	45	98.5	#N/A	18	25	#N/A		625	3	8
250	7209963	30	10	42.5	#N/A	18	25	#N/A		625	1	8
250	7209963	30	20	69	#N/A	18	25	#N/A		625	1	8
250	7209963	30	30	90.2	#N/A	18	25	#N/A		625	1	8

b(4

Strength	Batch	Dip Rate	Time	Release	VDT	Storage	Temp	Humid	Contain	n	Table
250	7209963	30	45	98.3	#N/A	18	25	#N/A	625	1	8
250	7209963	20	10	36.5	90	18	25	60	625	1	15
250	7209963	20	20	56.9	90	18	25	60	625	1	15
250	7209963	20	30	75.7	90	18	25	60	625	1	15
250	7209963	20	45	93.2	90	18	25	60	625	1	15
250	7209963	20	10	41.5	90	24	25	60	625	6	15
250	7209963	20	20	64.2	90	24	25	60	625	6	15
250	7209963	20	30	85.8	90	24	25	60	625	6	15
250	7209963	20	45	100.3	90	24	25	60	625	6	15
250	7209960	20	10	91.3	30	18	25	60	625	6	15
250	7209960	20	20	97.6	30	18	25	60	625	6	15
250	7209960	20	30	97.3	30	18	25	60	625	6	15
250	7209960	20	45	97.5	30	18	25	60	625	6	15
250	7209960	20	10	86.2	30	24	25	60	625	6	15
250	7209960	20	20	98.9	30	24	25	60	625	6	15
250	7209960	20	30	99.4	30	24	25	60	625	6	15
250	7209960	20	45	99.2	30	24	25	60	625	6	15
500	F734/46AM	10	10	95.5	20	0	25	#N/A	NA	3	2
500	F734/46AM	10	20	98.2	20	0	25	#N/A	NA	3	2
500	F734/46AM	10	30	98	20	0	25	#N/A	NA	3	2
500	F734/46AM	10	45	98.1	20	0	25	#N/A	NA	3	2
500	F734/46AM	15	10	98.7	30	0	25	#N/A	NA	3	2
500	F734/46AM	15	20	99	30	0	25	#N/A	NA	3	2
500	F734/46AM	15	30	98.6	30	0	25	#N/A	NA	3	2
500	F734/46AM	15	45	99	30	0	25	#N/A	NA	3	2
500	F734/46AM	20	10	98.1	10	0	25	#N/A	NA	3	2
500	F734/46AM	20	20	98.5	10	0	25	#N/A	NA	3	2
500	F734/46AM	20	30	98.7	10	0	25	#N/A	NA	3	2
500	F734/46AM	20	45	98.6	10	0	25	#N/A	NA	3	2
500	12945003	20	10	89	30	6	25	60		6	11
500	12945003	20	20	99.3	30	6	25	60		6	11
500	12945003	20	30	99.3	30	6	25	60		6	11
500	12945003	20	45	99.5	30	6	25	60		6	11
500	13528603	20	10	91.9	20	6	25	60		6	13
500	13528603	20	20	98.8	20	6	25	60		6	13
500	13528603	20	30	98.8	20	6	25	60		6	13
500	13528603	20	45	98.9	20	6	25	60		6	13
500	7209999	20	10	87.7	30	18	25	60	625	6	15
500	7209999	20	20	100.3	30	18	25	60	625	6	15
500	7209999	20	30	99.8	30	18	25	60	625	6	15
500	7209999	20	45	100.4	30	18	25	60	625	6	15
500	7209999	20	10	83.1	#N/A	24	25	60	625	6	15
500	7209999	20	20	100.5	#N/A	24	25	60	625	6	15
500	7209999	20	30	101.1	#N/A	24	25	60	625	6	15
500	7209999	20	45	101.5	#N/A	24	25	60	625	6	15
500	7209999	20	10	79.9	#N/A	24	25	60		6	17
500	7209999	20	20	98.8	#N/A	24	25	60		6	17
500	7209999	20	30	98.7	#N/A	24	25	60		6	17
500	7209999	20	45	99.2	#N/A	24	25	60		6	17

b(4)

b(4)

Strength	Batch	Dip Rate	Time	Release	VDT	Storage	Temp	Humid	Contain	n	Table
500	7210002	20	10	40	90	18	25	60		6	17
500	7210002	20	20	65.2	90	18	25	60		6	17
500	7210002	20	30	82.8	90	18	25	60		6	17
500	7210002	20	45	96.6	90	18	25	60		6	17
500	7210002	20	10	36.4	90	24	25	60		6	17
500	7210002	20	20	57.2	90	24	25	60		6	17
500	7210002	20	30	74	90	24	25	60		6	17
500	7210002	20	45	90.6	90	24	25	60		6	17
500	7210002	20	10	45.4	#N/A	24	25	60	625	6	17
500	7210002	20	20	72.4	#N/A	24	25	60	625	6	17
500	7210002	20	30	90.6	#N/A	24	25	60	625	6	17
500	7210002	20	45	99.8	#N/A	24	25	60	625	6	17

b(4)

Table 1: Lanthanum Carbonate Dissolution Apparatus 3 Optimised Formulation ((b) (4) magnesium stearate) Discrimination Experiments VDT= visual disintegration time (minutes)

Batch Number	Figure No.	Dip Rate (dpm)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
Optimised Formulation	3, 4	10	45	(b) (4) (62.4)	(b) (4) (95.2)	(b) (4) (98.1)	(b) (4) (98.1)
	2, 4	20	30	(76.7)	(92.8)	(93.6)	(93.2)
	1, 4	30	20	(82.2)	(97.0)	(98.4)	(97.7)
Optimised Formulation	3	10	>45	(b) (4) (31.9)	(b) (4) (45.5)	(b) (4) (59.6)	(b) (4) (79.9)
	2	20	45	(44.5)	(75.9)	(90.4)	(92.4)
	1	30	45	(45.6)	(76.2)	(91.6)	(94.8)
Optimised Formulation	3	10	>45	(b) (4) (18.6)	(b) (4) (26.5)	(b) (4) (32.0)	(b) (4) (38.1)
	2	20	>45	(22.1)	(35.2)	(44.1)	(56.2)
	1	30	>45	(24.7)	(39.1)	(52.9)	(70.5)

Table 2: Lanthanum Carbonate Dissolution Apparatus 3 Standard Optimised Formulation Discrimination Experiments Fresh and 7 day accelerated storage VDT= visual disintegration time (minutes)

Batch Number	Figure No.	Dip Rate (dpm)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
Fresh	5, 8, 9, 13	10	20	(b) (4) 95.5	(b) (4) 98.2	(b) (4) 98.0	(b) (4) 98.1
	5, 7, 10, 14	15	30	98.7	99.0	98.6	99.0
	5, 8, 11, 12, 15	20	10	98.1	98.5	98.7	(b) (4) (98.6)
7 days stored open at 40°C/75%RH	6	10	45	51.9	86.3	95.3	(b) (4) 95.4
	7	15	30	81.6	93.5	95.9	95.7
	8, 12	20	45	70.3	95.4	96.3	96.7
7 days stored open at 40°C/75%RH	6	10	45	49.8	78.9	96.0	(b) (4) (99.2)
	7	15	45	58.2	87.9	97.8	(b) (4) 97.9
	8	20	45	68.8	94.2	98.3	98.6
7 days stored open at 40°C/75%RH	6	10	30	50.1	81.7	95.1	96.0
	7	15	30	81.5	94.5	96.5	96.5
	8	20	30	69.2	97.7	97.7	97.7
7 days stored open at 40°C/75%RH	6	10	30	58.9	91.6	95.3	95.3
	7	15	30	70.3	95.3	95.6	95.2
	8	20	20	77.2	95.3	96.1	94.7
7 days stored open at 40°C/75%RH	6	10	45	53.8	82.1	94.2	94.2
	7	15	30	62.2	92.0	95.0	94.0
	8	20	30	68.0	94.9	94.3	95.8
7 days stored open at 40°C/75%RH	6	10	30	50.8	81.9	94.3	95.6
	7	15	30	68.3	95.0	(b) (4) (96.9)	(b) (4) (97.5)
	8	20	45	67.7	93.8	(b) (4) 95.9	(b) (4) 96.1

Table 3: Lanthanum Carbonate Dissolution Apparatus 3 Modified Optimised Formulation ((b) (4) magnesium stearate) Discrimination Experiments Fresh and 7 day accelerated storage VDT= visual disintegration time (minutes)

Batch Number	Figure No.	Dip Rate (dpm)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets)			
Fresh	5, 6, 9	10	30	(b) (4) (90.0) (83.8)	(94.8) (95.8)	(95.0) (95.8)	(95.2) (95.9)
	5, 7, 10	15	30				
	5, 8, 11, 12	20	20	(96.1)	96.0)	(96.0)	(96.0)
7 days stored open at 40°C/75%RH	6	10	45	(48.5)	(80.8)	(94.7)	(95.9)
	7	15	30	(63.7)	(93.0)	(95.2)	(95.4)
	8	20	30	(67.0)	(94.2)	(96.1)	(96.0)
7 days stored open at 40°C/75%RH	6	10	30	(59.5)	(88.9)	(94.1)	(94.2)
	7	15	30	(59.0)	(92.2)	(94.4)	(94.8)
	8	20	30	(66.6)	(93.4)	(94.1)	(93.9)
7 days stored open at 40°C/75%RH	6	10	30	(51.7)	(87.1)	(95.1)	(95.8)
	7	15	30	(57.9)	(84.2)	(95.0)	(94.8)
	8	20	30	(66.8)	(94.9)	(95.7)	(95.4)
7 days stored open at 40°C/75%RH	6	10	30	(51.5)	(82.9)	(94.7)	(95.2)
	7	15	30	(61.8)	(92.6)	(94.8)	(95.4)
	8	20	30	(b) (4) (82.4)	(94.3)	(96.0)	(95.6)
7 days stored open at 40°C/75%RH	6	10	30	(b) (4) (50.4)	(82.1)	(92.8)	(93.6)
	7	15	30	(58.8)	(89.6)	(93.7)	(94.0)
	8	20	30	(67.7)	(94.4)	(94.7)	(94.3)
7 days stored open at 40°C/75%RH	6	10	45	(50.3)	(82.0)	(94.7)	(95.3)
	7	15	30	(58.0)	(89.1)	(95.8)	(96.0)
	8, 12	20	30	(65.2)	(94.9)	(96.6)	(96.1)

Table 4: Lanthanum Carbonate Dissolution Apparatus 3 Standard Optimised Formulation Discrimination Experiments 14 day accelerated storage VDT= visual disintegration time (minutes)

Batch Number	Figure No.	Dip Rate (dpm)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets)			
				10 mins	20 mins	30 mins	45 mins
14 days stored open at 40°C/75%RH	9	10	45	(b) (4) (46.2) (63.8)	(b) (4) (76.8) (92.1)	(b) (4) (93.3) (95.6)	(b) (4) (94.8) (95.3)
	10	15	30				
	11	20	30	(67.0)	(96.3)	(97.3)	(97.3)
14 days stored open at 40°C/75%RH	9	10	45	(51.7)	(82.2)	(96.2)	(97.1)
	10	15	45	(68.1)	(96.9)	(98.7)	(99.2)
	11	20	30	(69.6)	(94.9)	(98.0)	(98.2)
14 days stored open at 40°C/75%RH	9	10	45	(47.5)	(78.4)	(93.2)	(96.3)
	10	15	30	(58.5)	(93.9)	(97.3)	(97.6)
	11	20	30	(67.7)	(96.9)	(97.7)	(97.8)
14 days stored open at 40°C/75%RH	9	10	30	(51.6)	(86.0)	(92.9)	(95.7)
	10	15	30	(73.0)	(95.0)	(96.1)	(95.9)
	11	20	30	(76.5)	(94.7)	(95.1)	(94.9)
14 days stored open at 40°C/75%RH	9	10	30	(48.0)	(78.4)	(92.6)	(95.7)
	10	15	30	(62.4)	(90.6)	(94.2)	(94.1)
	11	20	30	(70.3)	(94.2)	(95.4)	(95.7)
14 days stored open at 40°C/75%RH	9	10	45	(55.1)	(88.6)	(95.4)	(93.8)
	10	15	30	(66.0)	(93.7)	(94.7)	(94.9)
	11	20	30	(63.6)	(90.5)	(95.9)	(96.1)

Table 5: Lanthanum Carbonate Dissolution Apparatus 3 Modified Optimised Formulation (b) (4) magnesium stearate) Discrimination Experiments 14 accelerated storage VDT= visual disintegration time (minutes)

Batch Number	Figure No.	Dip Rate (dpm)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets)			
				10 mins	20 mins	30 mins	45 mins
14 days stored open at 40°C/75%RH	9	10	45	(b) (4) (50.4)	(b) (4) (80.0)	(b) (4) (93.9)	(b) (4) (95.4)
	10	15	30	(80.9)	(91.8)	(94.5)	(94.8)
	11	20	30	(70.6)	(83.5)	(94.7)	(94.6)
14 days stored open at 40°C/75%RH	9	10	30	(55.4)	(85.4)	(92.2)	(95.3)
	10	15	45	(67.5)	(91.3)	(92.9)	(93.0)
	11	20	30	(72.4)	(92.8)	(93.1)	(92.8)
14 days stored open at 40°C/75%RH	9	10	30	(51.2)	(82.9)	(93.5)	(94.7)
	10	15	30	(59.5)	(91.1)	(95.5)	(95.6)
	11	20	30	(64.8)	(92.2)	(95.0)	(95.5)
14 days stored open at 40°C/75%RH	9	10	30	(50.7)	(81.2)	(95.0)	(94.8)
	10	15	30	(55.4)	(87.0)	(95.3)	(94.6)
	11	20	30	(68.1)	(93.2)	(96.2)	(96.2)
14 days stored open at 40°C/75%RH	9	10	30	(57.0)	(85.5)	(93.6)	(93.5)
	10	15	30	(60.1)	(87.8)	(94.5)	(95.2)
	11	20	30	(68.5)	(92.9)	(94.4)	(94.1)
14 days stored open at 40°C/75%RH	9	10	45	(45.0)	(75.0)	(92.2)	(95.1)
	10	15	30	(56.1)	(90.3)	(94.5)	(94.8)
	11	20	30	(64.2)	(91.0)	(93.7)	(93.8)

Table 6: Lanthanum Carbonate Dissolution Apparatus 3 Optimised Formulation Discrimination Experiments 1 and 3 day 60°C/100%RH accelerated storage

Batch Number	Figure No.	Dip Rate (dpm)	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets)			
			10 mins	20 mins	30 mins	45 mins
Standard formula (b) (4) (b) (4)						
1 day 60C/100%RH open	12	(b) (4)	(b) (4) (38.9)	(b) (4) (76.1)	(b) (4) 96.3)	(b) (4) 97.3)
3 days 60C/100%RH open	12		(22.5)	(43.9)	66.6)	88.0)
(b) (4)						
1 day 60C/100%RH open	12		(38.2)	(69.8)	91.2)	94.3)
3 days 60C/100%RH open	12		(26.9)	(52.9)	76.0)	95.5)

Table 8: Lanthanum Carbonate Dissolution Apparatus 3 at 5-30dpm Optimised Formulation Stability Samples (18 months)

Batch Number	Figure No.	Dip Rate (dpm)	Store Time (months)	Store Temp (°C)	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets)			
					10 mins	20 mins	30 mins	45 mins
220002325 250mg 625cc (b) (4)	16	5	18	25	(b) (4) (25.6)	(b) (4) (37.2)	(b) (4) (43.6)	(b) (4) (55.3)
	16	10	18	25	(34.4)	(48.1)	(59.8)	(74.8)
	16	20	18	25	(45.0)	(69.1)	(89.4)	(98.5)
	16	30	18	25				
	16	5	18	30				
	16	10	18	30				
	16	20	18	30				
	16	30	18	30				

Table 7: Lanthanum Carbonate Dissolution Apparatus 3 Optimised Formulation Discrimination Experiments Fresh vs 7 or 8 day accelerated storage VDT= visual disintegration time (minutes)

Batch Number	Figure No.	Dip Rate (dpm)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
Fresh (b) (4)	13	10	>45	(55.2)	(81.7)	(92.8)	(93.9)
	14	15	30	(71.8)	(91.5)	(92.7)	(92.7)
	15	20	30	(66.0)	(94.7)	(94.7)	(94.5)
Fresh (b) (4)	13	10	>45	(64.5)	(91.6)	(94.8)	(97.7)
	14	15	>45	(77.1)	(94.9)	(95.4)	(95.8)
	15	20	>45	(79.8)	(94.8)	(94.7)	(95.1)
Fresh (b) (4)	13	10	>45	(84.1)	(90.4)	(95.3)	(96.2)
	14	15	>45	(70.6)	(94.9)	(96.6)	(95.9)
	15	20	45	(83.3)	(95.4)	(95.5)	(95.7)
Fresh (b) (4)	13	10	>45	(67.4)	(83.5)	(94.5)	(95.4)
	14	15	30	(71.6)	(95.0)	(96.9)	(97.5)
	15	20	30	(87.2)	(95.5)	(96.6)	(95.5)
7 days stored at 40/75%RH open	13	10	45	(37.9)	(70.7)	(89.1)	(94.9)
	14	15	45	(57.5)	(84.6)	(93.7)	(93.5)
	15	20	30	(62.6)	(88.7)	(94.1)	(94.6)
8 days stored at 40/75%RH open	13	10	>45	(40.9)	(67.0)	(85.9)	(94.3)
	14	15	30	(50.7)	(81.3)	(93.3)	(94.4)
	15	20	30	(60.9)	(88.1)	(95.3)	(95.8)
8 days stored at 40/75%RH open	13	10	>45	(39.2)	(66.5)	(85.8)	(94.9)
	14	15	30	(54.0)	(78.5)	(92.4)	(94.4)
	15	20	30	(57.4)	(85.3)	(95.1)	(95.2)
7 days stored at 40/75%RH open	13	10	>45	(29.6)	(50.2)	(74.5)	(92.3)
	14	15	>45	(41.8)	(69.7)	(89.1)	(95.5)
	15	20	>45	(51.7)	(78.0)	(94.0)	(96.7)

Table 9: Lanthanum Carbonate Dissolution Apparatus 3 at (b) (4) Optimised Formulation Stability Samples (6 months) VDT= visual disintegration time (minutes)

Batch Number	Dip Rate (dpm)	Store Time (months)	Store Temp (°C)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
D-$-2003-73 250 mg (b) (4)	(b) (4)	6	25°C/ 60%RH		(84.4)	(96.7)	(96.8)	(96.0)
		6	30°C/60%RH		(86.1)	(100.5)	(100.7)	(100.8)
		6	40°C/75%RH		(84.7)	(101.0)	(100.9)	(101.3)
D-$-2003-74 250 mg (b) (4)		6	25°C/ 60%RH	30	(90.0)	(101.8)	(101.2)	(101.3)
		6	30°C/60%RH	20	(90.0)	(97.7)	(98.6)	(97.8)
		6	40°C/75%RH	20	(82.4)	(100.2)	(100.4)	(100.3)
D-$-2003-76 500 mg (b) (4)		6	25°C/ 60%RH		(79.0)	(99.2)	(99.3)	(99.8)
		6	30°C/60%RH		(78.3)	(99.0)	(99.1)	(99.6)
		6	40°C/75%RH		(68.6)	(98.4)	(100.2)	(100.2)

Table 10: Lanthanum Carbonate Dissolution Apparatus 3 at (b) (4) Optimised Formulation Stability Samples (6 months) VDT= visual disintegration time (minutes)

Batch Number	Dip Rate (dpm)	Store Time (months)	Store Temp (°C)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
	(b) (4)							
D-$-2003-79 750 mg (b) (4)		6	25°C/ 60%RH	~45	(b) (4) (79.4)	(b) (4) (97.8)	(b) (4) (99.0)	(b) (4) (99.0)
		6	30°C/60%RH	~45	(b) (4) (73.1)	(b) (4) (95.0)	(b) (4) (96.3)	(b) (4) (96.6)
		6	40°C/75%RH		(b) (4) (72.4)	(b) (4) (97.0)	(b) (4) (98.0)	(b) (4) (98.2)
D-$-2003-82 1000 mg (b) (4)		6	25°C/ 60%RH	30	(b) (4) (74.1)	(b) (4) (97.4)	(b) (4) (102.5)	(b) (4) (104.4)
		6	30°C/60%RH	30	(b) (4) (75.9)	(b) (4) (99.6)	(b) (4) (102.5)	(b) (4) (102.7)
		6	40°C/75%RH		(b) (4) (65.3)	(b) (4) (96.9)	(b) (4) (99.0)	(b) (4) (99.5)
D-$-2003-83 1000 mg (b) (4)		6	25°C/ 60%RH	20	(b) (4) (72.2)	(b) (4) (98.1)	(b) (4) (99.9)	(b) (4) (100.1)
		6	30°C/60%RH	30	(b) (4) (72.8)	(b) (4) (98.2)	(b) (4) (102.1)	(b) (4) (102.5)
D-$-2003-84 1000 mg (b) (4)		6	25°C/ 60%RH	30	(b) (4) (74.6)	(b) (4) (98.0)	(b) (4) (101.6)	(b) (4) (102.1)
		6	30°C/60%RH	30	(b) (4) (72.4)	(b) (4) (96.8)	(b) (4) 99.0)	(b) (4) (100.0)

Table 11: Lanthanum Carbonate Dissolution Apparatus 3 at (b) (4) Optimised Formulation Stability Samples (6 months) VDT= visual disintegration time (minutes)

Batch Number	Dip Rate (dpm)	Store Time (months)	Store Temp °C)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
12945021	(b) (4)							
240000069 1000 mg (b) (4)-HDPE		6	25°C/60%RH	30	(b) (4) (83.6)	(b) (4) (98.4)	(b) (4) (98.5)	(b) (4) (98.7)
		6	30°C/65%RH	20	(b) (4) (84.1)	(b) (4) (98.5)	(b) (4) (98.8)	(b) (4) (99.3)
		6	40°C/75%RH		(b) (4) (64.8)	(b) (4) (94.2)	(b) (4) (99.8)	(b) (4) (99.8)
13528608								
240000073 1000 mg (b) (4)-HDPE		6	25°C/60%RH	30	(b) (4) (87.8)	(b) (4) (98.6)	(b) (4) (98.6)	(b) (4) (98.4)
		6	30°C/65%RH	20	(b) (4) (77.6)	(b) (4) (97.5)	(b) (4) (97.5)	(b) (4) (97.5)
13528603								
240000092 500 mg (b) (4)		6	25°C/60%RH	30	(b) (4) (82.3)	(b) (4) (99.6)	(b) (4) (99.1)	(b) (4) (99.2)
		6	30°C/65%RH	20	(b) (4) (76.1)	(b) (4) (97.4)	(b) (4) (97.5)	(b) (4) (97.3)
		6	40°C/75%RH	30	(b) (4) (57.5)	(b) (4) (94.3)	(b) (4) (98.3)	(b) (4) (99.5)
12945021								
240000093 1000 mg (b) (4)		6	25°C/60%RH	20	(b) (4) (86.5)	(b) (4) (99.7)	(b) (4) (100.6)	(b) (4) (99.7)
		6	30°C/65%RH	20	(b) (4) (77.4)	(b) (4) (99.9)	(b) (4) (101.2)	(b) (4) (100)
		6	40°C/75%RH	30	(b) (4) (55.1)	(b) (4) (87.9)	(b) (4) (100.7)	(b) (4) (99.9)
13528608								
240000094 1000 mg (b) (4)		6	25°C/60%RH	30	(b) (4) (81.6)	(b) (4) (98.6)	(b) (4) (99.0)	(b) (4) (98.6)
		6	30°C/65%RH	30	(b) (4) (76.5)	(b) (4) (96.8)	(b) (4) (97.1)	(b) (4) (97.7)
		6	40°C/75%RH	>30	(b) (4) (57.5)	(b) (4) (89.4)	(b) (4) (97.6)	(b) (4) (97.8)
12945903								
240000091 500 mg (b) (4)		6	25°C/ 60%RH	30	(b) (4) (89.0)	(b) (4) (99.3)	(b) (4) (99.3)	(b) (4) (99.5)
		6	30°C/ 65%RH	20	(b) (4) (80.2)	(b) (4) (99.4)	(b) (4) (99.5)	(b) (4) (99.3)
		6	40°C/ 75%RH	>30	(b) (4) (51.2)	(b) (4) (87.2)	(b) (4) (99.4)	(b) (4) (99.9)

Table 12: Lanthanum Carbonate Dissolution Apparatus 3 at (b) (4) Optimised Formulation Stability Samples (0-6 months) VDT= visual disintegration time (minutes)

Batch Number	Dip Rate (dpm)	Store Time (months)	Store Temp (°C)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
240000302 250 mg (b) (4) HDPE	(b) (4)	Initial		20	(b) (4)	(b) (4)	(b) (4)	(b) (4)
		1	25°C/60%RH	20				
		1	30°C/65%RH	20				
		1	40°C/75%RH	20				
240000067 500 mg (b) (4) HDPE		6	25°C/ 60%RH	30	(b) (4)	(b) (4)	(b) (4)	(b) (4)
		6	30°C/ 65%RH	20				
		6	40°C/75%RH	> 30				
240000068 500 mg (b) (4) HDPE		6	25°C/ 60%RH	30	(b) (4)	(b) (4)	(b) (4)	(b) (4)
		6	30°C/ 65%RH	30				
		6	40°C/75%RH	> 30				

Table 13: Lanthanum Carbonate Dissolution Apparatus 3 at (b) (4) Optimised Formulation Stability Samples (6 months) VDT= visual disintegration time (minutes)

Batch Number	Dip Rate (dpm)	Store Time (months)	Store Temp (°C)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
240000060 500 mg (b) (4)	(b) (4)	6	25°C/60%RH	20	(b) (4)	(b) (4)	(b) (4)	(b) (4)
		6	30°C/65%RH	30				
		6	40°C/75%RH	30				
240000061 500 mg (b) (4)		6	25°C/60%RH	20	(b) (4)	(b) (4)	(b) (4)	(b) (4)
		6	30°C/65%RH	30				
		6	40°C/75%RH	30				
240000062 1000 mg (b) (4)		6	25°C/60%RH	20	(b) (4)	(b) (4)	(b) (4)	(b) (4)
		6	30°C/65%RH	30				
		6	40°C/75%RH	30				
240000063 1000 mg (b) (4)		6	25°C/60%RH	20	(b) (4)	(b) (4)	(b) (4)	(b) (4)
		6	30°C/65%RH	30				
		6	40°C/75%RH	30				

Table 14: Lanthanum Carbonate Dissolution Apparatus 3 at (b) (4) Optimised Formulation Stability Samples (18 months)

Batch Number	Dip Rate (dpm)	Store Time (months)	Store Temp (°C)	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 15 mins	30 mins	45 mins	60 mins
220002325 250mg 62Scc (b) (4)	25	18	25°C/60%RH	(b) (4)	(b) (4)	(b) (4)	(b) (4)
	25	18	30°/60%RH				
	30	18	25°C/60%RH				
	30	18	30°C/60%RH				

Table 15: Lanthanum Carbonate Dissolution Apparatus 3 at (b) (4) Optimised Formulation Stability Samples (18 & 24 months) VDT= visual disintegration time (minutes)

Batch Number	Fig No.	Dip Rate (dpm)	Store Time (mons)	Store Temp (°C)	V D T	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
8851278 220002324 250 mg 625 cc (b) (4)		(b) (4)	18	25°C/ 60%RH	30	(b) (4)			
			18	30°C/60%RH	30				
	17		24	25°C/ 60%RH					
	17		24	30°C/60%RH					
8851380 220002325 250 mg 625 cc (b) (4)			18	25°C/ 60%RH	> 45				
	17		24	25°C/ 60%RH					
	17		24	30°C/60%RH	S1				
			24	30°C/60%RH	S2				
			24	30°C/60%RH	S3				mean of 12 = 80.0 mean of 24 = 80.8 passes S3
8851424 220002326 500 mg 625 cc (b) (4)			18	25°C/ 60%RH	30				
			18	30°C/65%RH	20				
	17		24	25°C/ 60%RH					
	17		24	30°C/60%RH					

Table 16: Lanthanum Carbonate Dissolution Apparatus 3 at (b) (4) Optimised Formulation Stability Samples (18 & 24 months) VDT= visual disintegration time (minutes)

Batch Number	Fig No.	Dip Rate (dpm)	Store Time (mons)	Store Temp (°C)	V D T	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
8851431 220002329 500 mg (b) (4)		(b) (4)	18	25°C/ 60%RH	> 45	(b) (4)			
			18	30°C/60%RH	> 45				
	18		24	25°C/ 60%RH	S1				
	18		24	25°C/ 60%RH	S2				mean of 12 =81.5
	18		24	30°C/60%RH	S1				
			24	30°C/80%RH	S2				mean of 12 = 78.3
			24	30°C/60%RH	S3				mean of 24 = 80.9 passes S3
8851381 220002330 750 mg 625 cc (b) (4)			18	25°C/ 60%RH	30				
			18	30°C/60%RH	45				
	17		24	25°C/ 60%RH					
	17		24	30°C/60%RH					

Table 17: Lanthanum Carbonate Dissolution Apparatus 3 at (b) (4) Optimised Formulation Stability Samples (18 & 24 months) VDT= visual disintegration time (minutes)

Batch Number	Figure No	Dip Rate (dpm)	Store Time (months)	Store Temp (°C)	VDT	Whole Tablet Dissolution Apparatus 3 Individual Drug Release (Mean in Brackets) 10 mins	20 mins	30 mins	45 mins
8851422 220002331 1000 mg 625 cc (b) (4)		(b) (4)	18	30°C/60%RH	30	(b) (4) (71.8)	(b) (4) 96.1)	(b) (4) 97.7)	(b) (4) 97.2)
	17		24	25°C/ 60%RH		(b) (4) (85.2)	99.0)	99.3)	(b) (4) 99.5)
	17		24	30°C/60%RH		(b) (4) (72.5)	96.8)	(100.1)	(b) (4) 100.8)
8851423 220002332 1000 mg 625 cc (b) (4)			18	25°C/ 60%RH	30	(b) (4) (57.3)	90.5)	(100.1)	(b) (4) 100.3)
			18	30°C/60%RH	45	(b) (4) (45.0)	(77.3)	(b) (4) 94.1)	(b) (4) 99.7)
	17		24	25°C/ 60%RH		(b) (4) (57.3)	88.8)	(99.2)	(b) (4) 101.2)
	17		24	30°C/60%RH		(b) (4) (45.5)	77.8)	94.8)	101.9)
8851428 220002327 500 mg 625 cc (b) (4)	17		24	25°C/ 60%RH		(b) (4) (45.4)	72.4)	90.8)	(b) (4) 99.8)
	17		24	30°C/60%RH		(b) (4) (35.4)	57.5)	76.9)	93.5)
8851429 220002328 500 mg (b) (4)	18		24	25°C/ 60%RH		(b) (4) (79.9)	98.8)	98.7)	99.2)
	18		24	30°C/60%RH		(b) (4) (76.1)	98.4)	(b) (4) 100.3)	100.2)

Apparatus 2 Data (Biowaiver Request)
Apart from three instances, all dissolution comparisons indicate that the lower strength tablets have similar dissolution to the 1000 mg tablet. The f2 values for both the 250 and 750 mg tablets were < 50 using Apparatus 2 at 50 rpm (0.1 N HCl); the remaining instance with f2 < 50 occurred under the same dissolution conditions with crushed tablets.

Reviewer Note: Use of Crushed Tablets for Dissolution Testing
The FDA does not accept dissolution data from crushed tablets because they are unlikely to reflect true dissolution behavior of intact tablets.

The difference in dissolution between the 250 mg and 1000 mg tablet may be attributed to the 250 mg tablet being more soluble than the 1000 mg table in the 0.1 N HCl medium. It is unclear why the dissolution of the 750 mg tablet would vary significantly from that of the 1000 mg tablet as both strengths have limited solubility in this medium. The applicant states that the 750 mg tablet shows lower release in this medium than the 1000 mg tablet, probably due to the variability of disintegration of the tablets and consequently dissolution of the drug in the medium in which sink conditions are not prevailing. Following this line of reasoning, the dissolution of the 1000 mg tablet would be expected to be lower, not higher as seen, unless there is inherent variability from one tablet strength to another.

The lower strength tablets were most similar to the 1000 mg tablet in pH 4.5 buffer; this may have been due to the limited solubility of all tablet strengths in this media resulting in the same relative saturation reflected in similar drug concentrations across the dissolution time course.

According to the applicant the similarity of all formulations in 0.25 N HCl using Apparatus 2 or 3 reflects the same mechanism of release. At pH 0.25 sink conditions prevail therefore release of drug is not limited by absolute solubility of each strength.

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/s/

Dianne Paraoan
6/10/05 01:27:05 PM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OMP/DDMAC/HFD-42**			FROM: Dianne Paraoan, HFD-110	
DATE 10 Jun 05	IND NO.	NDA NO. 21-468/S-004	TYPE OF DOCUMENT Prior Approval Supplement	DATE OF DOCUMENT 15 March 2005
NAME OF DRUG FOSRENOL (lanthanum carbonate)	PRIORITY CONSIDERATION		CLASSIFICATION OF DRUG 1S	DESIRED COMPLETION DATE 1 Jul 05

NAME OF FIRM: Shire Development Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
- ☐ MEETING PLANNED BY
- ☐ PRE–NDA MEETING
- ☐ END OF PHASE II MEETING
- ☐ RESUBMISSION
- ☐ SAFETY/EFFICACY
- ☐ PAPER NDA
- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(SPECIFY BELOW)*: Container and Patient Package Labels

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This submission is a prior approval supplement (S-004) for their proposed optimized formulation. You have already completed the review of their package insert. To be sent in a separate email to Lance McLeroy are the container labels and the patient package containers. The sponsor wishes to provide patients a one month supply in these patient package containers. A DMETS consult has also been submitted. Thanks!

The goal date is 15 Jul 05.

SIGNATURE OF REQUESTER Dianne C. Paraoan	METHOD OF DELIVERY (Check one) ☐ MAIL ☑ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Dianne Paraoan
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DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

REQUEST FOR CONSULTATION

TO *(Division/Office)*: **Mail: OMP/DDMAC/HFD-42**			FROM: Dianne Paraoan, HFD-110	
DATE 14 January 2005	IND NO.	NDA NO. 21-468	TYPE OF DOCUMENT Labeling	DATE OF DOCUMENT 15 March 2005
NAME OF DRUG FOSRENOL (lanthanum carbonate)	PRIORITY CONSIDERATION Standard		CLASSIFICATION OF DRUG 1S	DESIRED COMPLETION DATE 16 May 2005

NAME OF FIRM: Shire Development Inc.

REASON FOR REQUEST

I. GENERAL

- ☐ NEW PROTOCOL
- ☐ PROGRESS REPORT
- ☐ NEW CORRESPONDENCE
- ☐ DRUG ADVERTISING
- ☐ ADVERSE REACTION REPORT
- ☐ MANUFACTURING CHANGE/ADDITION
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- ☐ PRE--NDA MEETING
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- ☐ CONTROL SUPPLEMENT
- ☐ RESPONSE TO DEFICIENCY LETTER
- ☐ FINAL PRINTED LABELING
- ☐ LABELING REVISION
- ☐ ORIGINAL NEW CORRESPONDENCE
- ☐ FORMULATIVE REVIEW
- ☑ OTHER *(SPECIFY BELOW)*:

II. BIOMETRICS

STATISTICAL EVALUATION BRANCH	STATISTICAL APPLICATION BRANCH
☐ TYPE A OR B NDA REVIEW ☐ END OF PHASE II MEETING ☐ CONTROLLED STUDIES ☐ PROTOCOL REVIEW ☐ OTHER (SPECIFY BELOW):	☐ CHEMISTRY REVIEW ☐ PHARMACOLOGY ☐ BIOPHARMACEUTICS ☐ OTHER (SPECIFY BELOW):

III. BIOPHARMACEUTICS

- ☐ DISSOLUTION
- ☐ BIOAVAILABILTY STUDIES
- ☐ PHASE IV STUDIES
- ☐ DEFICIENCY LETTER RESPONSE
- ☐ PROTOCOL-BIOPHARMACEUTICS
- ☐ IN-VIVO WAIVER REQUEST

IV. DRUG EXPERIENCE

- ☐ PHASE IV SURVEILLANCE/EPIDEMIOLOGY PROTOCOL
- ☐ DRUG USE e.g. POPULATION EXPOSURE, ASSOCIATED DIAGNOSES
- ☐ CASE REPORTS OF SPECIFIC REACTIONS (List below)
- ☐ COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP
- ☐ REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY
- ☐ SUMMARY OF ADVERSE EXPERIENCE
- ☐ POISON RISK ANALYSIS

V. SCIENTIFIC INVESTIGATIONS

☐ CLINICAL	☐ PRECLINICAL

COMMENTS/SPECIAL INSTRUCTIONS:

This submission is a prior approval supplement (S-004) for their proposed optimized formulation.
Please review the package insert and containers. They will be sent via email. Thanks!

SIGNATURE OF REQUESTER Dianne C. Paraoan	METHOD OF DELIVERY (Check one) ☐ MAIL ☑ HAND
SIGNATURE OF RECEIVER	SIGNATURE OF DELIVERER

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Dianne Paraoan
3/30/05 11:15:43 AM

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 21-468/S-004

PRIOR APPROVAL SUPPLEMENT

Shire Development Inc.
Attention: Dennis Ahern, MS
725 Chesterbrook Blvd.
Wayne, PA 19087

Dear Mr. Ahern:

We have received your supplemental new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product:	Fosrenol® (lanthanum carbonate) 250 and 500 mg Chewable Tablets
NDA Number:	21-468
Supplement number:	004
Date of supplement:	March 15, 2005
Date of receipt:	March 15, 2005

This supplemental application proposes a reformulation to provide a ———————— than the currently marketed formulation, allowing ———— of smaller 250mg and 500 mg tablets (weighing ———— mg respectively). This formulation also enabled the introduction of higher strength tablets, namely 750 mg and 1000 mg. b(4)

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on May 14, 2005, in accordance with 21 CFR 314.101(a). If the application is filed, the user fee goal date will be July 15, 2005.

Send all electronic or mixed electronic and paper submissions to the Central Document Room at the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room (CDR)
5901-B Ammendale Road
Beltsville, MD 20705-1266

If your submission only contains paper, send it to the following address:

U.S. Postal Service:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
5600 Fishers Lane
Rockville, Maryland 20857

Courier/Overnight Mail:
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products, HFD-110
Attention: Division Document Room, 5002
1451 Rockville Pike
Rockville, Maryland 20852

If you have any questions, please call:

Ms. Dianne Paraoan
Regulatory Health Project Manager
(301) 594-5308

Sincerely,

{See appended electronic signature page}

Edward Fromm
Chief, Project Management Staff
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

Edward Fromm
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