CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

APPLICATION NUMBER:

208607Orig1s000

Generic or Proper Name:	Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg, and 54 mg
Sponsor:	ANI Pharmaceuticals (formally Impax Laboratories, Inc.)
Approval Date:	July 17, 2017

CENTER FOR DRUG EVALUATION AND RESEARCH

208607Orig1s000

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APPLICATION NUMBER:

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APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Silver Spring, MD 20993

ANDA 208607

ANDA APPROVAL

Impax Laboratories, Inc.
100 Somerset Corporate Blvd., Suite 3000
Bridgewater, NJ 08807
Attention: Marcy Macdonald
Vice President, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 18, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg, and 54 mg.

Reference is also made to your amendments received on May 31 and December 8, 2016; and January 31, March 17, March 20, May 17, and June 12, 2017.

We have completed the review of this ANDA and have concluded that adequate information has been presented to demonstrate that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the ANDA is **approved**, effective on the date of this letter. The Office of Bioequivalence has determined your Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg, and 54 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Concerta Extended-release Tablets, 18 mg, 27 mg, 36 mg, and 54 mg, of Janssen Pharmaceuticals, Inc. (Janssen). Your dissolution testing should be incorporated into the stability and quality control program using the USP dissolution method and specification for your application.

The RLD upon which you have based your ANDA, Janssen's Concerta Extended-release Tablets, 18 mg, 27 mg, 36 mg, and 54 mg, is subject to periods of patent protection. The following patents and expiration dates are currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
6,919,373 (the '373 patent)	January 31, 2018*
6,930,129 (the '129 patent)	January 31, 2018*
8,163,798 (the '798 patent)	January 31, 2018*
8,629,179 (the '179 patent)	January 31, 2018*
9,000,038 (the '038 patent)	January 31, 2018*
9,029,416 (the '416 patent)	July 31, 2017
9,144,549 (the '549 patent)	July 31, 2017

* with pediatric exclusivity added

Your ANDA contains paragraph IV certifications to each of the patents under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patents are invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg, and 54 mg, under this ANDA. You have notified the Agency that Impax Laboratories, Inc. (Impax) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that no action for infringement was brought against Impax within the statutory 45-day period.

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

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

REPORTING REQUIREMENTS

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

PROMOTIONAL MATERIALS

You may request advisory comments on proposed introductory advertising and promotional labeling materials prior to publication or dissemination. Please note that these submissions are voluntary. To do so, submit, in triplicate, a cover letter requesting advisory comments, the proposed materials in draft or mock-up form with annotated references, and the package insert (PI), Medication Guide, and patient PI (as applicable) to:

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

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

You must also submit final promotional materials and package insert(s), accompanied by a Form FDA 2253, at the time of initial dissemination or publication [21 CFR 314.81(b)(3)(i)]. Form FDA 2253 is available at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM083570.pdf. Information and Instructions for completing the form can be found at: http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM375154.pdf. For more information about submission of promotional materials to the Office of Prescription Drug Promotion (OPDP), see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions with respect to self-identification of facilities and payment of annual facility fees. Your ANDA identifies at least one facility that is subject to the self-identification requirement and payment of an annual facility fee. Self-identification must occur by June 1st of each year for the next fiscal year. Facility fees must be paid each year by the date specified in the *Federal Register* notice announcing facility fee amounts. All finished dosage forms (FDFs) or active pharmaceutical ingredients (APIs) manufactured in a facility that has not met its obligations to self-identify or to pay fees when they are due will be deemed misbranded. This means that it will be a violation of federal law to ship these products in interstate commerce or to import them into the United States. Such violations can result in prosecution of those responsible, injunctions, or seizures of misbranded products. Products misbranded because of failure to self-identify or pay facility fees are subject to being denied entry into the United States.

CONTENT OF LABELING

As soon as possible, but no later than 14 days from the date of this letter, submit, using the FDA automated drug registration and listing system (eLIST), the content of labeling [21 CFR 314.50(l)] in structured product labeling (SPL) format, as described at: http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm, that is identical in content to the approved labeling (including the package insert, and any patient package insert and/or Medication Guide that may be required). Information on submitting SPL files using eLIST may be found in the guidance for industry titled "SPL Standard for Content of Labeling Technical Qs and As" at: http://www.fda.gov/downloads/DrugsGuidanceComplianceRegulatoryInformation/Guidances/UCM072392.pdf. The SPL will be accessible via publicly available labeling repositories.

The Electronic Common Technical Document (eCTD) is CDER's standard format for electronic regulatory submissions. Beginning May 5, 2017, ANDAs must be submitted in eCTD format and beginning May 5, 2018, drug master files must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: www.fda.gov/ectd.

Sincerely yours,

{See appended electronic signature page}

For Heidi Lee, PharmD
Acting Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

Priya Shah

Digitally signed by Priya Shah
Date: 7/14/2017 12:45:16PM
GUID: 5256c7080002b0e78814870319c70608

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208607Orig1s000

LABELING

(b) (4)

(b) (4)

NDC 0115-1566-01

Methylphenidate Hydrochloride Extended-Release Tablets, USP

18 mg

C II

PHARMACIST: Dispense the Medication Guide provided separately to each patient.

Rx only
100 Tablets

Impax™

USUAL DOSAGE: Once daily. See accompanying outsert for complete prescribing information.

Each extended-release tablet contains 18 mg of Methylphenidate Hydrochloride, USP.

Dispense in a tightly-closed, light-resistant container as defined in the USP, with a child-resistant closure, as required.

Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.

Do not use if printed safety seal under cap is broken or missing.

Keep this and all medication out of reach of children.

Dist. by: Impax Generics
Hayward, CA 94544

Product of USA

LB# 899
Rev. 11/2016

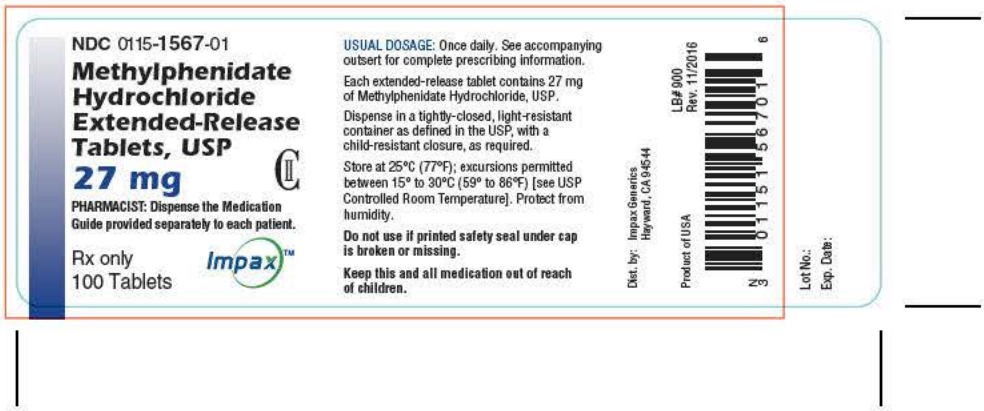
N 9 01151566019

Lot No.:
Exp. Date:

(b) (4)

(b) (4)

(b) (4)


NDC 0115-1567-01
Methylphenidate Hydrochloride Extended-Release Tablets, USP
27 mg
C II
PHARMACIST: Dispense the Medication Guide provided separately to each patient.
Rx only
100 Tablets
Impax™
USUAL DOSAGE: Once daily. See accompanying outsert for complete prescribing information.
Each extended-release tablet contains 27 mg of Methylphenidate Hydrochloride, USP.
Dispense in a tightly-closed, light-resistant container as defined in the USP, with a child-resistant closure, as required.
Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.
Do not use if printed safety seal under cap is broken or missing.
Keep this and all medication out of reach of children.
Dist. by: Impax Generics
Hayward, CA 94544
Product of USA
LB# 900
Rev. 11/2016
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Lot No.:
Exp. Date:

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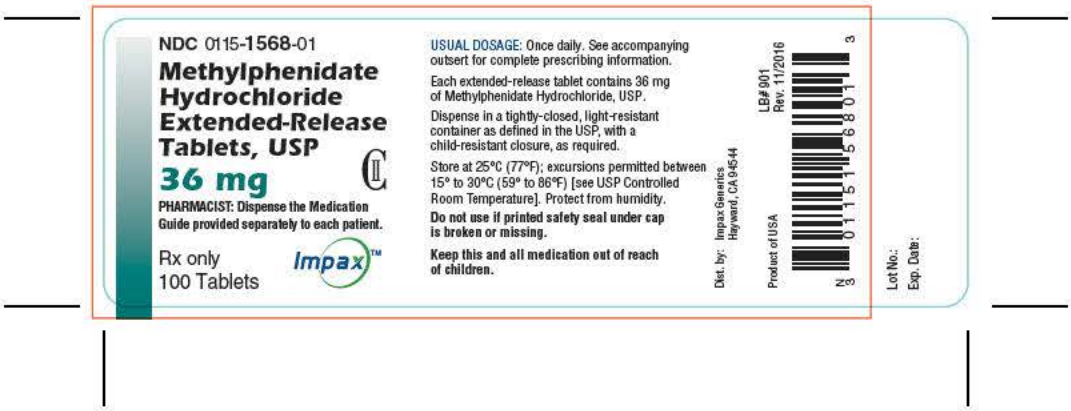
(b) (4)


NDC 0115-1568-01
Methylphenidate Hydrochloride Extended-Release Tablets, USP
36 mg
C II
PHARMACIST: Dispense the Medication Guide provided separately to each patient.
Rx only
100 Tablets
Impax™
USUAL DOSAGE: Once daily. See accompanying outsert for complete prescribing information.
Each extended-release tablet contains 36 mg of Methylphenidate Hydrochloride, USP.
Dispense in a tightly-closed, light-resistant container as defined in the USP, with a child-resistant closure, as required.
Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.
Do not use if printed safety seal under cap is broken or missing.
Keep this and all medication out of reach of children.
Dist. by: Impax Generics Hayward, CA 94544
LB# 901 Rev. 11/2016
Product of USA
N 3 01151568013
Lot No.:
Exp. Date:

(b) (4)

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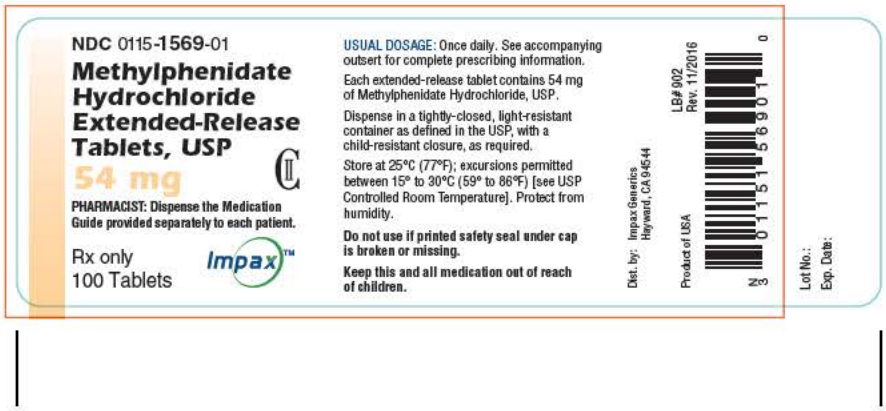
(b) (4)


NDC 0115-1569-01
Methylphenidate Hydrochloride Extended-Release Tablets, USP
54 mg
C II
PHARMACIST: Dispense the Medication Guide provided separately to each patient.
Rx only
100 Tablets
Impax™
USUAL DOSAGE: Once daily. See accompanying outsert for complete prescribing information.
Each extended-release tablet contains 54 mg of Methylphenidate Hydrochloride, USP.
Dispense in a tightly-closed, light-resistant container as defined in the USP, with a child-resistant closure, as required.
Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.
Do not use if printed safety seal under cap is broken or missing.
Keep this and all medication out of reach of children.
Dist. by: Impax Generics
Hayward, CA 94544
Product of USA
LB# 902
Rev. 11/2016
N 0 01151 56901 0
Lot No.:
Exp. Date:

(b) (4)

342-903

METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS USP, CII
Rx only

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS safely and effectively. See full prescribing information for METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS.

METHYLPHENIDATE HYDROCHLORIDE extended-release tablets, for oral use, CII
Initial U.S. Approval: 2000

WARNING: DRUG DEPENDENCE
See full prescribing information for complete boxed warning.
Methylphenidate hydrochloride extended-release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior.

----------INDICATIONS AND USAGE ----------
Methylphenidate hydrochloride extended-release tablets, USP are a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. (1)

----------DOSAGE AND ADMINISTRATION ----------
- Methylphenidate hydrochloride extended-release tablets should be taken once daily in the morning and swallowed whole with the aid of liquids. Methylphenidate hydrochloride extended-release tablets should not be chewed or crushed. Methylphenidate hydrochloride extended-release tablets may be taken with or without food. (2.1)
- For children and adolescents new to methylphenidate, the recommended starting dosage is 18 mg once daily. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 54 mg/day in children and 72 mg/day in adolescents. (2.2)
- For adult patients new to methylphenidate, the recommended starting dose is 18 or 36 mg/day. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 72 mg/day for adults. (2.2)
- For patients currently using methylphenidate, dosing is based on current dose regimen and clinical judgment. (2.3)

----------DOSAGE FORMS AND STRENGTHS ----------
Tablets: 18 mg, 27 mg, 36 mg, and 54 mg (3)

----------CONTRAINDICATIONS ----------
- Known hypersensitivity to the product (4.1)
- Marked anxiety, tension, or agitation (4.2)
- Glaucoma (4.3)
- Tics or a family history or diagnosis of Tourette's syndrome (4.4)
- Do not use methylphenidate hydrochloride extended-release tablets in patients currently using or within 2 weeks of using an MAO inhibitor (4.5)

----------WARNINGS AND PRECAUTIONS ----------
- Serious Cardiovascular Events: Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Sudden death, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Stimulant products generally should not be used in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious heart problems. (5.1)
- Increase in Blood Pressure: Monitor patients for changes in heart rate and blood pressure and use with caution in patients for whom an increase in blood pressure or heart rate would be problematic. (5.1)
- Psychiatric Adverse Events: Use of stimulants may cause treatment-emergent psychotic or manic symptoms in patients with no prior history, or exacerbation of symptoms in patients with preexisting psychiatric illness. Clinical evaluation **for Bipolar Disorder is recommended prior to stimulant use. Monitor for** aggressive behavior. (5.2)
- Seizures: Stimulants may lower the convulsive threshold. Discontinue in the presence of seizures. (5.3)
- Priapism: cases of painful and prolonged penile erections and priapism have been reported with methylphenidate products. Immediate medical attention should be sought if signs or symptoms of painful or prolonged penile erections or priapism are observed. (5.4)
- Peripheral Vasculopathy, including Raynaud's Phenomenon: Stimulants used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Careful observation for digital changes is necessary during treatment with ADHD stimulants. (5.5)
- Visual Disturbance: difficulties with accommodation and blurring of vision have been reported with stimulant treatment. (5.7)
- Long-Term Suppression of Growth: monitor height and weight at appropriate intervals in pediatric patients. (5.6)
- Gastrointestinal obstruction with preexisting GI narrowing. (5.8)
- Hematologic monitoring: Periodic CBC, differential, and platelet counts are advised during prolonged therapy. (5.9)

----------ADVERSE REACTIONS ----------
The most common adverse reaction in double-blind clinical trials (>5%) in children and adolescents was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis. (6.1 and 6.2)
The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased. (6.3)
To report SUSPECTED ADVERSE REACTIONS, contact Impax Laboratories, Inc. at 1-800-934-6729 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

----------DRUG INTERACTIONS ----------
- Do not use methylphenidate hydrochloride extended-release tablets in patients currently using or within 2 weeks of using an MAO inhibitor (7.1)
- Methylphenidate hydrochloride extended-release tablets may increase blood pressure; use cautiously with vasopressors (7.2)
- Inhibition of metabolism of coumarin anticoagulants, anticonvulsants, and some antidepressants (7.3)

----------USE IN SPECIFIC POPULATIONS ----------
- Caution should be exercised if administered to nursing mothers (8.3)
- Safety and efficacy has not been established in children less than six years old or elderly patients greater than 65 years of age (8.4 and 8.5)

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.
Revised: 3/2017

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed.

FULL PRESCRIBING INFORMATION

WARNING: DRUG DEPENDENCE
Methylphenidate hydrochloride extended-release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

1 INDICATIONS AND USAGE
Methylphenidate hydrochloride extended-release tablets, USP are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65 *[see Clinical Studies (14)]*.
A diagnosis of Attention Deficit Hyperactivity Disorder (ADHD; DSM-IV) implies the presence of hyperactive-impulsive or inattentive symptoms that caused impairment and were present before age 7 years. The symptoms must cause clinically significant impairment, e.g., in social, academic, or occupational functioning, and be present in two or more settings, e.g., school (or work) and at home. The symptoms must not be better accounted for by another mental disorder. For the Inattentive Type, at least six of the following symptoms must have persisted for at least 6 months: lack of attention to details/careless mistakes; lack of sustained attention; poor listener; failure to follow through on tasks; poor organization; avoids tasks requiring sustained mental effort; loses things; easily distracted; forgetful. For the Hyperactive-Impulsive Type, at least six of the following symptoms must have persisted for at least 6 months: fidgeting/squirming; leaving seat; inappropriate running/climbing; difficulty with quiet activities; "on the go;" excessive talking; blurting answers; can't wait turn; intrusive. The Combined Type requires both inattentive and hyperactive-impulsive criteria to be met.

1.1 Special Diagnostic Considerations
Specific etiology of this syndrome is unknown, and there is no single diagnostic test. Adequate diagnosis requires the use of medical and special psychological, educational, and social resources. Learning may or may not be impaired. The diagnosis must be based upon a complete history and evaluation of the patient and not solely on the presence of the required number of DSM-IV characteristics.

1.2 Need for Comprehensive Treatment Program
Methylphenidate hydrochloride extended-release tablets, USP are indicated as an integral part of a total treatment program for ADHD that may include other measures (psychological, educational, social). Drug treatment may not be indicated for all patients with ADHD. Stimulants are not intended for use in patients who exhibit symptoms secondary to environmental factors and/or other primary psychiatric disorders, including psychosis. Appropriate educational placement is essential and psychosocial intervention is often helpful. When remedial measures alone are insufficient, the decision to prescribe stimulant medication will depend upon the physician's assessment of the chronicity and severity of the patient's symptoms.

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
Methylphenidate hydrochloride extended-release tablets should be administered orally once daily in the morning with or without food.
Methylphenidate hydrochloride extended-release tablets must be swallowed whole with the aid of liquids, and must not be chewed, divided, or crushed *[see Patient Counseling Information (17)]*.

2.2 Patients New to Methylphenidate
The recommended starting dose of methylphenidate hydrochloride extended-release tablets for patients who are not currently taking methylphenidate or stimulants other than methylphenidate is 18 mg once daily for children and adolescents and 18 or 36 mg once daily for adults (see Table 1).

Table 1. Methylphenidate Hydrochloride Extended-Release Tablets Recommended Starting Doses and Dose Ranges

Patient Age	Recommended Starting Dose	Dose Range
Children 6–12 years of age	18 mg/day	18 mg – 54 mg/day
Adolescents 13–17 years of age	18 mg/day	18 mg – 72 mg/day not to exceed 2 mg/ kg/day
Adults 18–65 years of age	18 or 36 mg/day	18 mg – 72 mg/day

2.3 Patients Currently Using Methylphenidate
The recommended dose of methylphenidate hydrochloride extended-release tablets for patients who are currently taking methylphenidate twice daily or three times daily at doses of 10 to 60 mg/day is provided in Table 2. Dosing recommendations are based on current dose regimen and clinical judgment. Conversion dosage should not exceed 72 mg daily.

Table 2. Recommended Dose Conversion from Methylphenidate Regimens to Methylphenidate Hydrochloride Extended-Release Tablets

Previous Methylphenidate Daily Dose	Recommended Methylphenidate Hydrochloride Extended-Release Tablets Starting Dose
5 mg Methylphenidate twice daily or three times daily	18 mg every morning
10 mg Methylphenidate twice daily or three times daily	36 mg every morning
15 mg Methylphenidate twice daily or three times daily	54 mg every morning
20 mg Methylphenidate twice daily or three times daily	72 mg every morning

Other methylphenidate regimens: Clinical judgment should be used when selecting the starting dose.

2.4 Dose Titration
Doses may be increased in 18 mg increments at weekly intervals for patients who have not achieved an optimal response at a lower dose. Daily dosages above 54 mg in children and 72 mg in adolescents have not been studied and are not recommended. Daily dosages above 72 mg in adults are not recommended.
A 27 mg dosage strength is available for physicians who wish to prescribe between the 18 mg and 36 mg dosages.

2.5 Maintenance/Extended Treatment
There is no body of evidence available from controlled trials to indicate how long the patient with ADHD should be treated with methylphenidate hydrochloride extended-release tablets. It is generally agreed, however, that pharmacological treatment of ADHD may be needed for extended periods.
The effectiveness of methylphenidate hydrochloride extended-release tablets for long-term use, i.e., for more than 7 weeks, has not been systematically evaluated in controlled trials. The physician who elects to use methylphenidate hydrochloride extended-release tablets for extended periods in patients with ADHD should periodically re-evaluate the long-term usefulness of the drug for the individual patient with trials off medication to assess the patient's functioning without pharmacotherapy. Improvement may be sustained when the drug is either temporarily or permanently discontinued.

2.6 Dose Reduction and Discontinuation
If paradoxical aggravation of symptoms or other adverse events occur, the dosage should be reduced, or, if necessary, the drug should be discontinued.
If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

3 DOSAGE FORMS AND STRENGTHS
Methylphenidate hydrochloride extended-release tablets, USP are available in the following dosage strengths: 18 mg tablets are yellow and printed with **CP 342**, 27 mg tablets are gray and printed with **CP 340**, 36 mg tablets are white and printed with **CP 339**, and 54 mg tablets are brownish-red and printed with **CP 341**.

4 CONTRAINDICATIONS
4.1 Hypersensitivity to Methylphenidate
Hypersensitivity reactions, such as angioedema and anaphylactic reactions, have been observed in patients treated with methylphenidate hydrochloride extended-release tablets. Therefore, methylphenidate hydrochloride extended-release tablets are contraindicated in patients known to be hypersensitive to methylphenidate or other components of the product *[see Adverse Reactions (6.6)]*.

4.2 Agitation
Methylphenidate hydrochloride extended-release tablets are contraindicated in patients with marked anxiety, tension, and agitation, since the drug may aggravate these symptoms.

4.3 Glaucoma
Methylphenidate hydrochloride extended-release tablets are contraindicated in patients with glaucoma.

4.4 Tics
Methylphenidate hydrochloride extended-release tablets are contraindicated in patients with motor tics or with a family history or diagnosis of Tourette's syndrome *[see Adverse Reactions (6.4)]*.

4.5 Monoamine Oxidase Inhibitors
Methylphenidate hydrochloride extended-release tablets are contraindicated during treatment with monoamine oxidase (MAO) inhibitors, and also within a minimum of 14 days following discontinuation of a MAO inhibitor (hypertensive crises may result) *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS
5.1 Serious Cardiovascular Events
Sudden Death and Preexisting Structural Cardiac Abnormalities or Other Serious Heart Problems

Children and Adolescents
Sudden death has been reported in association with CNS stimulant treatment at usual doses in children and adolescents with structural cardiac abnormalities or other serious heart problems. Although some serious heart problems alone carry an increased risk of sudden death, stimulant products generally should not be used in children or adolescents with known serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, or other serious cardiac problems that may place them at increased vulnerability to the sympathomimetic effects of a stimulant drug.

Adults
Sudden deaths, stroke, and myocardial infarction have been reported in adults taking stimulant drugs at usual doses for ADHD. Although the role of stimulants in these adult cases is also unknown, adults have a greater likelihood than children of having serious structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, or other serious cardiac problems. Adults with such abnormalities should also generally not be treated with stimulant drugs.

Hypertension and Other Cardiovascular Conditions
Stimulant medications cause a modest increase in average blood pressure (about 2 to 4 mm Hg) and average heart rate (about 3 to 6 bpm) *[see Adverse Reactions (6.5)]*, and individuals may have larger increases. While the mean changes alone would not be expected to have short-term consequences, all patients should be monitored for larger changes in heart rate and blood pressure. Caution is indicated in treating patients whose underlying medical conditions might be compromised by increases in blood pressure or heart rate, e.g., those with preexisting hypertension, heart failure, recent myocardial infarction, or ventricular arrhythmia.

Assessing Cardiovascular Status in Patients Being Treated with Stimulant Medications
Children, adolescents, or adults who are being considered for treatment with stimulant medications should have a careful history (including assessment for a family history of sudden death or ventricular arrhythmia) and physical exam to assess for the presence of cardiac disease, and should receive further cardiac evaluation if findings suggest such disease (e.g., electrocardiogram and echocardiogram). Patients who develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease during stimulant treatment should undergo a prompt cardiac evaluation.

5.2 Psychiatric Adverse Events
Preexisting Psychosis
Administration of stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Bipolar Illness
Particular care should be taken in using stimulants to treat ADHD in patients with comorbid bipolar disorder because of concern for possible induction of a mixed/manic episode in such patients. Prior to initiating treatment with a stimulant, patients with comorbid depressive symptoms should be adequately screened to determine if they are at risk for bipolar disorder; such screening should include a detailed psychiatric history, including a family history of suicide, bipolar disorder, and depression.

Emergence of New Psychotic or Manic Symptoms
Treatment-emergent psychotic or manic symptoms, e.g., hallucinations, delusional thinking, or mania in patients without a prior history of psychotic illness or mania can be caused by stimulants at usual doses. If such symptoms occur, consideration should be given to a possible causal role of the stimulant, and discontinuation of treatment may be appropriate. In a pooled analysis of multiple short-term, placebo-controlled studies, such symptoms occurred in about 0.1% (4 patients with events out of 3482 exposed to methylphenidate or amphetamine for several weeks at usual doses) of stimulant-treated patients compared to 0 in placebo-treated patients.

Aggression
Aggressive behavior or hostility is often observed in patients with ADHD, and has been reported in clinical trials and the postmarketing experience of some medications indicated for the treatment of ADHD. Although there is no systematic evidence that stimulants cause aggressive behavior or hostility, patients beginning treatment for ADHD should be monitored for the appearance of or worsening of aggressive behavior or hostility.

5.3 Seizures
There is some clinical evidence that stimulants may lower the convulsive threshold in patients with prior history of seizures, in patients with prior EEG abnormalities in absence of seizures, and, very rarely, in patients without a history of seizures and no prior EEG evidence of seizures. In the presence of seizures, the drug should be discontinued.

5.4 Priapism
Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products, including methylphenidate hydrochloride extended-release tablets, in both pediatric and adult patients *[see Adverse Reactions (6.6)]*. Priapism was not reported with drug initiation but developed after some time on the drug, often subsequent to an increase in dose. Priapism has also appeared during a period of drug withdrawal (drug holidays or during discontinuation). Patients who develop abnormally sustained or frequent and painful erections should seek immediate medical attention.

5.5 Peripheral Vasculopathy, including Raynaud's Phenomenon
Stimulants, including methylphenidate hydrochloride extended-release tablets, used to treat ADHD are associated with peripheral vasculopathy, including Raynaud's phenomenon. Signs and symptoms are usually intermittent and mild; however, very rare sequelae include digital ulceration and/or soft tissue breakdown. Effects of peripheral vasculopathy, including Raynaud's phenomenon, were observed in post-marketing reports at different times and at therapeutic doses in all age groups throughout the course of treatment. Signs and symptoms generally improve after reduction in dose or discontinuation of drug. Careful observation for digital changes is necessary during treatment with ADHD stimulants. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

5.6 Long-Term Suppression of Growth
Careful follow-up of weight and height in children ages 7 to 10 years who were randomized to either methylphenidate or nonmedication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and nonmedication-treated children over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated children (i.e., treatment for 7 days per week throughout the year) have a temporary slowing in growth rate (on average, a total of about 2 cm less growth in height and 2.7 kg less growth in weight over 3 years), without evidence of growth rebound during this period of development. Published data are inadequate to determine whether chronic use of amphetamines may cause similar suppression of growth; however, it is anticipated that they likely have this effect as well. Therefore, growth should be monitored during treatment with stimulants, and patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.7 Visual Disturbance
Difficulties with accommodation and blurring of vision have been reported with stimulant treatment.

5.8 Potential for Gastrointestinal Obstruction
Because the methylphenidate hydrochloride extended-release tablet is nondeformable and does not appreciably change in shape in the GI tract, methylphenidate hydrochloride extended-release tablets should not ordinarily be administered to patients with preexisting severe gastrointestinal narrowing (pathologic or iatrogenic, for example: esophageal motility disorders, small bowel inflammatory disease, 'short gut' syndrome due to adhesions or decreased transit time, past history of peritonitis, cystic fibrosis, chronic intestinal pseudo-obstruction, or Meckel's diverticulum). There have been rare reports of obstructive symptoms in patients with known strictures in association with the ingestion of drugs in nondeformable controlled-release formulations. Due to the controlled-release design of the tablet, methylphenidate hydrochloride extended-release tablets should be used only in patients who are able to swallow the tablet whole *[see Patient Counseling Information (17)]*.

5.9 Hematologic Monitoring
Periodic CBC, differential, and platelet counts are advised during prolonged therapy.

6 ADVERSE REACTIONS
The following are discussed in more detail in other sections of the labeling:
- Drug Dependence *[see Box Warning]*
- Hypersensitivity to Methylphenidate *[see Contraindications (4.1)]*
- Agitation *[see Contraindications (4.2)]*
- Glaucoma *[see Contraindications (4.3)]*
- Tics *[see Contraindications (4.4)]*
- Monoamine Oxidase Inhibitors *[see Contraindications (4.5) and Drug Interactions (7.1)]*
- Serious Cardiovascular Events *[see Warnings and Precautions (5.1)]*
- Psychiatric Adverse Events *[see Warnings and Precautions (5.2)]*
- Seizures *[see Warnings and Precautions (5.3)]*
- Priapism *[see Warnings and Precautions (5.4)]*
- Long-Term Suppression of Growth *[see Warnings and Precautions (5.6)]*
- Visual Disturbance *[see Warnings and Precautions (5.7)]*
- Potential for Gastrointestinal Obstruction *[see Warnings and Precautions (5.8)]*
- Hematologic Monitoring *[see Warnings and Precautions (5.9)]*

The most common adverse reaction in double-blind clinical trials (>5%) in pediatric patients (children and adolescents) was abdominal pain upper. The most common adverse reactions in double-blind clinical trials (>5%) in adult patients were decreased appetite, headache, dry mouth, nausea, insomnia, anxiety, dizziness, weight decreased, irritability, and hyperhidrosis *[see Adverse Reactions (6.1)]*.
The most common adverse reactions associated with discontinuation (≥1%) from either pediatric or adult clinical trials were anxiety, irritability, insomnia, and blood pressure increased *[see Adverse Reactions (6.3)]*.
The development program for methylphenidate hydrochloride extended-release tablets included exposures in a total of 3906 participants in clinical trials. Children, adolescents, and adults with ADHD were evaluated in 6 controlled clinical studies and 11 open-label clinical studies (see Table 3). Safety was assessed by collecting adverse events, vital signs, weights, and ECGs, and by performing physical examinations and laboratory analyses.

Table 3. Methylphenidate Hydrochloride Extended-Release Tablets Exposure in Double-Blind and Open-Label Clinical Studies

Patient Population	N	Dose Range
Children	2216	18 to 54 mg once daily
Adolescents	502	18 to 72 mg once daily
Adults	1188	18 to 108 mg once daily

Adverse events during exposure were obtained primarily by general inquiry and recorded by clinical investigators using their own terminology. Consequently, to provide a meaningful estimate of the proportion of individuals experiencing adverse events, events were grouped in standardized categories using MedDRA terminology.
The stated frequencies of adverse events represent the proportion of individuals who experienced, at least once, a treatment-emergent adverse event of the type listed. An event was considered treatment-emergent if it occurred for the first time or worsened while receiving therapy following baseline evaluation.
Throughout this section, adverse reactions are reported. Adverse reactions are adverse events that were considered to be reasonably associated with the use of methylphenidate hydrochloride extended-release tablets based on the comprehensive assessment of the available adverse event information. A causal association for methylphenidate hydrochloride extended-release tablets often cannot be reliably established in individual cases. Further, because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in clinical trials of another drug and may not reflect the rates observed in clinical practice.
The majority of adverse reactions were mild to moderate in severity.

6.1 Commonly Observed Adverse Reactions in Double Blind, Placebo-Controlled Clinical Trials
Adverse reactions in either the pediatric or adult double-blind adverse reactions tables may be relevant for both patient populations.

Children and Adolescents
Table 4 lists the adverse reactions reported in 1% or more of methylphenidate hydrochloride extended-release tablets-treated children and adolescent subjects in 4 placebo-controlled, double-blind clinical trials.

Table 4. Adverse Reactions Reported by ≥1% of Methylphenidate Hydrochloride Extended-Release Tablets-Treated Children and Adolescent Subjects in 4 Placebo-Controlled, Double-Blind Clinical Trials of Methylphenidate Hydrochloride Extended-Release Tablets

System/Organ Class Adverse Reaction	Methylphenidate Hydrochloride Extended-Release Tablets (n=321) %	Placebo (n=318) %
Gastrointestinal Disorders		
Abdominal pain upper	6.2	3.8
Vomiting	2.8	1.6
General Disorders and Administration Site Conditions		
Pyrexia	2.2	0.9
Infections and Infestations		
Nasopharyngitis	2.8	2.2
Nervous System Disorders		
Dizziness	1.9	0
Psychiatric Disorders		
Insomnia*	2.8	0.3
Respiratory, Thoracic and Mediastinal Disorders		
Cough	1.9	0.9
Oropharyngeal pain	1.2	0.9

*Terms of Initial insomnia (methylphenidate hydrochloride extended-release tablets=0.6%) and Insomnia (methylphenidate hydrochloride extended-release tablets=2.2%) are combined into Insomnia.
The majority of adverse reactions were mild to moderate in severity.

Adults
Table 5 lists the adverse reactions reported in 1% or more of methylphenidate hydrochloride extended-release tablets-treated adults in 2 placebo-controlled, double-blind clinical trials.

Table 5. Adverse Reactions Reported by ≥1% of Methylphenidate Hydrochloride Extended-Release Tablets-Treated Adult Subjects in 2 Placebo-Controlled, Double-Blind Clinical Trials*

System/Organ Class Adverse Reaction	Methylphenidate Hydrochloride Extended-Release Tablets (n=415) %	Placebo (n=212) %
Cardiac Disorders		
Tachycardia	4.8	0
Palpitations	3.1	0.9
Ear and Labyrinth Disorders		
Vertigo	1.7	0
Eye Disorders		
Vision blurred	1.7	0.5
Gastrointestinal Disorders		
Dry mouth	14.0	3.8
Nausea	12.8	3.3
Dyspepsia	2.2	0.9
Vomiting	1.7	0.5
Constipation	1.4	0.9
General Disorders and Administration Site Conditions		
Irritability	5.8	1.4
Infections and Infestations		
Upper respiratory tract infection	2.2	0.9
Investigations		
Weight decreased	6.5	3.3
Metabolism and Nutrition Disorders		
Decreased appetite	25.3	6.6
Anorexia	1.7	0
Musculoskeletal and Connective Tissue Disorders		
Muscle tightness	1.9	0
Nervous System Disorders		
Headache	22.2	15.6
Dizziness	6.7	5.2
Tremor	2.7	0.5
Paresthesia	1.2	0
Sedation	1.2	0
Tension headache	1.2	0.5
Psychiatric Disorders		
Insomnia	12.3	6.1
Anxiety	8.2	2.4
Initial insomnia	4.3	2.8
Depressed mood	3.9	1.4
Nervousness	3.1	0.5
Restlessness	3.1	0
Agitation	2.2	0.5
Aggression	1.7	0.5
Bruxism	1.7	0.5
Depression	1.7	0.9
Libido decreased	1.7	0.5
Affect lability	1.4	0.9
Confusional state	1.2	0.5
Tension	1.2	0.5
Respiratory, Thoracic and Mediastinal Disorders		
Oropharyngeal pain	1.7	1.4
Skin and Subcutaneous Tissue Disorders		
Hyperhidrosis	5.1	0.9

*Included doses up to 108 mg.
The majority of ADRs were mild to moderate in severity.

6.2 Other Adverse Reactions Observed in Methylphenidate Hydrochloride Extended-Release Tablets Clinical Trials
This section includes adverse reactions reported by methylphenidate hydrochloride extended-release tablets-treated subjects in double-blind trials that do not meet the criteria specified for Table 4 or Table 5 and all adverse reactions reported by methylphenidate hydrochloride extended-release tablets-treated subjects who participated in open-label and postmarketing clinical trials.

(b) (4)

MEDICATION GUIDE
Methylphenidate Hydrochloride Extended-Release Tablets CII
(meth" il fen' i date hye" droe klor' ide)

Read the Medication Guide that comes with methylphenidate hydrochloride extended-release tablets before you or your child starts taking it and each time you get a refill. There may be new information. This Medication Guide does not take the place of talking to your doctor about your or your child's treatment with methylphenidate hydrochloride extended-release tablets.

What is the most important information I should know about methylphenidate hydrochloride extended-release tablets?

The following have been reported with use of methylphenidate HCl and other stimulant medicines:

1. Heart-related problems:
- **sudden death in patients who have heart problems or heart defects**
- **stroke and heart attack in adults**
- **increased blood pressure and heart rate**

Tell your doctor if you or your child has any heart problems, heart defects, high blood pressure, or a family history of these problems. Your doctor should check you or your child carefully for heart problems before starting methylphenidate hydrochloride extended-release tablets.

Your doctor should check your or your child's blood pressure and heart rate regularly during treatment with methylphenidate hydrochloride extended-release tablets.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking methylphenidate hydrochloride extended-release tablets.

2. Mental (Psychiatric) problems:

All Patients
- **new or worse behavior and thought problems**
- **new or worse bipolar illness**
- **new or worse aggressive behavior or hostility**

Children and Teenagers
- **new psychotic symptoms (such as hearing voices, believing things that are not true, are suspicious) or new manic symptoms**

Tell your doctor about any mental problems you or your child have, or about a family history of suicide, bipolar illness, or depression.

Call your doctor right away if you or your child has any new or worsening mental symptoms or problems while taking methylphenidate hydrochloride extended-release tablets, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

3. Painful and prolonged erections (priapism)

Painful and prolonged erections (priapism) have occurred with methylphenidate. If you or your child develop priapism, seek medical help right away. **Because of the potential for lasting damage, priapism should be evaluated by a doctor immediately.**

4. Circulation problems in fingers and toes

[Peripheral vasculopathy, including Raynaud's phenomenon]:
- fingers or toes may feel numb, cool, painful
- fingers or toes may change color from pale, to blue to red

Tell your doctor if you have or your child has numbness, pain, skin color change, or sensitivity to temperature in your fingers or toes.

Call your doctor right away if you have or your child has any signs of unexplained wounds appearing on fingers or toes while taking methylphenidate hydrochloride extended-release tablets.

What are methylphenidate hydrochloride extended-release tablets?

Methylphenidate hydrochloride extended-release tablets are a central nervous system stimulant prescription medicine. **It is used for the treatment of attention deficit and hyperactivity disorder (ADHD).** Methylphenidate hydrochloride extended-release tablets may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

Methylphenidate hydrochloride extended-release tablets should be used as a part of a total treatment program for ADHD that may include counseling or other therapies.

Methylphenidate hydrochloride extended-release tablets are a federally controlled substance (CII) because it can be abused or lead to dependence. Keep methylphenidate hydrochloride extended-release tablets in a safe place to prevent misuse and abuse. Selling or giving away methylphenidate hydrochloride extended-release tablets may harm others, and is against the law.
Tell your doctor if you or your child has (or has a family history of) ever abused or been dependent on alcohol, prescription medicines, or street drugs.

Who should not take methylphenidate hydrochloride extended-release tablets?

Methylphenidate hydrochloride extended-release tablets should not be taken if you or your child:
- is very anxious, tense, or agitated
- has an eye problem called glaucoma
- has tics or Tourette's syndrome, or a family history of Tourette's syndrome. Tics are hard-to-control repeated movements or sounds.
- is taking or has taken within the past 14 days an antidepression medicine called a monoamine oxidase inhibitor or MAOI.
- is allergic to anything in methylphenidate hydrochloride extended-release tablets. See the end of this Medication Guide for a complete list of ingredients.

Methylphenidate hydrochloride extended-release tablets should not be used in children less than 6 years old because it has not been studied in this age group.

Methylphenidate hydrochloride extended-release tablets may not be right for you or your child. Before starting methylphenidate hydrochloride extended-release tablets, tell your or your child's doctor about all health conditions (or a family history of) including:
- heart problems, heart defects, or high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- tics or Tourette's syndrome
- seizures or have had an abnormal brain wave test (EEG)
- circulation problems in fingers and toes
- esophagus, stomach, or small or large intestine problems

Tell your doctor if you or your child is pregnant, planning to become pregnant, or breastfeeding.

Can methylphenidate hydrochloride extended-release tablets be taken with other medicines?

Tell your doctor about all of the medicines that you or your child takes including prescription and nonprescription medicines, vitamins, and herbal supplements. Methylphenidate hydrochloride extended-release tablets and some medicines may interact with each other and cause serious side effects. Sometimes the doses of other medicines will need to be adjusted while taking methylphenidate hydrochloride extended-release tablets.

Your doctor will decide whether methylphenidate hydrochloride extended-release tablets can be taken with other medicines.

Especially tell your doctor if you or your child takes:
- antidepression medicines including MAOIs
- seizure medicines
- blood thinner medicines
- blood pressure medicines
- cold or allergy medicines that contain decongestants

Know the medicines that you or your child takes. Keep a list of your medicines with you to show your doctor and pharmacist.

Do not start any new medicine while taking methylphenidate hydrochloride extended-release tablets without talking to your doctor first.

How should methylphenidate hydrochloride extended-release tablets be taken?

- **Take methylphenidate hydrochloride extended-release tablets exactly as prescribed**. Your doctor may adjust the dose until it is right for you or your child.
- **Do not chew, crush, or divide the tablets.** Swallow methylphenidate hydrochloride extended-release tablets whole with water or other liquids. Tell your doctor if you or your child cannot swallow methylphenidate hydrochloride extended-release tablets whole. A different medicine may need to be prescribed.
- Methylphenidate hydrochloride extended-release tablets can be taken with or without food.
- Take methylphenidate hydrochloride extended-release tablets once each day in the morning. Methylphenidate hydrochloride extended-release tablets are an extended-release tablet. It releases medication into your or your child's body throughout the day.
- The methylphenidate hydrochloride extended-release tablet does not dissolve completely in the body after all the medicine has been released. You or your child may sometimes notice the empty tablet in a bowel movement. This is normal.
- From time to time, your doctor may stop methylphenidate hydrochloride extended-release tablets treatment for a while to check ADHD symptoms.
- Your doctor may do regular checks of the blood, heart, and blood pressure while taking methylphenidate hydrochloride extended-release tablets. Children should have their height and weight checked often while taking methylphenidate hydrochloride extended-release tablets. Methylphenidate hydrochloride extended-release tablets treatment may be stopped if a problem is found during these check-ups.
- **If you or your child takes too much methylphenidate hydrochloride extended-release tablets or overdoses, call your doctor or poison control center right away, or get emergency treatment.**

What are possible side effects of methylphenidate hydrochloride extended-release tablets?

See "What is the most important information I should know about methylphenidate hydrochloride extended-release tablets?" for information on reported heart and mental problems.

Other serious side effects include:

- slowing of growth (height and weight) in children
- seizures, mainly in patients with a history of seizures
- eyesight changes or blurred vision
- blockage of the esophagus, stomach, small or large intestine in patients who already have a narrowing in any of these organs

Common side effects include:

- decreased appetite
- dry mouth
- trouble sleeping
- dizziness
- stomach ache
- increased sweating
- headache
- nausea
- anxiety
- weight loss
- irritability

Stimulants may impair the ability of you or your child to operate potentially hazardous machinery or vehicles. You or your child should exercise caution until you or your child is reasonably certain that methylphenidate hydrochloride extended-release tablets do not adversely affect your or your child's ability to engage in such activities.

Talk to your doctor if you or your child has side effects that are bothersome or do not go away.

This is not a complete list of possible side effects. Ask your doctor or pharmacist for more information.

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

You may also report side effects to Impax Laboratories, Inc. at 1-800-934-6729.

How should I store methylphenidate hydrochloride extended-release tablets?

- Store methylphenidate hydrochloride extended-release tablets in a safe place at room temperature, 59 to 86°F (15 to 30°C). Protect from moisture.
- **Keep methylphenidate hydrochloride extended-release tablets and all medicines out of the reach of children.**

General information about methylphenidate hydrochloride extended-release tablets

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. Do not use methylphenidate hydrochloride extended-release tablets for a condition for which it was not prescribed. Do not give methylphenidate hydrochloride extended-release tablets to other people, even if they have the same condition. It may harm them and it is against the law.

This Medication Guide summarizes the most important information about methylphenidate hydrochloride extended-release tablets. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about methylphenidate hydrochloride extended-release tablets that was written for healthcare professionals. For more information about methylphenidate hydrochloride extended-release tablets call 1-800-934-6729.

What are the ingredients in methylphenidate hydrochloride extended-release tablets?

Active Ingredient: methylphenidate HCl USP

Inactive Ingredients: ammonium hydroxide, cetyl alcohol, ethylcellulose, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, n-butyl alcohol, polyethylene glycol, povidone, propylene glycol, shellac, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. The 18 mg tablet also contains the following additional inert ingredient: yellow iron oxide; and the 54 mg tablet also contains the following additional inert ingredients: red iron oxide and yellow iron oxide.

This Medication Guide has been approved by the U.S. Food and Drug Administration.

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Hayward, CA 94544

Blood and Lymphatic System Disorders: Leukopenia
Eye Disorders: Accommodation disorder, Dry eye
Vascular Disorders: Hot flush
Gastrointestinal Disorders: Abdominal discomfort, Abdominal pain, Diarrhea
General Disorders and Administrative Site Conditions: Asthenia, Fatigue, Feeling jittery, Thirst
Infections and Infestations: Sinusitis
Investigations: Alanine aminotransferase increased, Blood pressure increased, Cardiac murmur, Heart rate increased
Musculoskeletal and Connective Tissue Disorders: Muscle spasms
Nervous System Disorders: Lethargy, Psychomotor hyperactivity, Somnolence
Psychiatric Disorders: Anger, Hypervigilance, Mood altered, Mood swings, Panic attack, Sleep disorder, Tearfulness, Tic
Reproductive System and Breast Disorders: Erectile dysfunction
Respiratory, Thoracic and Mediastinal Disorders: Dyspnea
Skin and Subcutaneous Tissue Disorders: Rash, Rash macular
Vascular Disorders: Hypertension

6.3 Discontinuation Due to Adverse Reactions

Adverse reactions in the 4 placebo-controlled studies of children and adolescents leading to discontinuation occurred in 2 methylphenidate hydrochloride extended-release tablets patients (0.6%) including depressed mood (1, 0.3%) and headache and insomnia (1, 0.3%), and 6 placebo patients (1.9%) including headache and insomnia (1, 0.3%), irritability (2, 0.6%), headache (1, 0.3%), psychomotor hyperactivity (1, 0.3%), and tic (1, 0.3%).

In the 2 placebo-controlled studies of adults, 25 methylphenidate hydrochloride extended-release tablets patients (6.0%) and 6 placebo patients (2.8%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% in the methylphenidate hydrochloride extended-release tablets patients included anxiety (1.7%), irritability (1.4%), blood pressure increased (1.0%), and nervousness (0.7%). In placebo patients, blood pressure increased and depressed mood had an incidence of >0.5% (0.9%).

In the 11 open-label studies of children, adolescents, and adults, 266 methylphenidate hydrochloride extended-release tablets patients (7.0%) discontinued due to an adverse reaction. Those events with an incidence of >0.5% included insomnia (1.2%), irritability (0.8%), anxiety (0.7%), decreased appetite (0.7%), and tic (0.6%).

6.4 Tics

In a long-term uncontrolled study (n=432 children), the cumulative incidence of new onset of tics was 9% after 27 months of treatment with methylphenidate hydrochloride extended-release tablets.

In a second uncontrolled study (n=682 children) the cumulative incidence of new-onset tics was 1% (9/682 children). The treatment period was up to 9 months with mean treatment duration of 7.2 months.

6.5 Blood Pressure and Heart Rate Increases

In the laboratory classroom clinical trials in children (Studies 1 and 2), both methylphenidate hydrochloride extended-release tablets once daily and methylphenidate three times daily increased resting pulse by an average of 2 to 6 bpm and produced average increases of systolic and diastolic blood pressure of roughly 1 to 4 mm Hg during the day, relative to placebo. In the placebo-controlled adolescent trial (Study 4), mean increases from baseline in resting pulse rate were observed with methylphenidate hydrochloride extended-release tablets and placebo at the end of the double-blind phase (5 and 3 beats/minute, respectively). Mean increases from baseline in blood pressure at the end of the double-blind phase for methylphenidate hydrochloride extended-release tablets and placebo-treated patients were 0.7 and 0.7 mm Hg (systolic) and 2.6 and 1.4 mm Hg (diastolic), respectively. In one placebo-controlled study in adults (Study 6), dose-dependent mean increases of 3.9 to 9.8 bpm from baseline in standing pulse rate were observed with methylphenidate hydrochloride extended-release tablets at the end of the double-blind treatment vs. an increase of 2.7 beats/minute with placebo. Mean changes from baseline in standing blood pressure at the end of double-blind treatment ranged from 0.1 to 2.2 mm Hg (systolic) and -0.7 to 2.2 mm Hg (diastolic) for methylphenidate hydrochloride extended-release tablets and was 1.1 mm Hg (systolic) and -1.8 mm Hg (diastolic) for placebo. In a second placebo-controlled study in adults (Study 5), mean changes from baseline in resting pulse rate were observed for methylphenidate hydrochloride extended-release tablets and placebo at the end of the double-blind treatment (3.6 and –1.6 beats/minute, respectively). Mean changes from baseline in blood pressure at the end of the double–blind treatment for methylphenidate hydrochloride extended-release tablets and placebo-treated patients were –1.2 and –0.5 mm Hg (systolic) and 1.1 and 0.4 mm Hg (diastolic), respectively *[see Warnings and Precautions (5.1)]*.

6.6 Postmarketing Experience

The following additional adverse reactions have been identified during postapproval use of methylphenidate hydrochloride extended-release tablets. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency:
Blood and Lymphatic System Disorders: Pancytopenia, Thrombocytopenia, Thrombocytopenic purpura
Cardiac Disorders: Angina pectoris, Bradycardia, Extrasystoles, Supraventricular tachycardia, Ventricular extrasystoles
Eye Disorders: Diplopia, Mydriasis, Visual impairment
General Disorders: Chest pain, Chest discomfort, Drug effect decreased, Hyperpyrexia, Therapeutic response decreased
Hepatobiliary disorders: Hepatocellular injury, Acute hepatic failure
Immune System Disorders: Hypersensitivity reactions such as Angioedema, Anaphylactic reactions, Auricular swelling, Bullous conditions, Exfoliative conditions, Urticarias, Pruritus NEC, Rashes, Eruptions, and Exanthemas NEC
Investigations: Blood alkaline phosphatase increased, Blood bilirubin increased, Hepatic enzyme increased, Platelet count decreased, White blood cell count abnormal
Musculoskeletal, Connective Tissue and Bone Disorders: Arthralgia, Myalgia, Muscle twitching, Rhabdomyolysis
Nervous System Disorders: Convulsion, Grand mal convulsion, Dyskinesia, Serotonin syndrome in combination with serotonergic drugs
Psychiatric Disorders: Disorientation, Hallucination, Hallucination auditory, Hallucination visual, Mania, Logorrhea, Libido changes
Reproductive System and Breast Disorders: Priapism
Skin and Subcutaneous Tissue Disorders: Alopecia, Erythema
Vascular Disorders: Raynaud's phenomenon

7 DRUG INTERACTIONS

7.1 MAO Inhibitors

Methylphenidate hydrochloride extended-release tablets should not be used in patients being treated (currently or within the preceding 2 weeks) with MAO inhibitors *[see Contraindications (4.5)]*.

7.2 Vasopressor Agents

Because of possible increases in blood pressure, methylphenidate hydrochloride extended-release tablets should be used cautiously with vasopressor agents *[see Warnings and Precautions (5.1)]*.

7.3 Coumarin Anticoagulants, Antidepressants, and Selective Serotonin Reuptake Inhibitors

Human pharmacologic studies have shown that methylphenidate may inhibit the metabolism of coumarin anticoagulants, anticonvulsants (e.g., phenobarbital, phenytoin, primidone), and some antidepressants (tricyclics and selective serotonin reuptake inhibitors). Downward dose adjustment of these drugs may be required when given concomitantly with methylphenidate. It may be necessary to adjust the dosage and monitor plasma drug concentrations (or, in the case of coumarin, coagulation times), when initiating or discontinuing concomitant methylphenidate.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C

Methylphenidate has been shown to have teratogenic effects in rabbits when given in doses of 200 mg/kg/day, which is approximately 100 times and 40 times the maximum recommended human dose on a mg/kg and mg/m^2 basis, respectively. A reproduction study in rats revealed no evidence of harm to the fetus at oral doses up to 30 mg/kg/day, approximately 15-fold and 3-fold the maximum recommended human dose of methylphenidate hydrochloride extended-release tablets on a mg/kg and mg/m^2 basis, respectively. The approximate plasma exposure to methylphenidate plus its main metabolite PPAA in pregnant rats was 1-2 times that seen in trials in volunteers and patients with the maximum recommended dose of methylphenidate hydrochloride extended-release tablets based on the AUC.

The safety of methylphenidate for use during human pregnancy has not been established. There are no adequate and well-controlled studies in pregnant women. Methylphenidate hydrochloride extended-release tablets should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.2 Labor and Delivery

The effect of methylphenidate hydrochloride extended-release tablets on labor and delivery in humans is unknown.

8.3 Nursing Mothers

It is not known whether methylphenidate is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised if methylphenidate hydrochloride extended-release tablets are administered to a nursing woman.

In lactating female rats treated with a single oral dose of 5 mg/kg radiolabeled methylphenidate, radioactivity (representing methylphenidate and/or its metabolites) was observed in milk and levels were generally similar to those in plasma.

8.4 Pediatric Use

Methylphenidate hydrochloride extended-release tablets should not be used in children under six years, since safety and efficacy in this age group have not been established. Long-term effects of methylphenidate in children have not been well established.

8.5 Geriatric Use

Methylphenidate hydrochloride extended-release tablets have not been studied in patients greater than 65 years of age.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methylphenidate is a Schedule II controlled substance under the Controlled Substances Act.

9.2 Abuse

As noted in the Box Warning, methylphenidate hydrochloride extended-release tablets should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse.

In two placebo-controlled human abuse potential studies, single oral doses of methylphenidate hydrochloride extended-release tablets were compared to single oral doses of immediate-release methylphenidate (IR MPH) and placebo in subjects with a history of recreational stimulant use to assess relative abuse potential. For the purpose of this assessment, the response for each of the subjective measures was defined as the maximum effect within the first 8 hours after dose administration.

In one study (n=40), both methylphenidate hydrochloride extended-release tablets (108 mg) and 60 mg IR MPH compared to placebo produced statistically significantly greater responses on the five subjective measures suggestive of abuse potential. In comparisons between the two active treatments, however, methylphenidate hydrochloride extended-release tablets (108 mg) produced variable responses on positive subjective measures that were either statistically indistinguishable from (Abuse Potential, Drug Liking, Amphetamine, and Morphine Benzedrine Group [Euphoria]) or statistically less than (Stimulation – Euphoria) responses produced by 60 mg IR MPH.

In another study (n=49), both doses of methylphenidate hydrochloride extended-release tablets (54 mg and 108 mg) and both doses of IR MPH (50 mg and 90 mg) produced statistically significantly greater responses compared to placebo on the two primary scales used in the study (Drug Liking, Euphoria). When doses of methylphenidate hydrochloride extended-release tablets (54 mg and 108 mg) were compared to IR MPH (50 mg and 90 mg), respectively, methylphenidate hydrochloride extended-release tablets produced statistically significantly lower subjective responses on these two scales than IR MPH. Methylphenidate hydrochloride extended-release tablets (108 mg) produced responses that were statistically indistinguishable from the responses on these two scales produced by IR MPH (50 mg). Differences in subjective responses to the respective doses should be considered in the context that only 22% of the total amount of methylphenidate in methylphenidate hydrochloride extended-release tablets is available for immediate release from the drug overcoat *[see System Components and Performance (11.1)]*.

Although these findings reveal a relatively lower response to methylphenidate hydrochloride extended-release tablets on subjective measures suggestive of abuse potential compared to IR MPH at roughly equivalent total MPH doses, the relevance of these findings to the abuse potential of methylphenidate hydrochloride extended-release tablets in the community is unknown.

9.3 Dependence

As noted in the Box Warning, careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

10 OVERDOSAGE

10.1 Signs and Symptoms

Signs and symptoms of methylphenidate hydrochloride extended-release tablets overdosage, resulting principally from overstimulation of the CNS and from excessive sympathomimetic effects, may include the following: vomiting, agitation, muscle twitching, convulsion, grand mal convulsion, confusional state, hallucinations (auditory and/or visual), hyperhidrosis, headache, pyrexia, tachycardia, palpitations, heart rate increased, sinus arrhythmia, hypertension, rhabdomyolysis, mydriasis, and dry mouth.

10.2 Recommended Treatment

Treatment consists of appropriate supportive measures. The patient must be protected against self-injury and against external stimuli that would aggravate overstimulation already present. Gastric contents may be evacuated by gastric lavage as indicated. Before performing gastric lavage, control agitation and seizures if present and protect the airway. Other measures to detoxify the gut include administration of activated charcoal and a cathartic. Intensive care must be provided to maintain adequate circulation and respiratory exchange; external cooling procedures may be required for pyrexia.

Efficacy of peritoneal dialysis or extracorporeal hemodialysis for methylphenidate hydrochloride extended-release tablets overdosage has not been established.

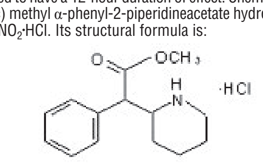
The prolonged release of methylphenidate from methylphenidate hydrochloride extended-release tablets should be considered when treating patients with overdose.

10.3 Poison Control Center

As with the management of all overdosage, the possibility of multiple-drug ingestion should be considered. The physician may wish to consider contacting a poison control center for up-to-date information on the management of overdosage with methylphenidate.

11 DESCRIPTION

Methylphenidate hydrochloride extended-release tablets, USP are a central nervous system (CNS) stimulant. Methylphenidate hydrochloride extended-release tablets, USP are available in four tablet strengths. Each extended-release tablet for once-a-day oral administration contains 18, 27, 36, or 54 mg of methylphenidate HCl USP and is designed to have a 12-hour duration of effect. Chemically, methylphenidate HCl is d,l (racemic) methyl α-phenyl-2-piperidineacetate hydrochloride. Its empirical formula is $C_{14}H_{19}NO_2 \cdot HCl$. Its structural formula is:



Methylphenidate HCl USP is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone. Its molecular weight is 269.77.

Methylphenidate hydrochloride extended-release tablets, USP also contain the following inert ingredients: ammonium hydroxide, cetyl alcohol, ethylcellulose, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, n-butyl alcohol, polyethylene glycol, povidone, propylene glycol, shellac, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. The 18 mg tablet also contains the following additional inert ingredient: yellow iron oxide; and the 54 mg tablet also contains the following additional inert ingredients: red iron oxide and yellow iron oxide.

USP dissolution test is pending.

11.1 System Components and Performance

Methylphenidate hydrochloride extended-release tablets, USP use a diffusion process to deliver methylphenidate hydrochloride at a controlled rate. The drug delivery system comprises a core tablet coated with a diffusion controlling polymer coat followed by a top immediate-release drug layer. In an aqueous environment, such as the gastrointestinal tract, the top immediate-release drug layer dissolves within one hour, providing an initial dose of methylphenidate. Water penetrates the core tablet through the diffusion controlling polymer coat, and methylphenidate in the core tablet is released in a controlled fashion. The biologically inert components of the tablet pass through the gastrointestinal tract and are eliminated in the stool. It is possible that methylphenidate hydrochloride extended-release tablets, USP may be visible on abdominal x-rays under certain circumstances, especially when digital enhancing techniques are utilized.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate HCl is a central nervous system (CNS) stimulant. The mode of therapeutic action in Attention Deficit Hyperactivity Disorder (ADHD) is not known. Methylphenidate is thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron and increase the release of these monoamines into the extraneuronal space.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the d- and l-isomers. The d-isomer is more pharmacologically active than the l-isomer.

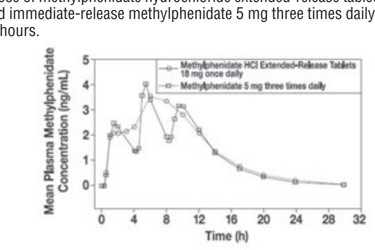
12.3 Pharmacokinetics

Absorption

Methylphenidate is readily absorbed. Following oral administration of methylphenidate hydrochloride extended-release tablets, plasma methylphenidate concentrations increase rapidly, reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours, after which a gradual decrease begins. Mean times to reach peak plasma concentrations across all doses of methylphenidate hydrochloride extended-release tablets occurred between 6 and 10 hours.

Methylphenidate hydrochloride extended-release tablets once daily minimizes the fluctuations between peak and trough concentrations associated with immediate-release methylphenidate three times daily (see Figure 1). The relative bioavailability of methylphenidate hydrochloride extended-release tablets once daily and methylphenidate three times daily in adults is comparable.

Figure 1. Mean methylphenidate plasma concentrations in 36 adults, following a single dose of methylphenidate hydrochloride extended-release tablets 18 mg once daily and immediate-release methylphenidate 5 mg three times daily administered every 4 hours.



The mean single-dose pharmacokinetic parameters in 36 healthy adults following the administration of methylphenidate hydrochloride extended-release tablets 18 mg once daily and methylphenidate 5 mg three times daily are summarized in Table 6.

(b) (4)

Table 6. Pharmacokinetic Parameters (Mean ± SD) After Single Dose in Healthy Adults

Parameters	Methylphenidate Hydrochloride Extended-Release Tablets (18 mg once daily) (n=36)	Methylphenidate (5 mg three times daily) (n=35)
C_{max} (ng/mL)	3.7 ± 1.0	4.2 ± 1.0
T_{max} (h)	6.8 ± 1.8	6.5 ± 1.8
AUC_{inf} (ng•h/mL)	41.8 ± 13.9	38.0 ± 11.0
$t_{½}$ (h)	3.5 ± 0.4	3.0 ± 0.5

The pharmacokinetics of methylphenidate hydrochloride extended-release tablets were evaluated in healthy adults following single- and multiple-dose administration (steady state) of doses up to 144 mg/day. The mean half-life was about 3.6 hours. No differences in the pharmacokinetics of methylphenidate hydrochloride extended-release tablets were noted following single and repeated once-daily dosing, indicating no significant drug accumulation. The AUC and $t_{1/2}$ following repeated once-daily dosing are similar to those following the first dose of methylphenidate hydrochloride extended-release tablets in a dose range of 18 to 144 mg.

Dose Proportionality

Following administration of methylphenidate hydrochloride extended-release tablets in single doses of 18, 36, and 54 mg/day to healthy adults, C_{max} and $AUC_{(0\ inf)}$ of d-methylphenidate were proportional to dose, whereas l-methylphenidate C_{max} and $AUC_{(0\ inf)}$ increased disproportionately with respect to dose. Following administration of methylphenidate hydrochloride extended-release tablets, plasma concentrations of the l-isomer were approximately 1/40 the plasma concentrations of the d-isomer.

In healthy adults, single and multiple dosing of once-daily methylphenidate hydrochloride extended-release tablets doses from 54 to 144 mg/day resulted in linear and dose-proportional increases in C_{max} and AUC_{inf} for total methylphenidate (MPH) and its major metabolite, α-phenyl-piperidine acetic acid (PPAA). There was no time dependency in the pharmacokinetics of methylphenidate. The ratio of metabolite (PPAA) to parent drug (MPH) was constant across doses from 54 to 144 mg/day, both after single dose and upon multiple dosing.

In a multiple-dose study in adolescent ADHD patients aged 13 to 16 administered their prescribed dose (18 to 72 mg/day) of methylphenidate hydrochloride extended-release tablets, mean C_{max} and AUC_{TAU} of d- and total methylphenidate increased proportionally with respect to dose.

Distribution

Plasma methylphenidate concentrations in adults and adolescents decline biexponentially following oral administration. The half-life of methylphenidate in adults and adolescents following oral administration of methylphenidate hydrochloride extended-release tablets was approximately 3.5 hours.

Metabolism and Excretion

In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little or no pharmacologic activity. In adults the metabolism of methylphenidate hydrochloride extended-release tablets once daily as evaluated by metabolism to PPAA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once-daily doses of methylphenidate hydrochloride extended-release tablets is similar.

After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.

Food Effects

In patients, there were no differences in either the pharmacokinetics or the pharmacodynamic performance of methylphenidate hydrochloride extended-release tablets when administered after a high-fat breakfast. There is no evidence of dose dumping in the presence or absence of food.

Alcohol Effect

An *in vitro* study was conducted to explore the effect of alcohol on the release characteristics of methylphenidate from the methylphenidate hydrochloride extended-release 18 mg tablet dosage form. At an alcohol concentration up to 40% there was no increased release of methylphenidate in the first hour. The results with the 18 mg tablet strength are considered representative of the other available tablet strengths.

Special Populations

Gender

In healthy adults, the mean dose-adjusted $AUC_{(0\ inf)}$ values for methylphenidate hydrochloride extended-release tablets were 36.7 ng•h/mL in men and 37.1 ng•h/mL in women, with no differences noted between the two groups.

Race

In adults receiving methylphenidate hydrochloride extended-release tablets, dose-adjusted $AUC_{(0\ nf)}$ was consistent across ethnic groups; however, the sample size may have been insufficient to detect ethnic variations in pharmacokinetics.

Age

Increase in age resulted in increased apparent oral clearance (CL/F) (58% increase in adolescents compared to children). Some of these differences could be explained by body-weight differences among these populations. This suggests that subjects with higher body weight may have lower exposures of total methylphenidate at similar doses.

The pharmacokinetics of methylphenidate hydrochloride extended-release tablets have not been studied in children less than 6 years of age.

Renal Insufficiency

There is no experience with the use of methylphenidate hydrochloride extended-release tablets in patients with renal insufficiency. After oral administration of radiolabeled methylphenidate in humans, methylphenidate was extensively metabolized and approximately 80% of the radioactivity was excreted in the urine in the form of PPAA. Since renal clearance is not an important route of methylphenidate clearance, renal insufficiency is expected to have little effect on the pharmacokinetics of methylphenidate hydrochloride extended-release tablets.

Hepatic Insufficiency

There is no experience with the use of methylphenidate hydrochloride extended-release tablets in patients with hepatic insufficiency.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

In a lifetime carcinogenicity study carried out in B6C3F1 mice, methylphenidate caused an increase in hepatocellular adenomas and, in males only, an increase in hepatoblastomas at a daily dose of approximately 60 mg/kg/day. This dose is approximately 30 times and 4 times the maximum recommended human dose of methylphenidate hydrochloride extended-release tablets on a mg/kg and mg/m^2 basis, respectively. Hepatoblastoma is a relatively rare rodent malignant tumor type. There was no increase in total malignant hepatic tumors. The mouse strain used is sensitive to the development of hepatic tumors, and the significance of these results to humans is unknown.

Methylphenidate did not cause any increases in tumors in a lifetime carcinogenicity study carried out in F344 rats; the highest dose used was approximately 45 mg/kg/day, which is approximately 22 times and 5 times the maximum recommended human dose of methylphenidate hydrochloride extended-release tablets on a mg/kg and mg/m^2 basis, respectively.

In a 24-week carcinogenicity study in the transgenic mouse strain p53+/-, which is sensitive to genotoxic carcinogens, there was no evidence of carcinogenicity. Male and female mice were fed diets containing the same concentration of methylphenidate as in the lifetime carcinogenicity study; the high-dose groups were exposed to 60 to 74 mg/kg/day of methylphenidate.

Mutagenesis

Methylphenidate was not mutagenic in the *in vitro* Ames reverse mutation assay or the *in vitro* mouse lymphoma cell forward mutation assay. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an *in vitro* assay in cultured Chinese Hamster Ovary cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility

Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week Continuous Breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 80-fold and 8-fold the highest recommended human dose of methylphenidate hydrochloride extended-release tablets on a mg/kg and mg/m^2 basis, respectively.

14 CLINICAL STUDIES

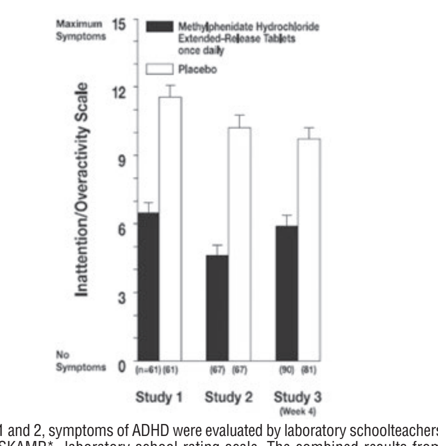
Methylphenidate hydrochloride extended-release tablets were demonstrated to be effective in the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in 4 randomized, double-blind, placebo-controlled studies in children and adolescents and 2 double-blind placebo-controlled studies in adults who met the Diagnostic and Statistical Manual 4th edition (DSM-IV) criteria for ADHD.

14.1 Children

Three double-blind, active- and placebo-controlled studies were conducted in 416 children aged 6 to 12 years. The controlled studies compared methylphenidate hydrochloride extended-release tablets given once daily (18, 36, or 54 mg), methylphenidate given three times daily over 12 hours (15, 30, or 45 mg total daily dose), and placebo in two single-center, 3-week crossover studies (Studies 1 and 2) and in a multicenter, 4-week, parallel-group comparison (Study 3). The primary comparison of interest in all three trials was methylphenidate hydrochloride extended-release tablets versus placebo.

Symptoms of ADHD were evaluated by community schoolteachers using the Inattention/Overactivity with Aggression (IOWA) Conners scale. Statistically significant reduction in the Inattention/Overactivity subscale versus placebo was shown consistently across all three controlled studies for methylphenidate hydrochloride extended-release tablets. The scores for methylphenidate hydrochloride extended-release tablets and placebo for the three studies are presented in Figure 2.

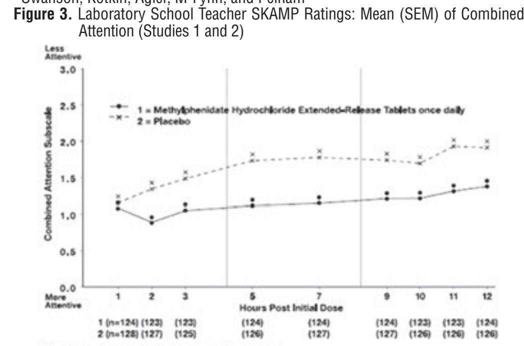
Figure 2. Mean Community School Teacher IOWA Conners Inattention/Overactivity Scores with Methylphenidate Hydrochloride Extended-Release Tablets once daily (18, 36, or 54 mg) and placebo. Studies 1 and 2 involved a 3-way crossover of 1 week per treatment arm. Study 3 involved 4 weeks of parallel-group treatments with a Last Observation Carried Forward analysis at week 4. Error bars represent the mean plus standard error of the mean.



In Studies 1 and 2, symptoms of ADHD were evaluated by laboratory schoolteachers using the SKAMP* laboratory school rating scale. The combined results from these two studies demonstrated statistically significant improvements in attention and behavior in patients treated with methylphenidate hydrochloride extended-release tablets versus placebo that were maintained through 12 hours after dosing. Figure 3 presents the laboratory schoolteacher SKAMP ratings for methylphenidate hydrochloride extended-release tablets and placebo.

*Swanson, Kotkin, Agler, M-Fynn, and Pelham

Figure 3. Laboratory School Teacher SKAMP Ratings: Mean (SEM) of Combined Attention (Studies 1 and 2)



14.2 Adolescents

In a randomized, double-blind, multicenter, placebo-controlled trial (Study 4) involving 177 patients, methylphenidate hydrochloride extended-release tablets were demonstrated to be effective in the treatment of ADHD in adolescents aged 13 to 18 years at doses up to 72 mg/day (1.4 mg/kg/day). Of 220 patients who entered an open 4-week titration phase, 177 were titrated to an individualized dose (maximum of 72 mg/day) based on meeting specific improvement criteria on the ADHD Rating Scale and the Global Assessment of Effectiveness with acceptable tolerability. Patients who met these criteria were then randomized to receive either their individualized dose of methylphenidate hydrochloride extended-release tablets (18 – 72 mg/day, n=87) or placebo (n=90) during a two-week double-blind phase. At the end of this phase, mean scores for the investigator rating on the ADHD Rating Scale demonstrated that methylphenidate hydrochloride extended-release tablets were statistically significantly superior to placebo.

14.3 Adults

Two double-blind, placebo-controlled studies were conducted in 627 adults aged 18 to 65 years. The controlled studies compared methylphenidate hydrochloride extended-release tablets administered once daily and placebo in a multicenter, parallel-group, 7-week dose-titration study (Study 5) (36 to 108 mg/day) and in a multicenter, parallel-group, 5-week, fixed-dose study (Study 6) (18, 36, and 72 mg/day).

Study 5 demonstrated the effectiveness of methylphenidate hydrochloride extended-release tablets in the treatment of ADHD in adults aged 18 to 65 years at doses from 36 mg/day to 108 mg/day based on the change from baseline to final study visit on the Adult ADHD Investigator Rating Scale (AISRS). Of 226 patients who entered the 7-week trial, 110 were randomized to methylphenidate hydrochloride extended-release tablets and 116 were randomized to placebo. Treatment was initiated at 36 mg/day and patients continued with incremental increases of 18 mg/day (36 to 108 mg/day) based on meeting specific improvement criteria with acceptable tolerability. At the final study visit, mean change scores (LS Mean, SEM) for the investigator rating on the AISRS demonstrated that methylphenidate hydrochloride extended-release tablets were statistically significantly superior to placebo.

Study 6 was a multicenter, double-blind, randomized, placebo-controlled, parallel-group, dose-response study (5-week duration) with 3 fixed-dose groups (18, 36, and 72 mg). Patients were randomized to receive methylphenidate hydrochloride extended-release tablets administered at doses of 18 mg (n=101), 36 mg (n=102), 72 mg/day (n=102), or placebo (n=96). All three doses of methylphenidate hydrochloride extended-release tablets were statistically significantly more effective than placebo in improving CAARS (Conners' Adult ADHD Rating Scale) total scores at double-blind end point in adult subjects with ADHD.

15 REFERENCES

American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 4th ed. Washington, DC: American Psychiatric Association, 1994.

16 HOW SUPPLIED/STORAGE AND HANDLING

Methylphenidate hydrochloride extended-release tablets, USP are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow, modified capsule shape, printed with **CP 342** on one side and blank on the other side. The 27 mg tablets are gray, modified capsule shape, printed with **CP 340** on one side and blank on the other side. The 36 mg tablets are white, modified capsule shape, printed with **CP 339** on one side and blank on the other side. The 54 mg tablets are brownish-red, modified capsule shape, printed with **CP 341** on one side and blank on the other side. All four dosage strengths are supplied in bottles containing 100 tablets.

18 mg	100-count bottle	NDC 0115-1566-01
27 mg	100-count bottle	NDC 0115-1567-01
36 mg	100-count bottle	NDC 0115-1568-01
54 mg	100-count bottle	NDC 0115-1569-01

Storage and Handling

Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.

17 PATIENT COUNSELING INFORMATION

See Medication Guide

Priapism

Advise patients, caregivers, and family members of the possibility of painful or prolonged penile erections (priapism). **Instruct the patient to seek immediate medical attention in the event of priapism** *[see Warnings and Precautions (5.4)]*.

Circulation Problems in Fingers and Toes [Peripheral Vasculopathy, including Raynaud's Phenomenon]

Instruct patients beginning treatment with methylphenidate hydrochloride extended-release tablets about the risk of peripheral vasculopathy, including Raynaud's phenomenon, and associated signs and symptoms: fingers or toes may feel numb, cool, painful, and/or may change color from pale, to blue, to red.

Instruct patients to report to their physician any new numbness, pain, skin color change, or sensitivity to temperature in fingers or toes.

Instruct patients to call their physician immediately with any signs of unexplained wounds appearing on fingers or toes while taking methylphenidate hydrochloride extended-release tablets.

Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients.

General Considerations

Prescribers or other health professionals should inform patients, their families, and their caregivers about the benefits and risks associated with treatment with methylphenidate and should counsel them in its appropriate use. A patient Medication Guide is available for methylphenidate hydrochloride extended-release tablets. The prescriber or health professional should instruct patients, their families, and their caregivers to read the Medication Guide and should assist them in understanding its contents. Patients should be given the opportunity to discuss the contents of the Medication Guide and to obtain answers to any questions they may have. The complete text of the Medication Guide is reprinted at the end of this document.

Administration Instructions

Patients should be informed that methylphenidate hydrochloride extended-release tablets should be swallowed whole with the aid of liquids. Tablets should not be chewed, divided, or crushed. The medication is contained within a nonabsorbable shell designed to release the drug at a controlled rate. The tablet shell, along with insoluble core components, is eliminated from the body; patients should not be concerned if they occasionally notice in their stool something that looks like a tablet.

Driving or Operating Heavy Machinery

Stimulants may impair the ability of the patient to operate potentially hazardous machinery or vehicles. Patients should be cautioned accordingly until they are reasonably certain that methylphenidate hydrochloride extended-release tablets do not adversely affect their ability to engage in such activities.

For more information call 1-800-934-6729.
LB# 903

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Impax Generics
Hayward, CA 94544

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208607Orig1s000

Labeling Review

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	May 2, 2017
ANDA Number(s)	208607
Review Number	3
Applicant Name	Impax Laboratories, Inc.
Established Name & Strength(s)	Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg
Proposed Proprietary Name	None
Submission Received Date	March 17, 2017 (amendment)
Labeling Reviewer	Lily Chua
Labeling Team Leader	Adolph Vezza

Review Conclusion

☒ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☐ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List

Generic Name/Dosage Form/Strengths: Multiple Methylphenidate ER products (TSI)
No Actions prior to contacting Policy Lead;
Notes: Broad policy issue covering multiple products containing Extended Release methylphenidate. Contact OGDP Lead prior to any communication or action.
OGD Policy Lead (Maryll Toufanian).

1. LABELING COMMENTS

1.1 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission dated March 17, 2017.

1.2 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s)

Review #1 finalized date: November 21, 2016
Review #2 finalized date: February 28, 2017

From Response to ECD, received March 17, 2017:
PRESCRIBING INFORMATION:
a. FULL PRESCRIBING INFORMATION: We encourage you to add "USP" to the established name in the DOSAGE FORMS AND STRENGTHS, and DESCRIPTION sections of the package insert.
Response: Impax has added "USP in the DOSAGE FORMS AND STRENGTHS and DESCRIPTION sections.
b. FULL PRESCRIBING INFORMATION, DESCRIPTION, last sentence: Please revise (b) (4) (b) (4) **To read "USP dissolution test is pending."**
Response: Impax has revised the last sentence of the DESCRIPTION section to read "USP dissolution test is pending."

Reviewer Comments: Responses are acceptable.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Not submitted in this amendment.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: "DEA form required" is no longer required in CII labeling.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES TSI: issue affecting multiple drug products. NOH Issued, Hearing granted. OCS granted extension for Mallinckrodt to submit data by March 20, 2017.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)* **NDA# /Supplement# (S-000 if original):** NDA 021121/S-038 **Supplement Approval Date:** January 4, 2017 **Proprietary Name:** CONCERTA® **Established Name:** Methylphenidate HCl Extended-Release Tablets **Description of Supplement:** of new safety information that we believe should be included in the labeling for all Methylphenidate products. This information pertains to the association between the use of stimulants used to treat Attention Deficit Hyperactivity Disorder and serotonin syndrome.
☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:**
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** NDA 021121/ (b) (4), S-037 is approved CMC supplement with no labeling associated with it.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: Acceptable.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-16 dated 09/28/2015 and DAILYMED]

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results

	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	5/3/2017	YES	Methylphenidate Hydrochloride Extended-Release Tablets	Packaging and Storage: Preserve in tight containers. Store at controlled room temperature. Labeling: The labeling states the Dissolution test with which the product complies if other than Test 1.
PF	5/3/2017	YES	Same as above.	Same as above.

Reviewer Comments: From CMC update 05/02/2017: The Applicant has proposed USP test 4 for finished product batch release and stability and is found adequate based on our biopharmaceutics review. However, the acceptance criteria that will be implemented based on biopharm recommendation is different than the USP test 4 tolerance limit. The Applicant in response to our IR accepted the Agency recommended acceptance criteria and stated that they will petition the USP to include the specification in the monograph.

"USP dissolution test is pending." is listed in the DESCRIPTION section.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 5/3/2017.

Table 3 provides Orange Book patents for the Model Labeling NDA 021121 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
Patent Number	**Patent Expiration**	**Patent Use Code**	**Patent Use Code Definition**	**Patent Certification**	**Date of Patent Cert Submission**	**Labeling Impact (enter Carve-out or None)**
6919373*PED	Jan 31, 2018	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
6930129*PED	Jan 31, 2018	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
8163798*PED	Jan 31, 2018			P IV	05/28/2016	None
8629179*PED	Jan 31, 2018			P IV	05/28/2016	None
9000038*PED	Jan 31, 2018	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
9000038*PED	Jan 31, 2018	U-1693	METHOD OF TREATING ADHD IN CHILDREN 6 YEARS OF AGE AND OLDER AND ADOLESCENTS	P IV	05/28/2016	None
9029416	Jul 31, 2017	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
9144549	Jul 31, 2017	U-1747	FOR CLAIMS 1-3,6-13,16-24 AND 26-32: METHOD OF TREATING ADHD	P IV	05/28/2016	None
9144549	Jul 31, 2017	U-1748	FOR CLAIMS 1-4,6-14,16-24 AND 26-32: METHOD OF TREATING ADHD IN CHILDREN 6 YEARS OF AGE AND OLDER AND ADOLESCENTS	P IV	05/28/2016	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: From Cover Letter received August 11, 2016: CorePharma, LLC wishes to notify the FDA that the patent owner and NDA holder of NDA 021121 did not initiate an action for Patent Infringement against CorePharma within the statutory 45-day period.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter "Carve-out" or "None")**
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: There is no unexpired exclusivity for this product in the Orange Book database.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **YES**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **NO**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)

Previous Labeling Review	Currently Proposed	Assessment
ammonium hydroxide, cetyl alcohol, ethylcellulose, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, n-butyl alcohol, polyethylene glycol, povidone, propylene glycol, shellac, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. The 18 mg tablet also contains the following additional inert ingredient: yellow ron oxide; and the 54 mg tablet also contains the following additional inert ngredients: red iron oxide and yellow iron oxide. (b) (4)	ammonium hydroxide, cetyl alcohol, ethylcellulose, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, n-butyl alcohol, polyethylene glycol, povidone, propylene glycol, shellac, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. The 18 mg tablet also contains the following additional inert ingredient: yellow iron oxide; and the 54 mg tablet also contains the following additional inert ingredients: red ron oxide and yellow iron oxide. USP dissolution test is pending.	(b) (4) has been revised to read "USP dissolution test is pending." This change is acceptable. No change otherwise.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products

Previous Labeling Review	Currently Proposed	Assessment

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Methylphenidate hydrochloride extended-release tablets, USP are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow, modified capsule shape, printed with CP 342 on one side and blank on the other side. The 27 mg tablets are gray, modified capsule shape, printed with CP 340 on one side and blank on the other side. The 36 mg tablets are white, modified capsule shape, printed with CP 339 on one side and blank on the other side. The 54 mg tablets are brownish-red, modified capsule shape, printed with CP 341 on one side and blank on the other side. All four dosage strengths are supplied in bottles containing 100 tablets. **18 mg 100-count bottle NDC 0115-1566-01** **27 mg 100-count bottle NDC 0115-1567-01** **36 mg 100-count bottle NDC 0115-1568-01** **54 mg 100-count bottle NDC 0115-1569-01** **Storage and Handling** **Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.**	**Methylphenidate hydrochloride extended-release tablets, USP are available in 18mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow, modified capsule shape, printed with CP 342 on one side and blank on the other side. The 27mg tablets are gray,modified capsule shape, printed with CP 340 on one side and blank on the other side. The 36mg tablets are white, modified capsule shape, printed with CP 339 on one side and blank on the other side. The 54 mg tablets are brownishred, modified capsule shape, printed with CP 341 on one side and blank on the other side. All four dosage strengths are supplied n bottles containing 100 tablets.** **18 mg 100-count bottle NDC 0115-1566-01** **27 mg 100-count bottle NDC 0115-1567-01** **36 mg 100-count bottle NDC 0115-1568-01** **54 mg 100-count bottle NDC 0115-1569-01** **Storage and Handling** **Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.**	**No Change**

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
(b) (4) **Distributed by:** **Impax Generics** **Hayward, CA 94544**	**Distributed by:** **Impax Generics** **Hayward, CA 94544**	**No Change**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: From CMC update 05/02/2017: The Applicant has proposed USP test 4 for finished product batch release and stability and is found adequate based on our biopharmaceutics review. However, the acceptance criteria that will be implemented based on biopharm recommendation is different than the USP test 4 tolerance limit. The Applicant in response to our IR accepted the Agency recommended acceptance criteria and stated that they will petition the USP to include the specification in the monograph.

From CMC review dated 5/3/2017:

DESCRIPTION section

Is the information accurate? [X] Yes [ ] No

Is the drug product subject of a USP monograph? [X] Yes [ ] No

Meets Dissolution Test 4.

HOW SUPPLIED section

i) Is the information accurate? [X] Yes [ ] No

ii) Are the storage conditions acceptable? [X] Yes [ ] No

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code
18 mg	14 2	Yellow tablet printed with "CP 342" on one side and blank on the other side
27 mg	14 25	Gray tablet printed with "CP 340" on one side and blank on the other side
36 mg	14 78	White tablet printed with "CP 339" on one side and blank on the other side
54 mg	14 78	Brownish-red tablet printed with "CP 341" on one side and blank on the other side

From 3.2.P.7.1: 100s CRC. The container system includes a tamper-evident heat seal. The sealing of the finished drug product meets the requirements in 21 CFR 1302.06 "Sealing of controlled substances."
The container label has this statement "Do not use if printed safety seal under cap is broken or missing."

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (18 mg, 27 mg, 36 mg and 54 mg)	Final	(bottles of 100s)	12/08/2016	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	January 2017	03/17/2017	Satisfactory
Medication Guide	Final	Attached to Prescribing Information	03/17/2017	Satisfactory
SPL Data Elements		3/2017	03/17/2017	Satisfactory

Lily Chua

Digitally signed by Lily Chua
Date: 5/08/2017 08:52:19AM
GUID: 5277fc6700089cebb6783d59b3e106fa

Adolph Vezza

Digitally signed by Adolph Vezza
Date: 5/15/2017 10:14:33AM
GUID: 508da70600028a9e6a494d73e6454d09

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	January 30, 2017 and February 27, 2017
ANDA Number(s)	208607
Review Number	2
Applicant Name	CorePharma, LLC
Established Name & Strength(s)	Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg
Proposed Proprietary Name	None
Submission Received Date	December 8, 2016 and January 31, 2017 (amendments)
Labeling Reviewer	Lily Chua
Labeling Team Leader	Adolph Vezza

Review Conclusion

☐ ACCEPTABLE – No Comments.

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for the Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List

Generic Name/Dosage Form/Strengths: Multiple Methylphenidate ER products (TSI)
No Actions prior to contacting Policy Lead;
Notes: Broad policy issue covering multiple products containing Extended Release methylphenidate. Contact OGDP Lead prior to any communication or action.
OGD Policy Lead (Maryll Toufanian).

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on January 30, 2017 and February 27, 2017 based on your submissions dated December 8, 2016 and January 31, 2017:

PRESCRIBING INFORMATION

a. FULL PRESCRIBING INFORMATION: We encourage you to add "USP" to the established name in the DOSAGE FORMS AND STRENGTHS, and DESCRIPTION sections of the package insert.
b. FULL PRESCRIBING INFORMATION, DESCRIPTION, last sentence: Please revise (b) (4) (b) (4) to read "USP dissolution test is pending."

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission (s) dated (add date)

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
NA

2. PREVIOUS LABELING REVIEW, DEFICIENCIES, FIRM'S RESPONSE, AND REVIEWER'S ASSESSMENT

In this section, we include any previous labeling review deficiencies, the firm's response and reviewer's assessment to firm's response as well as any new deficiencies found in this cycle. Include the previous review cycle and the review's submission date(s)

Review #1 finalized date: November 21, 2016

From Response to ECD, received December 8, 2016:

Container Label

a. Please increase the prominence of the expression of strength statement.

Response: CorePharma increased the prominence of the expression of strength statement, increasing the font size from 9.5 pt. to 12.5 pt.

b. Please revise the storage statement to read "Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity."

Response: Revised the storage statement as follows:

From: Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity. To: Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.

c. Ensure to include a place holder for the lot number and the expiration date.

Response: Included place holder for the lot number and the expiration date in the unvarnished area.

2. Prescribing Information

a. HIGHLIGHTS OF PRESCRIBING INFORMATION: Please revise "METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, USP" to read "METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS" in the first sentence. [Delete "USP"].

Response: Revised first sentence of **HIGHLIGHTS OF PRESCRIBING INFORMATION**, to delete "USP":

HIGHLIGHTS, Title: Please revise the title to read "METHYLPHENIDATE HYDROCHLORIDE extended-release tablets, for oral use, CII".

Response: Revised **HIGHLIGHTS** title to read: **METHYLPHENIDATE HYDROCHLORIDE extended-release tablets, for oral use, CII**

c. HIGHLIGHTS, DOSAGE FORMS AND STRENGTHS: Please revise to read "Tablets: 18 mg, 27 mg, 36 mg, and 54 mg (3)".

Response: HIGHLIGHTS, DOSAGE FORMS AND STRENGTHS revised to: Tablets: 18 mg, 27 mg, 36 mg, and 54 mg (3)

d. CONTENTS*: Please revise the subsection title to read: "13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility".

Response: CONTENTS*, subsection title revised.

e. FULL PRESCRIBING INFORMATION

i. DESCRIPTION, 3rd paragraph, inert ingredients: Please include "ammonium hydroxide".

Response: In the **DESCRIPTION** section, 3rd paragraph, added the following ingredient: ammonium hydroxide

ii. See comment 2(d) above.

Response: Revised subsection title to: 13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

iii. HOW SUPPLIED: Please include the shape with the descriptions of the tablets.

Response: Added the following shape with the description of the tablets: modified capsule shape

iv. HOW SUPPLIED, Storage and Handling: Please revise the storage statement to read "Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.

Response: Revised HOW SUPPLIED, Storage and Handling statement: From:

Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity. To: Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.

3. Medication Guide

Inactive Ingredients: Please include "ammonium hydroxide".

Response: Added to the Inactive Ingredients: ammonium hydroxide

4. Structured Product Labeling (SPL) Data Elements

Response: SPL revised for the above changes and Data Elements updated to include ammonium hydroxide in Inactive Ingredients.

From Cover Letter received January 31, 2017:

CorePharma, LLC (a wholly owned subsidiary of Impax Laboratories, Inc.) submits this Unsolicited Amendment, Labeling, for ANDA 208607, Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg, and 54 mg. The labeling has been updated to include important safety updates currently presented in the Reference Listed Drug's labeling (CONCERTA: NDA 021121 / Reference ID: 4036863).

Reviewer Comments: Responses are acceptable.

2.1 CONTAINER AND CARTON LABELS

Did the firm submit container and/or carton labels that were **NOT** requested in the previous labeling review?
NO

If yes, state the reason for the submission, and comment below whether the proposed revisions are acceptable or deficient.

Reviewer Comments: Acceptable.

2.2 ADDITIONAL BACKGROUND INFORMATION PERTINENT TO THE REVIEW

In this section, include any correspondence or internal information pertinent to the review. Include the correspondence(s) and/or information date(s) [e.g. resolution of any pending chemistry review or issue].

Reviewer Comments: "DEA form required" is no longer required in CII labeling.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? YES
If Yes, please explain in section 2.2 Additional Background Information Pertinent to the Review

Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES
TSI: issue Affecting multiple drug products. Revised BE guidance, which posted November 5, 2015; downgrade occurred. Mallinckrodt sued FDA.

3.2 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)

☒ **MOST RECENTLY APPROVED NDA MODEL LABELING**

(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA model labeling information.)

NDA# /Supplement# (S-000 if original): NDA 021121/S-038
Supplement Approval Date: January 4, 2017
Proprietary Name: CONCERTA®
Established Name: Methylphenidate HCl Extended-Release Tablets
Description of Supplement: of new safety information that we believe should be included in the labeling for all Methylphenidate products. This information pertains to the association between the use of stimulants used to treat Attention Deficit Hyperactivity Disorder and serotonin syndrome.

☐ **MOST RECENTLY APPROVED ANDA MODEL LABELING**

ANDA#/Supplement# (S-000 if original): Click here to enter text.
Supplement Approval Date: Click here to enter text.
Proprietary Name: Click here to enter text.
Established Name: Click here to enter text.
Description of Supplement:

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** NDA 021121/S-035 approved April 17, 2015, pertains to the association between the use of stimulants used to treat Attention Deficit Hyperactivity Disorder (ADHD) (b) (4) (b) (4) S-037 is approved CMC supplement with no labeling associated with it.

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments: Per comment issued by the CMC reviewer on 2/12/2017, we will ask firm to revise (b) (4) to read "USP dissolution test is pending." We will also encourage firm to add "USP" to the established name in the DOSAGE FORMS AND STRENGTHS, and DESCRIPTION sections of the package insert.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: ANRPT-16 dated 09/28/2015 and DAILYMED]

3.4 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results

	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
USP	1/30/2017	YES	Methylphenidate Hydrochloride Extended-Release Tablets	Packaging and Storage: Preserve in tight containers. Store at controlled room temperature. Labeling: The labeling states the Dissolution test with which the product complies if other than Test 1.
PF	1/30/2017	YES	Same as above.	Same as above.

Reviewer Comments: From comment from CMC review dated 02/03/2017: If the Biopharm accepted method and SPECIFICATION are the same as USP, the firm can cite [redacted] (b) (4) If not labeling should cite "USP Dissolution test Pending". However, the Biopharm review is pending as of 2/3/2017.

From comment from CMC review dated 02/12/2017: Biopharm reviewer proposed more stringent specifications for this product based on the submitted dissolution data. Therefore, the labeling should cite "USP Dissolution test Pending".

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 1/30/2017.

Table 3 provides Orange Book patents for the Model Labeling NDA 021121 and ANDA patent certifications.

(For applications that have no patents, N/A is entered in the patent number column)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
6919373*PED	Jan 31, 2018	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
6930129*PED	Jan 31, 2018	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None

Table 3: Impact of Model Labeling Patents on ANDA Labeling						
8163798*PED	Jan 31, 2018			P IV	05/28/2016	None
8629179*PED	Jan 31, 2018			P IV	05/28/2016	None
9000038*PED	Jan 31, 2018	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
9000038*PED	Jan 31, 2018	U-1693	METHOD OF TREATING ADHD IN CHILDREN 6 YEARS OF AGE AND OLDER AND ADOLESCENTS	P IV	05/28/2016	None
9029416	Jul 31, 2017	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
9144549	Jul 31, 2017	U-1747	FOR CLAIMS 1-3,6-13,16-24 AND 26-32: METHOD OF TREATING ADHD	P IV	05/28/2016	None
9144549	Jul 31, 2017	U-1748	FOR CLAIMS 1-4,6-14,16-24 AND 26-32: METHOD OF TREATING ADHD IN CHILDREN 6 YEARS OF AGE AND OLDER AND ADOLESCENTS	P IV	05/28/2016	None

Reviewer Assessment:

Is the applicant's "patent carve out" acceptable? **NA**

Reviewer Comments: From Cover Letter received August 11, 2016: CorePharma, LLC wishes to notify the FDA that the patent owner and NDA holder of NDA 021121 did not initiate an action for Patent Infringement against CorePharma within the statutory 45-day period.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling					
Exclusivity Code	**Exclusivity Expiration**	**Exclusivity Code Definition**	**Exclusivity Statement**	**Date of Exclusivity Submission**	**Labeling Impact (enter "Carve-out" or "None")**
N/A					

Reviewer Assessment:

Is the applicant's "exclusivity carve out" acceptable? **NA**

Reviewer Comments: There is no unexpired exclusivity for this product in the Orange Book database.

4. DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT

Tables 5, 6, and 7 describe any changes in the inactive ingredients, dosage form description, package sizes, and manufacturer/distributor/packer statements of the Prescribing Information or Drug Facts for OTC products when compared to the previous labeling review.

Reviewer Assessment:

Are there changes to the inactives in the DESCRIPTION section or Inactive Ingredients (OTC)? **YES**
Are there changes to the dosage form description(s) or package size(s) in HOW SUPPLIED or package size(s) for OTC? **YES**
Are there changes to the manufacturer/distributor/packer statements? **NO**
If yes, then comment below in Tables 5, 6, and 7.

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Previous Labeling Review	**Currently Proposed**	**Assessment**
cetyl alcohol, ethylcellulose, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, n-butyl alcohol, polyethylene glycol, povidone, propylene glycol, shellac, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. The 18 mg tablet also contains the following additional inert ingredient: yellow iron oxide; and the 54 mg tablet also contains the following additional inert ingredients: red ron oxide and yellow iron oxide. (b) (4)	ammonium hydroxide, cetyl alcohol, ethylcellulose, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, n-butyl alcohol, polyethylene glycol, povidone, propylene glycol, shellac, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. The 18 mg tablet also contains the following additional inert ingredient: yellow ron oxide; and the 54 mg tablet also contains the following additional inert ngredients: red iron oxide and yellow iron oxide. (b) (4)	Ammonium hydroxide has been added. This change is acceptable. No change otherwise.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Methylphenidate hydrochloride extended-release tablets, USP are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow printed with CP 342 on one side and blank on the other side. The 27 mg tablets are gray printed with CP 340 on one side and blank on the other side. The 36 mg tablets are white printed with CP 339 on one side and blank on the other side. The 54 mg tablets are brownish-red printed with CP 341 on one side and blank on the other side. All four dosage strengths are supplied in bottles containing 100 tablets. 18 mg 100-count bottle NDC 0115-1566-01 27 mg 100-count bottle NDC 0115-1567-01 36 mg 100-count bottle NDC 0115-1568-01 54 mg 100-count bottle NDC 0115-1569-01 Storage and Handling Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from humidity.	Methylphenidate hydrochloride extended-release tablets, USP are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow, modified capsule shape, printed with CP 342 on one side and blank on the other side. The 27 mg tablets are gray, modified capsule shape, printed with CP 340 on one side and blank on the other side. The 36 mg tablets are white, modified capsule shape, printed with CP 339 on one side and blank on the other side. The 54 mg tablets are brownish-red, modified capsule shape, printed with CP 341 on one side and blank on the other side. All four dosage strengths are supplied in bottles containing 100 tablets. 18 mg 100-count bottle NDC 0115-1566-01 27 mg 100-count bottle NDC 0115-1567-01 36 mg 100-count bottle NDC 0115-1568-01 54 mg 100-count bottle NDC 0115-1569-01 Storage and Handling Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity.	The shape has been included with the descriptions of the tablets. The storage statement has been revised to read “Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature].” These changes are acceptable. No change otherwise.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**

Table 7: Manufacturer/Distributor/Packer Statements		
Distributed by: **Impax Generics** **Hayward, CA 94544**	**Distributed by:** **Impax Generics** **Hayward, CA 94544**	**No Change**

5. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: From CMC review dated 02/12/2017:

DESCRIPTION section

Is the information accurate? [X] Yes [ ] No

Is the drug product subject of a USP monograph? [X] Yes [ ] No

Meets Dissolution Test 4.

HOW SUPPLIED section

i) Is the information accurate? [X] Yes [ ] No

ii) Are the storage conditions acceptable? [X] Yes [ ] No

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? [ ] Yes [ ] No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code
18 mg	14.2	Yellow tablet printed with "CP 342" on one side and blank on the other side.
27 mg	14.25	Gray tablet printed with "CP 340" on one side and blank on the other side.
36 mg	14.78	White tablet printed with "CP 339" on one side and blank on the other side
54 mg	14.78	Brownish-red tablet printed with "CP 341" on one side and blank on the other side

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

From CMC review dated 02/03/2017: If the Biopharm accepted method and SPECIFICATION are the same as USP, the firm can cite [redacted] (b) (4) If not labeling should cite "USP Dissolution test Pending". However, the Biopharm review is pending as of 2/3/2017.

From CMC review dated 02/12/2017: Biopharm reviewer proposed more stringent specifications for this product based on the submitted dissolution data. Therefore, the labeling should cite "USP Dissolution test Pending".

From 3.2.P.7.1: 100s CRC. The container system includes a tamper-evident heat seal. The sealing of the finished drug product meets the requirements in 21 CFR 1302.06 "Sealing of controlled substances."
The container label has this statement "Do not use if printed safety seal under cap is broken or missing."

6. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline reviewer(s):

Reviewer Comments: NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 8 and 9 provide a summary of recommendations for all labeling pieces for this application.

For each row, you **MUST** choose an item "Final, Draft, or "NA". If you enter "NA" under the second column, you do NOT need to enter "NA" for the remaining columns.

Table 8: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (18 mg, 27 mg, 36 mg and 54 mg)	Final	(bottles of 100s)	12/08/2016	Satisfactory
Table 9 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	Final	January, 2017	1/31/2017	Revise
Medication Guide	Final	January, 2017	1/31/2017	Satisfactory
SPL Data Elements		1/2017	1/31/2017	Satisfactory

Adolph Vezza

Digitally signed by Adolph Vezza
Date: 2/28/2017 10:10:56AM
GUID: 508da70600028a9e6a494d73e6454d09

Lily Chua

Digitally signed by Lily Chua
Date: 2/03/2017 08:50:42AM
GUID: 5277fc6700089cebb6783d59b3e106fa

LABELING REVIEW

Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs (OGD)
Center for Drug Evaluation and Research (CDER)

Date of This Review	August 16, 2016
ANDA Number(s)	208607
Review Number	1
Applicant Name	CorePharma, LLC
Established Name & Strength(s)	Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg
Proposed Proprietary Name	None
Submission Received Date	April 18, 2016 and May 31, 2016
Labeling Reviewer	Lily Chua
Labeling Team Leader	Adolph Vezza

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

☒ Minor Deficiency* – Refer to Labeling Deficiencies and Comments for Letter to Applicant.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Easily Correctable Deficiency if all other OGD reviews are acceptable. Otherwise, the labeling minor deficiencies will be included in the Complete Response (CR) letter to the applicant.

☒ On Policy Alert List

Generic Name/Dosage Form/Strengths: Multiple Methylphenidate ER products (TSI)
No Actions prior to contacting Policy Lead;
Notes: Broad policy issue covering multiple products containing Extended Release methylphenidate. Contact OGDP Lead prior to any communication or action.
OGD Policy Lead (Maryll Toufanian).

TABLE OF CONTENTS

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on August 16, 2016 based on your submissions dated April 18, 2016 and May 28, 2016:

1. CONTAINER LABEL
   a. Please increase the prominence of the expression of strength statement.
   b. Please revise the storage statement to read "Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity."
   c. Ensure to include a place holder for the lot number and the expiration date.

2. PRESCRIBING INFORMATION
   a. HIGHLIGHTS OF PRESCRIBING INFORMATION: Please revise "**METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS, USP**" to read "**METHYLPHENIDATE HYDROCHLORIDE EXTENDED-RELEASE TABLETS**" in the first sentence. [Delete "**USP**"].
   b. HIGHLIGHTS, Title: Please revise the title to read "**METHYLPHENIDATE HYDROCHLORIDE extended-release tablets, for oral use, CII**".
   c. HIGHLIGHTS, DOSAGE FORMS AND STRENGTHS: Please revise to read "Tablets: 18 mg, 27 mg, 36 mg, and 54 mg (3)".
   d. CONTENTS*: Please revise the subsection title to read: "**13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility**".
   e. FULL PRESCRIBING INFORMATION
      i. DESCRIPTION, 3rd paragraph, inert ingredients: Please include "ammonium hydroxide".
      ii. See comment 2(d) above.
      iii. HOW SUPPLIED: Please include the shape with the descriptions of the tablets.
      iv. HOW SUPPLIED, Storage and Handling: Please revise the storage statement to read "Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity."

3. MEDICATION GUIDE
   Inactive Ingredients: Please include "ammonium hydroxide".

4. STRUCTURED PRODUCT LABELING (SPL) Data Elements
   Inactive Ingredients: Please include "AMMONIUM HYDROXIDE".

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with the reference listed drug labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –

http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

1.2 COMMENTS FOR LETTER TO APPLICANT WHEN LABELING IS ACCEPTABLE

The Division of Labeling has no further questions/comments at this time based on your labeling submission(s) dated (add date).

1.3 POST APPROVAL REVISIONS

These comments will NOT be sent to the applicants at this time.
These comments will be addressed post approval (in the first labeling supplement review).
NA

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Has the ANDA been accepted for filing? YES
Are there any pending issues in DLR's SharePoint Drug Facts? NO
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? YES TSI: issue Affecting multiple drug products. Revised BE guidance, which posted November 5, 2015; downgrade occurred. Mallinckrodt sued FDA.

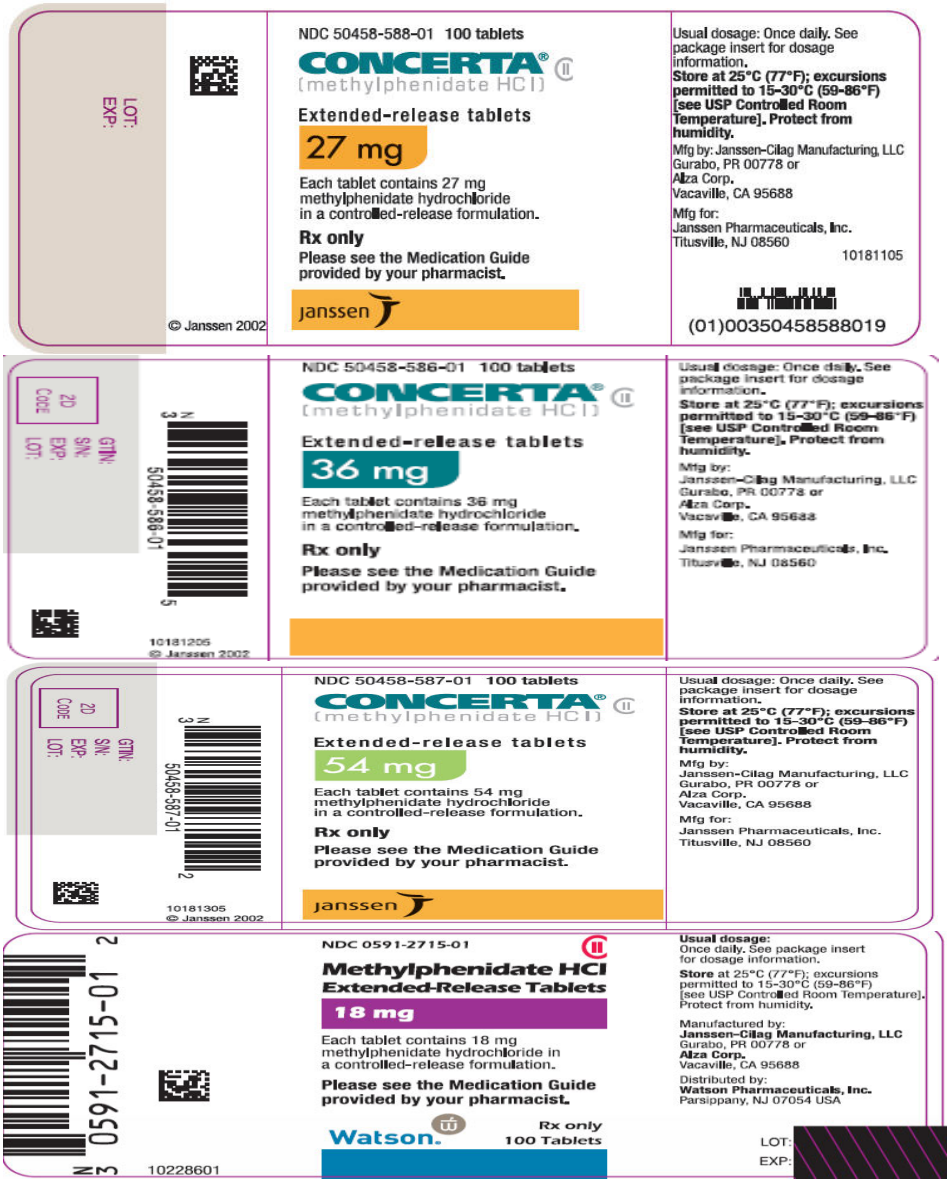
2.2 MODEL LABELING

2.2.1 MODEL PRESCRIBING INFORMATION

Table 1: Review Model Labeling for Prescribing Information and Patient Labeling (Check the box used as the Model Labeling)
☒ **MOST RECENTLY APPROVED NDA MODEL LABELING** *(If NDA is listed in the discontinued section of the Orange Book, also enter ANDA RLD information.)* **NDA#/Supplement# (S-000 if original):** NDA 021121/S-035 **Supplement Approval Date:** April 17, 2015 **Proprietary Name:** CONCERTA® **Established Name:** Methylphenidate HCl Extended-Release Tablets **Description of Supplement:** new safety information that we believe should be included in the labeling for Concerta (methylphenidate HCl). This information pertains to the association between the use of stimulants used to treat Attention Deficit Hyperactivity Disorder (ADHD) and rhabdomyolysis.
☐ **MOST RECENTLY APPROVED ANDA RLD LABELING** **ANDA#/Supplement# (S-000 if original):** Click here to enter text. **Supplement Approval Date:** Click here to enter text. **Proprietary Name:** Click here to enter text. **Established Name:** Click here to enter text. **Description of Supplement:** Click here to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):** NDA 021121/ (b) (4) S-037 is pending CMC supplement with no labeling associated with it.

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: ANRPT-16 dated 09/28/2015 and DAILYMED**)**



2.3 UNITED STATES PHARMACOPEIA (USP) & PHARMACOPEIA FORUM (PF)

We searched the USP and PF to determine if the drug product under review is the subject of a USP monograph or proposed USP monograph.

Table 2: USP and PF Search Results

	Date Searched	Monograph? YES or NO	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statement (NA if no monograph)
USP	8/16/2016	YES	Methylphenidate Hydrochloride Extended-Release Tablets	Packaging and Storage: Preserve in tight containers. Labeling: The labeling states the Dissolution Test with which the product complies if other than Test 1.
PF	8/16/2016	YES	Same as above.	Packaging and Storage: Preserve in tight containers. Store at controlled room temperature. •(IRA 1-Mar-2016) Labeling: The labeling states the Dissolution test with which the product complies if other than Test 1.

From Labeling QbR: Methylphenidate Hydrochloride Extended-Release Tablets, USP utilizes Dissolution Test 4. The insert labeling includes the statement [redacted] (b) (4) in the last paragraph of the DESCRIPTION section.

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 8/16/2016.

Table 3 provides Orange Book patents for the Model Labeling (NDA 021121) and ANDA patent certifications. (For applications that have no patents, N/A is entered in the patent number column.)

Table 3: Impact of Model Labeling Patents on ANDA Labeling

Patent Number	Patent Expiration	Patent Use Code	Patent Use Code Definition	Patent Certification	Date of Patent Cert Submission	Labeling Impact (enter Carve-out or None)
6919373*PED	Jan 31, 2018	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
6930129*PED	Jan 31, 2018	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
8163798*PED	Jan 31, 2018			P IV	05/28/2016	None
8629179*PED	Jan 31, 2018			P IV	05/28/2016	None
9000038*PED	Jan 31, 2018	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
9000038*PED	Jan 31, 2018	U-1693	METHOD OF TREATING ADHD IN CHILDREN 6 YEARS OF AGE AND OLDER AND ADOLESCENTS	P IV	05/28/2016	None
9029416	Jul 31, 2017	U-666	METHOD OF TREATING ADHD	P IV	05/28/2016	None
9144549	Jul 31, 2017	U-1747	FOR CLAIMS 1-3,6-13,16-24 AND 26-32: METHOD OF TREATING ADHD	P IV	05/28/2016	None
9144549	Jul 31, 2017	U-1748	FOR CLAIMS 1-4,6-14,16-24 AND 26-32: METHOD OF TREATING ADHD IN CHILDREN 6 YEARS OF AGE AND OLDER AND ADOLESCENTS	P IV	05/28/2016	None

From Cover Letter received August 11, 2016: CorePharma, LLC wishes to notify the FDA that the patent owner and NDA holder of NDA 021121 did not initiate an action for Patent Infringement against CorePharma within the statutory 45-day period.

Table 4 provides Orange Book exclusivities for the Model Labeling and ANDA exclusivity statements.

Table 4: Impact of Model Labeling Exclusivities on ANDA Labels and Labeling

Exclusivity Code	Exclusivity Expiration	Exclusivity Code Definition	Exclusivity Statement	Date of Exclusivity Submission	Labeling Impact (enter Carve-out or None)
N/A		There is no unexpired exclusivity for this product in the Orange Book database.			

2.5 MANUFACTURING FACILITY

Table 5 provides a description of the drug product manufacturing facility.

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements		
Name and Address of ANDA Manufacturer/Distributor/Packer (From 3.2.P.3.1)	**Name and Address on ANDA Container/Carton**	**Name and Address on ANDA Prescribing Information**
(b) (4)	Dist. by: Impax Generics Hayward, CA 94544 Product of USA	Distributed by: Impax Generics Hayward, CA 94544

3. ASSESSMENT OF ANDA LABELING AND LABELS

The results for each material reviewed in this section provide the basis for the labeling comments to the applicant.

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT and go to 3.3 CONTAINER/CLOSURE)

3.1 RX (PRESCRIPTION) DRUG PRODUCT

3.1.1 RX: PRESCRIBING INFORMATION

Reviewer Assessment:

Is the Prescribing Information same as the model labeling, except for differences allowed under 21 CFR 314.94(a)(8)? **YES**
Are the specific requirements for format met under 21 CFR 201.57(new) or 201.80(old)? **YES**
Is the established name for this ANDA acceptable? **YES**
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
Are the required USP recommendations reflected in the labeling? **YES**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the Manufacturer statement acceptable? **YES**

Reviewer Comments: We will ask firm to revise to read "Tablets: 18 mg, 27 mg, 36 mg, and 54 mg (3)" in HIGHLIGHTS, DOSAGE FORMS AND STRENGTHS section. We will also ask firm to revise the subsection title to read: "13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility", include "ammonium hydroxide" with the inactive ingredients, include the shape with the descriptions of the tablets and revise the storage statement to read "Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity." in HOW SUPPLIED section.

3.1.1.1 RX: DESCRIPTION

We reviewed the DESCRIPTION section for accuracy (with input from the chemistry review, if appropriate) and acceptability from Labeling perspective. We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Labeling Inactive Ingredients**

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
butylated hydroxytoluene, carnauba wax, cellulose acetate, hypromellose, lactose, phosphoric acid, poloxamer, polyethylene glycol, polyethylene oxides, povidone, propylene glycol, sodium chloride, stearic acid, succinic acid, synthetic iron oxides, titanium dioxide, and triacetin.	cetyl alcohol, ethylcellulose, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, n-butyl alcohol, polyethylene glycol, povidone, propylene glycol, shellac, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. The 18 mg tablet also contains the following additional inert ingredient: yellow iron oxide; and the 54 mg tablet also contains the following additional inert ingredients: red iron oxide and yellow iron oxide. (b) (4)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling Memorandum of Understanding (MOU)?
YES, chemistry review pending
(Note: The MOU became effective on November 1, 2014. MOU does not apply to amendment reviews for ANDAs originally reviewed before November 1, 2014.)

If the chemistry review follows the MOU, labeling reviewer is not responsible for reviewing for accuracy of the DESCRIPTION section for chemical properties, system components of the drug product, etc. Please refer to the MOU, Appendix A, DESCRIPTION section for delineation of responsibilities. If chemistry review does NOT follow the MOU, labeling reviewer will follow the traditional review approach of reviewing the entire DESCRIPTION section.)

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? (If Chemistry follows the MOU, refer to the Labeling section of Chemistry review.) **NO**
For products required to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments: We will ask firm to include Ammonium Hydroxide with the inactive ingredients.
From 3.2.P.1
Methylphenidate Hydrochloride Extended- Release Tablets, USP contain the following excipients
• Lactose Monohydrate, NF (b) (4) • Hypromellose (b) (4)
• Magnesium Stearate, NF, (b) (4)
• Ethylcellulose (b) (4)
• Triethyl Citrate • Povidone , USP (b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)
(b) (4)

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 7 and will be referred to the appropriate review discipline for evaluation.

Table 7: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	CONCERTA□ (methylphenidate HCl) Extended-release Tablets are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow and imprinted with "alza 18". The 27 mg tablets are gray and imprinted with "alza 27". The 36 mg tablets are white and imprinted with "alza 36". The 54 mg tablets are brownish-red and imprinted with "alza 54". All four dosage strengths are supplied in bottles containing 100 tablets. 18 mg 100-count bottle NDC 50458-585-01 27 mg 100-count bottle NDC 50458-588-01 36 mg 100-count bottle NDC 50458-586-01 54 mg 100-count bottle NDC 50458-587-01 Storage and Handling Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity.
ANDA Labeling	Methylphenidate hydrochloride extended-release tablets, USP are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow printed with CP 342 on one side and blank on the other side. The 27 mg tablets are gray printed with CP 340 on one side and blank on the other side. The 36 mg tablets are white printed with CP 339 on one side and blank on the other side. The 54 mg tablets are brownish-red printed with CP 341 on one side and blank on the other side. All four dosage strengths are supplied in bottles containing 100 tablets. 18 mg 100-count bottle NDC 0115-1566-01 27 mg 100-count bottle NDC 0115-1567-01 36 mg 100-count bottle NDC 0115-1568-01 54 mg 100-count bottle NDC 0115-1569-01 Storage and Handling Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from humidity.

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **YES, chemistry review pending**
If the chemistry review does NOT follow the MOU, is the description (scoring, color and imprint) of the finished product in the HOW SUPPLIED section consistent with the information in Module 3.2.P.5.1 for Drug Product Specification? **YES**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NO**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **YES**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage or dispensing statement acceptable as compared to the Model Labeling? **YES**
Is the storage or dispensing statement acceptable as compared to the USP? **YES**

Reviewer Comments: Table 3.2.P.1-1 Drug Product Appearance

Dosage Strength	Description
18 mg	Yellow tablet printed with "CP 342" on one side and blank on the other side
27 mg	Gray tablet printed with "CP 340" on one side and blank on the other side
36 mg	White tablet printed with "CP 339" on one side and blank on the other side
54 mg	Brownish-red tablet printed with "CP 341" on one side and blank on the other side

3.1.2 RX: MEDICATION GUIDE

Is Medication Guide required? **YES**
If YES go to Reviewer Assessment below, if NO go to section 3.1.3.

Reviewer Assessment:

Was Medication Guide submitted? **YES**
Is the Medication Guide same as the model labeling, except for allowable differences? **YES**
Does the Medication Guide meet the requirements of 21 CFR 208.20? **YES**
Has the Applicant committed to provide a sufficient number of medication guides? **YES**
Is the phonetic spelling of the proprietary or established name present? **YES**

Is FDA 1-800-FDA-1088 phone number included? **YES**

Reviewer Comments: We will ask firm to include "ammonium hydroxide" with the inactive ingredients.
From Labeling QbR:
In accordance with 21 CFR §208.24, CorePharma will ensure that the appropriate number of Medication Guides are available for distribution to the patients. For this reason, the inclusion of four Medication Guides 100 count bottle will be provided (one accompanying the package outsert and additional medication guide pads will be provided to ensure at least 3 additional medication guides per 100 count bottle). The font size for the Medication Guide is 10 point font size.

3.1.3 RX: OTHER PATIENT LABELING

Are other patient labeling required? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.

Reviewer Assessment:

Was other patient labeling submitted? **NA**
Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:

3.1.4 RX: CONTAINER LABEL

Was container label (other than Blisters) submitted? **YES**
(For BLISTER labels go to section 3.1.5.)

We evaluated the container labels for the inclusion of all required statements and safety considerations.

Reviewer Assessment:

Is the established name acceptable? **YES**
Is title case used in expressing the established name? **YES**
Does labeling comply with Tall Man lettering recommendations found on FDA webpage? **NA**
Is container label too small to contain all required information? **NO** If yes, does the container meet the "too small" exemption found in 21 CFR 201.10(i)? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **YES**
Is the following information properly displayed?

- Net quantity statement: **YES**
- Route(s) of administration (other than oral): **NA**
- Warnings (if any) or cautionary statements (if any): **NA**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d)**:** **YES**
- Controlled substance symbol: **YES**
- Usual Dosage statement: **YES**
- Product strength equivalency statement: **NA**
- NDC: **YES**
- Bar code per 21 CFR 201.25(c)(2): **YES**

Is the Manufacturer/Distributor/Packager statement acceptable? **YES**
For foreign manufacturers, does the labeling have the country of origin? **NA**
Are the required USP recommendations reflected on the label(s)? **YES**
Is the storage or dispensing statement consistent with the How Supplied section of the insert? **YES**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **YES**
Are the labels of related products differentiated to avoid selection errors? **YES**
Does the ANDA require the same color coding as the Model Labeling? **NO**
Are the requirements of 21 CFR 201.15 met for all required label statements? **YES**
Are the requirements of 21 CFR 201.100 met for all required label statements? **YES**

Reviewer Comments: We will ask firm to increase the prominence of the expression of strength statement, revise the storage statement to read "Store at 25°C (77°F); excursions permitted between 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. Protect from humidity." and ensure to include a place holder for the lot number and the expiration date.

From QbR: Is there adequate differentiation between your proposed product and your approved products?

Product	1st Strength	2nd Strength	3rd Strength	4th Strength	5th Strength	6th Strength
Methylphenidate Hydrochloride Tablets, USP ANDA 091159 (Approved)	5 mg - (b) (4)	10 mg - (b) (4)	20 mg - (b) (4)	N/A	N/A	N/A
Methylphenidate Hydrochloride Extended-release Capsules ANDA 205105 (Pending)	10 mg - (b) (4)	20 mg - (b) (4)	30 mg-	40 mg-	50 mg –	60 mg - (b) (4)
Methylphenidate Hydrochloride Extended-Release Tablets ANDA 208607	18 mg -	27 mg –	36 mg –	54 mg - (b) (4)	N/A	N/A

3.1.4.1 RX: CONTAINER LABEL FOR PARENTERAL SOLUTIONS

Is container for parenteral solution? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.2.

Reviewer Assessment:

Is the product strength expressed as total quantity per total volume followed by the concentration per milliliter (mL), as described in the USP, General Chapter <1> Injection? **NA**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:

3.1.4.2 RX: CONTAINER LABEL FOR SOLID INJECTABLE

Is container for solid injectable (other than Pharmacy Bulk Package)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.4.3.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:

3.1.4.3 RX: CONTAINER LABEL FOR PHARMACY BULK PACKAGE

Is container a Pharmacy Bulk Package (parenteral preparations for admixtures)? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.5.

Reviewer Assessment:

Is the strength in terms of the total amount of drug per vial? **NA**
Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **NA**
Does the container label include graduation marks? **NA**
Are instructions for reconstitution and resultant concentration provided, if space permits? **NA**
Does label contain the required information on proper aseptic technique including time frame in which the container may be used once it has been entered? **NA**

Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **NA**

Reviewer Comments:

3.1.5 RX: UNIT DOSE BLISTER LABEL

Is container a Unit Dose Blister Pack? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.1.6.

Reviewer Assessment:

Does each blister include only one dosage unit (e.g., one tablet, one capsule)? **NA**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **NA**

Reviewer Comments:

3.1.6 RX: CARTON (OUTER OR SECONDARY PACKAGING) LABELING

Was carton labeling submitted? **NO**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Are the answers to the Container Label questions the same for the Carton Labeling? **NA** If no, please explain the differences in the Reviewer Comments section.
If container is too small or otherwise unable to accommodate a label with enough space to include all required information, is all required information present on the carton labeling? **NA**
If country of origin is not on Container, does it appear on outer packaging labeling? **NA**

Reviewer Comments:

3.2 OTC (OVER THE COUNTER) DRUG PRODUCT

3.2.1 OTC: LABELING THAT INCLUDES DRUGS FACTS INFORMATION

Reviewer Assessment:

Is Drug Facts Labeling format acceptable per 21 CFR 201.66? **NA**
Does "Questions?" have a toll-free number no less than 6 pt. font size per 21 CFR 201.66(c)(9) or "1-800-FDA-1088" per 21 CFR 201.66 (c)(5)(vii)? **NA**
Did firm submit a Labeling Format Information Table to evaluate the font size? **NA**
Is the applicant's "patent carve out" acceptable? **NA**
Is the applicant's "exclusivity carve out" acceptable? **NA**
Is the established name for this ANDA acceptable? **NA**
Is title case used in expressing the established name? **NA**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **NA**
Is the following information properly displayed?

- Pharmacological category: **NA**
- Net quantity statement: **NA**
- Route(s) of administration (other than oral): **NA**
- Warnings (if any) or cautionary statements (if any): **NA**
- NDC: **NA**
- Bar code per 21 CFR 201.25(c)(2): **NA**

Is the Manufacturer/Distributor/Packager statement acceptable? **NA**
For foreign manufacturers, does the labeling have the country of origin? **NA**

Are the required USP recommendations reflected in the labeling? **NA**
Is the storage statement acceptable? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
Are multiple strengths differentiated by use of different color or other acceptable means? **NA**
Are the labels of related products differentiated to avoid selection errors? **NA**

Reviewer Comments:

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

We compared the list of inactive ingredients contained in this product to those contained in the Model Labeling.

Table 8: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Inactive Ingredients**
Click here to enter text.	Click here to enter text.

Reviewer Assessment:

Are the inactive ingredients information consistent with "Components and Composition" information as provided in Module 3.2.P.1? **NA**
Are the inactive ingredients listed in alphabetical order? **NO**
For products required/recommended to be qualitatively and quantitatively the same in regards to active and inactive ingredients (Q1/Q2), are the ANDA ingredients consistent with the Model Labeling? **NA**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **NA**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **NA** Has the statement been verified by chemistry? **NA**

Reviewer Comments:

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

We compared the descriptions of the model product to the ANDA finished product. Product differences, such as scoring configuration and storage conditions, are highlighted in Table 9 and will be referred to the appropriate review discipline for evaluation.

Table 9: Comparison of Model Labeling to ANDA finished product	
Model Labeling	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.
ANDA	**Description of Finished Product** (Source: Click here to enter text.) Click here to enter text. **Package Configurations** (Source: Click here to enter text.) Click here to enter text. **Storage Conditions** (Source: Click here to enter text.) Click here to enter text.

Reviewer Assessment:

Is the description (scoring, color and imprint) of the finished product consistent with the Drug Product Quality submission? **NA**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **NA**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **NA**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **NA**
Is the storage statement acceptable as compared to the Model Labeling? **NA**
Is the storage statement acceptable as compared to USP? **NA**

Reviewer Comments:

3.2.2 OTC: PATIENT LABELING

Is patient labeling required? **NA**
If YES go to Reviewer Assessment below, if NO go to section 3.3.

Reviewer Assessment:

Was patient labeling submitted? **NA**
Is the patient labeling the same as the model labeling, except for allowable differences? **NA**

Reviewer Comments:

3.3 CONTAINER/CLOSURE

We evaluated the container/closure system of this product to determine if special child-resistant packaging is required based on packaging configuration. Additionally, we evaluated other aspects of the container closure that relate to the dosage form, product formulation, and product class. Below is a description of the container/closure for the ANDA product.

Reviewer Assessment:

Describe container closure (e.g., 30s CRC, 100s non-CRC) and cite source of information in **Reviewer Comments** text box.
Does the container require a child-resistant closure (CRC) as described in the Poison Prevention Act and regulations? **YES**
Are the tamper evident requirements met for OTC and Controlled Substances? (If quality review follows the chemistry-labeling MOU, obtain answer from Appendix D of chemistry review; if quality review does not follow the MOU, labeling reviewer is responsible for assessing for tamper evidence) **YES**

For ophthalmic products:

Does this ophthalmic product cap color match the American Academy of Ophthalmology (AAO) packaging color-coding scheme? **NA**

For parenteral products:

Is there text on the cap/ferrule overseal of this injectable product? **NA**
If YES, does text comply with the recommendations in USP General Chapter <1>? **NA**
What is the cap color? NA

NOTE: Black closure system is prohibited, except for Potassium Chloride for Injection Concentrate.

Reviewer Comments: From 3.2.P.7.1: 100s CRC. The container system includes a tamper-evident heat seal. The sealing of the finished drug product meets the requirements in 21 CFR 1302.06 "Sealing of controlled substances." The container label has this statement "Do not use if printed safety seal under cap is broken or missing."

3.4 CALCULATIONS FOR CONTENTS IN LABELING

Is calculation of ingredient(s) required? **NO**
If YES, go to Table 10 and Reviewer Assessment below, if NO go to section 3.5.

We verified the calculation on the following content.

Table 10: Ingredients		
Ingredient	**Stated Content**	**Location of the Information**
Click here to enter text.	Click here to enter text.	Click here to enter text.

(Note: For Rx products, if chemistry review follows the MOU, chemistry reviewer will verify the accuracy of the active and inactive ingredient amount(s) if information is in the DESCRIPTION and HOW SUPPLIED sections for all products, and additionally, DOSAGE AND ADMINISTRATION section for parenteral products. See Chemistry-Labeling MOU, Appendix A, Miscellaneous section for discussion on calculations.)

Reviewer Assessment:

Does the chemistry review follow the Chemistry/Labeling MOU? **YES, chemistry review pending**
Are the stated contents in the table above acceptable? **NA**
Aluminum content in small volume parenterals, large volume parenterals, and pharmacy bulk packages, which are used in TPNs, need to be in the labeling per 21 CFR 201.323.
Did the chemistry reviewer verify the aluminum content? **NA**
Are the labeling requirements met per 21 CFR 201.323? **NA**

Reviewer Comments:

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

We evaluated the SPL data elements to ensure they are consistent with the information submitted in the ANDA.

Table 11: ANDA Tablet/Capsule Size and Imprint				
Tablet/Capsule Strength	**ANDA Tablet/Capsule Size (mm) and imprint code from SPL**		**ANDA Tablet/Capsule Size (mm) and imprint code (From 3.2.P.1)**	
	Size (mm)	**Imprint Code**	**Size (mm)**	**Imprint Code**
18 mg	14mm	CP;342	14.2 mm	CP342
27 mg	14mm	CP;340	14.25 mm	CP 340
36 mg	15mm	CP;339	14.78 mm	CP 339
54 mg	15mm	CP;341	14.78 mm	CP 341

Reviewer Assessment:

For solid oral dosage forms: Do size and imprint code from the SPL data elements match the information provided in the quality submission? **YES**
Are all the other data elements (strength, inactive ingredients, product characteristics, packaging etc.) consistent with the information submitted in the ANDA labeling? **NO**

Reviewer Comments: We will ask firm to include "ammonium hydroxide" with the Inactive Ingredients.

4. COMMENTS FOR CHEMISTRY REVIEWER

Describe issue(s) sent to and/or received from the chemistry (also known as drug product quality) reviewer:

Reviewer Comments: Question for Drug Product quality reviewer: Is section 11.1 System Components and Performance acceptable?

5. COMMENTS FOR OTHER REVIEW DISCIPLINES

Describe questions/issue(s) sent to and/or received from other review discipline reviewer(s):

Reviewer Comments: From Labeling QbR: Methylphenidate Hydrochloride Extended-Release Tablets, USP utilizes [redacted] (b) (4) The insert labeling includes the statement [redacted] (b) (4) in the last

paragraph of the DESCRIPTION section.

6. SPECIAL CONSIDERATIONS

NA

7. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Tables 12 and 13 provide a summary of recommendations for each labeling piece analyzed in this review.

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container (18 mg, 27 mg, 36 mg and 54 mg)	**Draft**	(bottles of 100s)	05/31/2016	Revise
Table 13 Review Summary of Prescribing Information and Patient Labeling				
	Final or Draft or NA	**Revision Date and/or Code**	**Submission Received Date**	**Recommendation**
Prescribing Information	**Final**	January, 2016	05/31/2016	Revise
Medication Guide	**Final**	January, 2016	05/31/2016	Revise
SPL Data Elements		1/2016	04/18/2016	Revise

Adolph Vezza

Digitally signed by Adolph Vezza
Date: 11/21/2016 03:15:46PM
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Lily Chua

Digitally signed by Lily Chua
Date: 8/19/2016 06:43:21AM
GUID: 5277fc6700089cebb6783d59b3e106fa

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208607Orig1s000

CHEMISTRY REVIEW(S)

Recommendation: Approvable

A/NDA 208607
Review 1

Drug Name/Dosage Form	Methylphenidate Hydrochloride Extended-Release Tablets, USP
Strength	18 mg, 27 mg, 36 mg and 54 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Impax Laboratories, Inc. (ownership changed from Corepharma)
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission (SD# 1)	04/18/2016	*Quality*
Quality Response to Information Request (SD# 2)	05/31/2016	*Quality*
Quality Response to Information Request (SD# 10)	3/17/2017	*Quality*
Quality Response to Information Request (SD# 11)	3/20/2017	*Quality*
Quality Response to Information Request (SD# 12)	5/17/2017	*Quality*

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Jian Yang OPQ/ONDP/DLCAPI/LCBI	Ronald Michalak OPQ/ONDP/DLCAPI/LCBIII
Drug Product	Murali Divi OPQ/OLDP/DMRP/MRBII	Yue Teng Ragine Maheswaran OPQ/OLDP/DMRP/MRBII
Process	Iwona Weidlich OPQ/OPF/DPAI/PABIII	Arwa El Hagrasy OPQ/OPF/DPAI/PABIII
Facility	Viviana Matta OPQ/OPF/DIA/IABI	Zhihao Peter Qiu OPQ/OPF/DIA/IABI
Biopharmaceutics	Poonam Delvadia OPQ/ONDP/DB/BBIII	Sandra Suarez OPQ/ONDP/DB/BBIII
Regulatory Business Process Manager	Camille Smith OPQ/OPRO/DRBPMI/RBPMII	
Application Technical Lead	Ragine Maheswaran OPQ/OLDP/DMRP/MRBII	
Laboratory (OTR)	N/A	N/A
ORA Lead	N/A	N/A
Environmental	N/A	N/A

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II		(b) (4)	Adequate	Jian Yang	Adequate on 3/20/2017
	Type II					
	Type III *(if applicable)*	See Submission Section 1.4.2 for all the type III DMF information				
	Type IV *(if applicable)*					
	Other					

B. Other Documents: *IND, RLD, or sister applications* N/A

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	NDA 021121	**CONCERTA®**

2. CONSULTS N/A

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other (DBE consult to ORS)	Adequate		11/20/ 2016	L. Zhao

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

From CMC review standpoint, 208607 is recommended for approval.

II. Summary of Quality Assessments

A. Product Overview

The drug product is a generic version of RLD NDA #21121, Concerta® (RLD) manufactured by Janssen Pharmaceuticals.
Drug Product Description:
18 mg: Yellow, modified capsule shape tablet printed with "CP 342" on one side and blank on the other side
27 mg: Gray, modified capsule shape tablet printed with "CP 340" on one side and blank on the other side
36 mg: White, modified capsule shape tablet printed with "CP 339" on one side and blank on the other side
54 mg: Brownish-red, modified capsule shape tablet printed with "CP 341 " on one side and blank on the other side

0	⇦ **Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	Treatment of Attention Deficit Hyperactivity Disorder
Duration of Treatment	• For children and adolescents new to methylphenidate, the recommended starting dosage is 18 mg once daily. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 54 mg/day in children and 72 mg/day in adolescents. • For adult patients new to methylphenidate, the recommended starting dose is 18 or 36 mg/day. Dosage may be increased by 18 mg/day at weekly intervals and should not exceed 72 mg/day for adults. (Should be taken once daily in the morning and swallowed whole with the aid of liquids; Should not be chewed or crushed; May be taken with or without food.)

Maximum Daily Dose	72 mg
Alternative Methods of Administration	*N/A*

B. Quality Assessment Overview

Drug Substance: The drug substance, Methylphenidate is compendial. It is a white to off white crystalline powder and is freely soluble in water and methanol and slightly soluble in acetone. Methylphenidate Hydrochloride drug substance is classified as BCS class I drug according to the Biopharmaceutics Classification System (BCS). Methylphenidate Hydrochloride is a racemic mixture of the d and l threo-isomers. It is not hygroscopic and does not exhibit polymorphism.

Drug Product: The drug product, Methylphenidate hydrochloride extended-release tablet is compendial and is available in 18, 27, 36, or 54 mg strengths designed to have 12-hour duration of effect. Methylphenidate HCl extended-release tablets, USP also contains the following inert ingredients: cetyl alcohol, ethylcellulose, ferrosoferric oxide, hypromellose, lactose monohydrate, magnesium stearate, n-butyl alcohol, polyethylene glycol, povidone, propylene glycol, shellac, sodium lauryl sulfate, titanium dioxide, and triethyl citrate. The 18 mg tablet also contains the following additional inert ingredient: yellow iron oxide; and the 54 mg tablet also contains the following additional inert ingredients: red iron oxide and yellow iron oxide.

(b) (4)

The applicant submitted 18 month CRT stability data and 6 month accelerated data. Based on the data 24 month expiration period is granted.

(b) (4)

(b) (4)

Facility: All facilities associated with the manufacturing, testing and packaging of Methylphenidate Hydrochloride Extended-Release Tablets, USP under pending ANDA-208607-ORIG-1 are recommended for approval.

Biopharmaceutics:
The final dissolution method and acceptance criteria for Methylphenidate HCl Extended Release Tablets, are as follows:

Time Points (hr)	Implemented by the Applicant in Response to IR#1*
0.5	10% - 30%
2	28% - 48%
6	70% - 90%
10	NLT 85%

The Dissolution testing was conducted using USP Test Method 4.
The Bioequivalence review is adequate and biowaiver is granted for lower strengths. The applicant provided the comparative dissolution data of the test and reference products in three additional pH media (pH 1.2, 4.5 and 6.8 buffers). The firm's dissolution data showed no evidence of dose dumping.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

Product property / Impact of Change / CQAs	**Initial Risk Ranking** *(FMECA RPN)*	*Reviewer's Comments*	*Updated Risk Ranking after Review Cycle #1b*	**Reviewer's comments**
Physical stability (solid state)	12 Low	✓ No polymorphic form exists based on prior knowledge (O-2). ✓ Freely soluble API (b) (4)	Low	Same as before
Chemical Stability	12		Low	Same as before

		(b) (4)		(b) (4)
Assay	27 Medium		Low	
Content uniformity	48 Medium		Low	
Microbial limits	9 Low		Low	
Dose dumping from mechanical failure	20 Low		Low	
Dissolution	96 High	✓ Functionally coated ER tablets ✓ Different release mechanism than RLD (O+1). ✓ Biphasic release mechanism (O+1). (b) (4) ✓ Tablet not scored	Low	✓ Adequate controls are in place for extended release coating. ✓ The firm provided adequate justification along with a statistical analysis report based on available ANDA exhibit batch data to demonstrate that the product meets proposed specifications throughout the shelf life.

Yue Teng

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Ragine Maheswaran

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Date: 6/29/2017 01:03:01PM
GUID: 508da703000288694c718e4706287c61

Recommendation:
Drug Substance: Adequate
Drug Product: Adequate

ANDA 208607
Review 1c

Drug Name/Dosage Form	Methylphenidate Hydrochloride Extended-Release Tablets, USP
Strength	18 mg, 27 mg, 36 mg and 54 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Impax Laboratories, Inc.
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original submission (SD# 1)	04/18/2016	*Quality*
Quality Response to Information Request (SD# 2)	05/31/2016	*Quality*
Quality Response to Information Request (SD# 10)	3/17/2017	*Quality*
Quality Response to Information Request (SD# 11)	3/20/2017	*Quality*
Quality Response to Information Request (SD# 12)	5/17/2017	*Quality*
Quality Response to Information Request (SD# 13)	6/12/2017	*Quality*

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Murali Divi	Branch II/ DMRP
Drug Product	Murali Divi	Branch II/ DMRP
Process		
Microbiology		
Facility		
Biopharmaceutics		
Regulatory Business		

Process Manager		
Application Technical Lead	Ragine Maheswaran	Branch II/ DMRP
Laboratory (OTR)		
ORA Lead		
Environmental Analysis (EA)		

Quality Review Data Sheet

a) RELATED/SUPPORTING DOCUMENTS

1. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	II	(b) (4)	Methylphenidate Hydrochloride, USP	Adequate	Jian Yang	Adequate on 3/20/2017

2. Other Documents: *IND, RLD, or sister applications*

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	NDA 021121	CONCERTA®

b) CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other (DBE consult to ORS)	Adequate		11/20/ 2016	L. Zhao

CHAPTERS: Primary Quality Assessment

APPEARS THIS WAY ON ORIGINAL

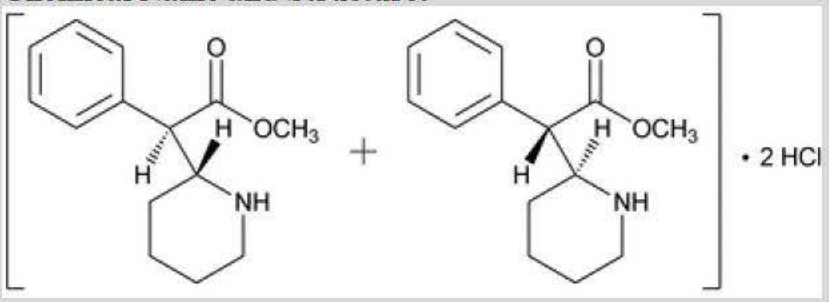
CHAPTER I: Drug Substance

DRUG SUBSTANCE

Product Background:

ANDA#: 208607

Chemical Name and Structure:



Compendial Name : Methylphenidate Hydrochloride, USP
Chemical Name (s) : 2-Piperidineacetic acid, α-phenyl-, methyl ester, hydrochloride, (*R**,*R**)-(±)-
Methyl α-phenyl-2-piperidineacetate hydrochloride;
(*RS*)-Methyl-2-phenyl-2-[(*RS*)-piperidin-2-yl] acetate, hydrochloride[1]

DMF # (if applicable): (b) (4)

Applicant Name/DMF Holder: (b) (4)

Review Summary:
The drug substance, Methylphenidate is compendial. It is a white to off white crystalline powder that is freely soluble in water and methanol and slightly soluble in acetone. Firm provided adequate information about the physicochemical properties of Methylphenidate Hydrochloride drug substance. Methylphenidate Hydrochloride drug substance classified as highly soluble based on dose solubility volume less than 250 mL. It has high permeability therefore Methylphenidate Hydrochloride is considered as BCS class I drug according to the Biopharmaceutics Classification System (BCS). Methylphenidate Hydrochloride is a racemic mixture of the d and l threo-isomers. Methylphenidate Hydrochloride is not hygroscopic. No reported polymorphic forms for Methylphenidate Hydrochloride.

List Submissions being reviewed (table):

Submission(s) Reviewed	Document Date
Original	4/18/2016

Quality Response to Information Request (SD# 2)	05/31/2016
Quality Response to Information Request (SD# 10)	3/17/2017
Quality Response to Information Request (SD# 11)	3/20/2017
Quality Response to Information Request (SD# 12)	5/17/2017
Quality Response to Information Request (SD# 13)	6/12/2017

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: DMF# (b) (4) for Methylphenidate is adequate.

S.1 General Information

Summary of the info provided. Information from Application

Chemical Abstract Service Registry (CAS) Number : 23655-65-4 [1]

Molecular Formula : $C_{14}H_{19}NO_2 \cdot HCl$[1]

Molecular Weight : 269.77 g/mol [1]

Pharmacological Class : Treatment of Attention Deficit Hyperactivity Disorder

Description : White to off-white fine crystalline powder

Solubility : Freely soluble in water and in methanol; soluble in alcohol; slightly soluble in chloroform and in acetone.

Solubility as a function of pH at room temperature 37°C±1°C :

Table 2.3.S.1-2: Summary of Solubility of the Drug Substance as a Function of pH

(b) (4)

Hygroscopicity : Methylphenidate hydrochloride does not show hygroscopic behavior.

Melting endotherm : NA

Partition coefficient (LogP) :

Table 2.3.S.1-3: Log P/Log D of methylphenidate hydrochloride

(b) (4)

Photostability : NA

Melting Range : The melting point of methylphenidate hydrochloride is 199.9 - 200.0°C, when tested with a 0.5°C/min gradient.

Specific Optical Rotation : NA

Reviewer's Assessment:
The information on drug substance general properties is satisfactory. The DMF (b) (4) is adequate.

S.2 Manufacture

Commercial Synthetic Scheme and Process Flow Diagram

Reviewer's Assessment:
Refer to DMF (b) (4)

Control of Materials

Reviewer's Assessment
Refer to DMF (b) (4)

Control of Critical Steps and Intermediates

Reviewer's Assessment:
Refer to DMF (b) (4)

Summary of Process Validation Studies Conducted

Reviewer's Assessment:
Refer to DMF (b) (4)

Summary of Manufacturing Process Development

Reviewer's Assessment: adequate after 1a.

LABELING

{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

Is the information accurate? X Yes ☐ No
If "No," explain.

Is the drug product subject of a USP monograph? X Yes ☐ No
Meets Dissolution Test 4.

Note: If there is a potential that USP statement needs to be added or modified in the Description, alert the labeling reviewer.

HOW SUPPLIED section

i) Is the information accurate? X Yes ☐ No

If "No," explain.

ii) Are the storage conditions acceptable? X Yes ☐ No

If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable:

Did the applicant provide quality data to support in-use conditions (e.g. diluent compatibility studies)? ☐ Yes ☐ No X N/A

If "No," explain.

For OTC Drugs and Controlled Substances:

Is tamper evident feature provided in the container/closure? ☐ Yes ☐ No

If "No," explain.

For solid oral drug products, only: drug product length(s) of commercial batch(es):

ANDA Strength	Length (mm)	Imprint Code
18 mg	14.2	Yellow tablet printed with "CP 342" on one side and blank on the other side.
27 mg	14.25	Gray tablet printed with "CP 340" on one side and blank on the other side.
36 mg	14.78	White tablet printed with "CP 339" on one side and blank on the other side
54 mg	14.78	Brownish-red tablet printed with "CP 341" on one side and blank on the other side

Describe issue(s) sent to and/or received from the OGD Labeling Reviewer:

Biopharm reviewer proposed more stringent specifications for this product based on the submitted dissolution data. Therefore, the labeling should cite "USP Dissolution test Pending".

List of Deficiencies:

N/A

Primary Drug Product Reviewer Name and Date: Murali Divi, 6/12/2017

Secondary Drug Product Reviewer Name and Date: Helen Teng, 6/15/2017

Murali Divi

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Yue Teng

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BIOPHARMACEUTICS

Product Background:

NDA/ANDA: A208607-ORIG-1

Drug Product Name / Strength: Methylphenidate Hydrochloride Extended Release (ER) Tablet [18mg, 27mg, 36mg, and 54mg]

Route of Administration: Oral

Applicant Name: Corepharma LLC.

In the present submission, the Applicant is seeking approval of Methylphenidate hydrochloride (HCl) ER oral tablets [18mg, 27mg, 36mg, and 54mg] for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65.[1] All four proposed strengths are modified capsule shaped tablets printed on one side and blank on the other side (Printed with CP 342, CP 340, CP 339, and CP 341 respectively for 18mg, 27mg, 36mg, and 54mg).[1,2] The 18mg, 27mg, 36mg, and 54mg tablets are yellow, gray, white and brownish-red colored tablets. The reference listed drug (RLD) for the proposed ANDA submission is CONCERTA® from Janssen Pharms approved under N021121 (18mg, 27mg, 36mg, and 54mg approved on Aug 1, 2000; April 1, 2002; Aug 1, 2000; and December 8, 2000 respectively) for the same indication. Concerta tablets should be taken once daily in the morning with or without food and swallowed whole with the aid of liquids (should not be chewed, divided, or crushed).[3] The recommended dosage of methylphenidate HCl depends on the patient's age.[3]

As of January 25, 2017, there is one approved generic of Concerta® available on the market and there are (b) (4) generic applications including this ANDA pending approval that references Concerta® as the RLD.[4,5] There are two generic methylphenidate extended release tablets submissions (A202608, A091695) referencing Concerta® that are rated with therapeutic equivalence (TE) code of BX.[5] The Applicant of this ANDA has provided paragraph IV patent certification and intends to market the drug product prior to the expiration of U.S. Patents related to the reference product Concerta®.[6] As of January 26, 2017, this ANDA at CDER Informatics Platform (Panorama) has been given a prioritization factor of "Drug Shortage".[7]

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[1] Global Submit – A208607 – 0004(5) dated 12/08/2016. **Module 1.14.2.3. Final Labeling Text PI – LB#903 – PDF**. (Accessed on January 25, 2017)

[2] Global Submit – A208607- 0001(2) dated 05/31/2016. **Module 3.2.P.1. Description and composition of the drug product.** (Accessed on January 25, 2017)

[3] **Prescribing Information – CONCERTA® – Methylphenidate HCl ER Tablets** (Accessed on January 25, 2017)

[4] **DAARTS.** Methylphenidate Hydrochloride (Accessed January 24, 2017).

[5] **Orange Book - Approved Drug Products with Therapeutic Equivalence Evaluations**: (Accessed on January 24, 2017).

[6] Global Submit – A208607- 0001(2) dated 05/31/2016. **Module 1.3.5.2. Patent Certification.** (Accessed on January 26, 2017)

The draft product-specific bioequivalence (BE) guidance on methylphenidate HCl ER tablets recommends fasted and fed *in vivo* BE studies (single-dose, two-treatment, four-period, two-sequence, fully replicated crossover) at the highest strength, 54mg, comparing it to the corresponding strength of the RLD. The lower strengths (18mg, 27mg, and 36mg) are eligible for waiver of *in vivo* testing provided recommendations are met.[8] The Applicant has submitted a biowaiver request for the lower strengths under 21 CFR 320.22(d)(2);[9] however, according to this reviewer, the waiver should be requested under 21 CFR 320.24(b)(6) since the proposed product is modified release (MR) dosage form and 21CFR 320.22(d)(2) is not applicable to this dosage form. The *in vivo* fasted and fed BE studies on the highest strength and biowaiver requests for the lower strengths of the proposed methylphenidate ER oral tablets are deemed adequate by the Office of Bioequivalence (OB), OGD based on the consult response from the Division of Quantitative Methods and Modeling (DQMM), Office of Research and Standards (ORS), OGD.[10,11]

The RLD, Concerta®, is an ER once-a-day formulation composed of both immediate release (IR) and extended release (ER) (b) (4) .[12] Concerta® is an osmotic pump that uses osmotic pressure to deliver methylphenidate HCl at a controlled rate. The system consists of tri-layered core surrounded by a semi-permeable membrane and an immediate release drug overcoat [Figure A1(a) of Attachment]. The tri-layer core contains two layers of drug substance and excipient and a push layer containing osmotically active excipients. In an aqueous environment, the IR drug overcoat dissolves within one hour and water then permeates slowly through semi-permeable membrane into the tablet core. The osmotically active excipients in the push layer expands as water is absorbed thus pushing methylphenidate HCl present in drug layers of the core and methylphenidate HCl is released from a laser drilled orifice present on the drug-layered end of the tablet. The drug release rate is controlled by the semi-permeable membrane that limits the rate of fluid permeating into the tablet core.

CorePharma's proposed generic drug product formulation consists (b) (4)

(b) (4)

[7] CDER Informatics Platform – ANDA-208607-ORIG-1 (Accessed on January 26, 2017)
[8] Product –Specific Recommendations for Generic Drug Development: Methylphenidate HCl ER Tablets (Accessed on January 26, 2017)
[9] Global Submit – A208607- 0001(2) dated 05/31/2016. Module 1.12.15. Request for Waiver. (Accessed on January 26, 2017)
[10] CDER Informatics Platform – ANDA-208607-ORIG-1, Bioequivalence Primary Review - A208607N000DB_N04182016.docx. (Accessed on January 26, 2017)
[11] CDER Informatics Platform – ANDA-208607-ORIG-1, Bioequivalence Primary Review – Addendum based on consult response from DQMM\ORS\OGD -A208607N000DB_CRR04182016.docx. (Accessed on January 26, 2017)
[12] Global Submit – A208607- 0001(2) dated 05/31/2016. Module 3.2.P.2. Pharmaceutical Development Report. (Accessed on January 26, 2017)
[13] Global Submit – A208607- 0001(2) dated 05/31/2016. Module 3.2.P.1. Description and Composition of the Drug Product. (Accessed on January 26, 2017)

(b) (4)

In addition to dissolution testing by the recommended method at the FDA's dissolution database (USP method), the product specific BE guidance also recommends dissolution testing in multiple buffer media of pH 1.2, 4.5, and 6.8 using USP I at 100 rpm and/or USP II at 50 rpm (agitation speeds may have to be increased if appropriate). The USP (USP 39 – NF 34) lists the dissolution methods presented in Table 1 for methylphenidate HCl ER tablets. The Applicant proposed USP test 4 dissolution method for the finished product batch release and stability testing. The Applicant initially developed and validated the in-house dissolution method (b) (4) (b) (4)) before the USP test 3 and test 4 became official in the monograph (effective December 01, 2015).[14] The Applicant conducted an equivalency test to compare the in house and the USP test 4 dissolution method.[15] The specification table states in-house method (b) (4) (b) (4)

Table 1. USP Dissolution Methods for Methylphenidate HCl ER Oral Tablets (USP 39-NF 34; As of January 26, 2017)

USP Dissolution Test	USP Apparatus	Agitation Speed	Dissolution Medium	Volume of Dissolution Medium	Sampling Time Points	Tolerances (% Dissolved)
Test 1	2	50 rpm	Water	500 mL	1 hr	25-45
					2 hr	40-65
					3.5 hr	55-80
					5 hr	70-90
					7 hr	NLT 80
Test 2	7	30 cycles/min	Acidified water (pH 3)[a]	50 mL	1 hr intervals for a duration of 10 hrs	1 hr = 12-32 4 hr = 40-60 10 = NLT 85 3-6 (avg) = 9-15 (1/hr)
Test 3	1	100 rpm	pH 6.8 phosphate buffer[b]	900 mL	0.75 hr	12-30
					4 hr	55-80
					10 hr	NLT 80
Test 4	2	50 rpm	0.001 N HCl	500 mL	1 hr	20-40
					2 hr	35-55
					6 hr	65-85

[14] Global Submit – A208607- 0001(2) dated 05/31/2016. **Module 3.2.P.2. Dissolution Development Report: RPT-15-12-IR-002-01R.** (Accessed on January 26, 2017)
[15] Global Submit – A208607- 0001(2) dated 05/31/2016. **Module 3.2.P.5.3. Method Verification/Equivalency Report - RPT-00148-01 Dissolution by HPLC.** (Accessed on January 26, 2017)
[16] Global Submit – A208607- 0001(2) dated 05/31/2016. **Module 3.2.P.5.1. Drug Product Specifications SPF-0003-rev-02.** (Accessed on January 26, 2017)
[17] Global Submit – A208607- 0001(2) dated 05/31/2016. **Module 3.2.P.5.2. Analytical Procedures – TMD-0007-version-01.** (Accessed on January 26, 2017)

					10 hr	NLT 80
[a] Adjusted with phosphoric acid to a pH 3						
[b] 6.8g/L of monobasic potassium phosphate in water; adjusted with 2N sodium hydroxide or 10% phosphoric acid to pH of 6.8						

Methylphenidate HCl is a racemic mixture of the d and l threo-isomers. (b) (4)

(b) (4)

(b) (4) The initial risk assessment performed by FDA indicated low risk with respect to physical stability, chemical stability, microbial limits, and dose dumping from mechanical failure; whereas, medium risk for assay and content uniformity (Table A1 of Attachment).[20] The risk ranking for dissolution is high due to the functionally coated ER tablets, different release mechanism than RLD, and biphasic release mechanism.

The Applicant submitted eighteen months long term (25°C ± 2°C with 60%RH ± 5%RH), twelve months intermediate (30°C ± 2°C/65%RH ± 5% RH); and six months accelerated (40°C ± 2°C with 75%RH ± 5%RH) stability data on three batches of 18mg and 54mg and four batches of 27mg and 36mg strengths in the proposed packaging (100 count bottle) and the long term stability study is ongoing.[21],[22] Based on the available stability results, the tentative expiration dating period proposed is 24 months at controlled room temperature in the proposed market containers. In response to the drug product reviewer's information request # 1 and 2 the Applicant provided updated stability data.[23],[22] The acceptance limits for the attributes of drug product batches in stability (container integrity, appearance, assay, water, impurities, dissolution, and microbial limits) are same as that used to confirm the quality of the finished drug product for batch release.[16],[21] Batch release specification includes additional tests (identification, uniformity of dosage units, and residual solvents) as well.[16] The below biopharmaceutics review focuses on the evaluation of the *in vitro* dissolution test and acceptance criteria proposed for quality control (QC) purpose for both batch release and stability testing, and risk ranking with respect to dissolution and responses to information request # 1, and 2.

Review Summary:

The biopharmaceutics assessment focused on the evaluation of the dissolution method, dissolution acceptance criteria, dissolution analytical method, and risk assessment on dissolution

[18] Global Submit – A208607- 0001(2) dated 05/31/2016. **Module 3.2.S.1.3. General Properties.** (Accessed on January 26, 2017)

[19] Global Submit – A208607 - 0001(2) dated 05/31/2016. **Module 3.2.S.4.1. Drug substance specification – Proposed Specification: LTR-8630-rev01.** (Accessed on January 26, 2017)

[20] CDER Informatics Platform - ANDA-208607-ORIG-1– **Risk Assessment - ANDA 208607 FMECA for Methylphenidate ER Tablets** (Accessed on January 26, 2017)

[21] Global Submit – A208607 - 0001(2) dated 05/31/2016. **Module 3.2.P.8.3. Stability Data.** (Accessed on January 26, 2017)

[22] Global Submit – A208607 - 0011(12) dated 05/17/2017. **Module 3.2.P.8.3. Stability Data.** (Accessed on May 25, 2017)

[23] CDER Informatics Platform - ANDA-208607-ORIG-1– **Drug Product Primary Review - A208607_R1_DPDSDL.docx** (Accessed on January 26, 2017)

as critical quality attribute (CQA). The proposed dissolution method (USP test 4, see below) (b) (4) (b) (4) dissolution sample analysis are adequate for batch release and stability, and in-process testing. The in-house dissolution method (b) (4) (b) (4) (b) (4) The proposed USP test 4 dissolution method therefore can be considered clinically relevant and hence is suitable for lifecycle management of the proposed product (b) (4) (b) (4) The Applicant has addressed all deficiencies communicated in information request letter # 1, 2, and 3 (Refer section "List of Deficiencies"). The proposed dissolution method is adequate and the Applicant has implemented the recommended dissolution acceptance criteria (b) (4) (b) (4) finished product batch release, and stability for the proposed methylphenidate HCl ER tablets.

ONDP-Division of Biopharmaceutics reviewed the original submission and amendments under A208607. This ANDA is adequate and recommended for approval from a Biopharmaceutics perspective.

The Dissolution Method and Acceptance Criteria for the Proposed Generic Methylphenidate HCl ER Oral Tablets (18mg, 27mg, 36mg, and 54mg) for Batch Release and Stability Testing

Method Source	USP Apparatus	Rotation Speed	Dissolution Medium	Medium Volume	Medium Temperature	Proposed Acceptance Criteria (% dissolved of label claim)	Implemented Acceptance Criteria based on FDA's Recommendation* (% dissolved of label claim)
USP test 4	2 (Paddle)	50 rpm	0.001N HCl (b) (4)	500mL	37°C ± 0.5°C	1 hr: NLT (b) (4)% 2 hr: (b) (4)% 6 hr: NLT (b) (4)% 10 hr: NLT (b) (4)%	0.5 hr: 10% - 30% 2 hr: 28% - 48% 6hr: 70% - 90% 10 hr: NLT 85%

* Recommended as supported by the submitted dissolution data

(b) (4)

[redacted]

List Submissions being reviewed (table):

SUBMISSION(S) DATE	SEQUENCE NO.
05/31/2016	0001(2)
03/20/2017	0010(11)
05/17/2017	0011(12)
06/12/2017	0012(13)

Highlight Key Outstanding Issues from Last Cycle: This is fourth review cycle. There are no outstanding issues.

The Applicant adequately responded to the information request (IR) #s 1, 2, and 3 (Refer "List of Deficiencies ") related to dissolution method and acceptance criteria for in-process control, finished product batch release and stability.

Concise Description Outstanding Issues Remaining: This is fourth review cycle. There are no outstanding issues remaining. The Applicant has accepted the recommendation on in-process dissolution acceptance criteria for ER coated tablets (before IR drug layering) communicated in IR # 3 letter. Refer section "Control Strategy" for details.

BCS Designation

The proposed product of methylphenidate HCl is a combination of immediate release and extended release mechanism for drug release from a coated matrix tablet (ER matrix tablet + ER coating + IR drug layering) and hence biowaiver based on BCS is not applicable for the proposed product.

Reviewer's Assessment: *Not Applicable*

Dissolution Method and Acceptance Criteria

The Applicant conducted multi-time point dissolution testing for finished product batch release and stability studies using the (b) (4) and the proposed dissolution method [USP test 4 – USP Apparatus 2, 50 rpm, 500mL of 0.001 N HCl (b) (4) for the proposed methylphenidate HCl ER oral tablets.[24,25] The Applicant also performed multipoint comparative dissolution for comparison to the RLD in multiple media [pH 1.2 (0.1 N HCl), pH 4.5 (b) (4) (b) (4), and pH 6.8 (b) (4) (b) (4) The Applicant also performed *in vitro* alcohol dose dumping studies using the in-house method on both the proposed product and RLD for all strengths in 0.1 N HCl containing 0%, 5%, 20%, and 40% alcohol. The Applicant provided complete dissolution data [individual data (n=12 units), mean, %CV] obtained from the tests mentioned above conducted on the proposed and RLD tablets and is available at the cited references.[26,27,28] The complete dissolution data on batch # SB69900300 (Bulk Lot #) / SB69900301 (Packaged Lot #) (54 mg) used in the *in vivo* pivotal fasted (Study # 4002731) and fed (Study # 4002730) BE study are also provided along with the data on the RLD (54 mg – 13KG402).[29,30,31] The Applicant provided dissolution data at the

[24] Global Submit – A208607 – 0001(2) dated 05/31/2016. **Module 2.7.1. Summary of Results of Individual Studies - PDF.** (Accessed on January 26, 2017)
[25] Global Sumit – A208607 – 0001(2) dated 05/31/2016. **Module 3.2.P.2. Dissolution Development Report: RPT-15-12-IR-002-01R.** (Accessed on January 27, 2017)
[26] Global Submit – A208607 – 0001(2) dated 05/31/2016. **Module 2.7.1. RPT 15-03-ir-001-02R – Comparative Dissolution.** (Accessed on January 26, 2017)
[27] Global Submit – A208607 – 0001(2) dated 05/31/2016. **Module 2.7.1. RPT 15-03-IR-002-01r – Multimedia Dissolution.** (Accessed on January 26, 2017)
[28] Global Submit – A208607 – 0001(2) dated 05/31/2016. **Module 2.7.1. RPT 15-03-ir-003-00r – Dose Dumping.** (Accessed on January 26, 2017)
[29] Global Submit – A208607 – 0001(2) dated 05/31/2016. **Module 5.3.1.2. Fed BE study – 4002730 – Synopsis.** (Accessed on January 27, 2017)
[30] Global Submit – A208607 – 0001(2) dated 05/31/2016. **Module 5.3.1.2. Fasted BE study – 4002731 – Synopsis.** (Accessed on January 27, 2017)
[31] Global Submit – A208607 – 0001(2) dated 05/31/2016. **Module 2.7.1. Background and Overview - PDF.** (Accessed on January 27, 2017)

multiple time points (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 hrs) for multiple batches of each strength [Three batches – 18 mg and 54 mg; Four batches – 27 mg and 36 mg].[32]

Selection of the Dissolution Method: The Applicant proposed the following dissolution method (Table 2) for routine quality control i.e., batch release and stability of the proposed generic methylphenidate HCl ER tablets.[17,25]

Table 2. Proposed Dissolution Method for the Corepharma's Generic Methylphenidate HCl ER Tablets

Proposed Dissolution Method Conditions (USP Test 4)	
Apparatus	USP Apparatus 2 (Paddle)
Agitation Speed	50 rpm
Dissolution Medium	0.001N HCl**
Medium Volume	500 mL
Medium Temperature	37°C ± 0.5°C
Specification Time Points	1, 2, 6, and 10hrs
	(b) (4)

During the dissolution method development efforts by the Applicant, the USP monograph for methylphenidate HCl ER tablets listed only two dissolution performance tests (Test 1 and Test 2, Table 1). The Applicant states that the USP test 1 (Apparatus 2) and test 2 (Apparatus 7) method appears to be for the products Ritalin SR (N018029; Methylphenidate HCl ER Tablets) labeled for multiple doses per day, and Concerta® (RLD for this ANDA) based on OROS® technology labeled for dosing every 24 hrs respectively.[25] The Applicant also states that the FDA approval letter[33] details the dissolution method (USP Apparatus 2, 50 rpm, 500 mL of 0.001 N HCl which is USP dissolution test 4) for Mallinckrodt's generic version of Concerta® (A202608; currently BX rated) that does not use OROS® technology but comprises of a polymeric core surrounded by a diffusion controlling membrane with an IR drug overcoat (similar to the proposed product). Based on the above information and since Apparatus 7 is suitable for osmotic pump delivery systems, and Apparatus 2 has well established calibration procedures, the Applicant selected Apparatus 2 for the proposed generic methylphenidate HCl ER tablets. The selection of Apparatus 2 is further supported by comparable dissolution profiles for Concerta® and the proposed generic generated in USP Apparatus 2 and 7 (Figure 1). The selection of Apparatus 2 for the proposed generic methylphenidate HCl ER tablets is adequate. (b) (4)

[32] Global Submit – A208607 – 0001(2) dated 05/31/2016. Module 3.2.P.5.4. Batch Analyses. (Accessed on January 27, 2017)

[33] FDA Approval Letter for ANDA 202608 – Generic Concerta® from Mallinckrodt (Accessed on January 27, 2017)

(b) (4)

(b) (4)

(b) (4)

Corepharma initially adopted

(b) (4)

instead of using 0.001 N HCl (USP test 4)

(b) (4)

. The other dissolution method conditions (500mL of dissolution medium and 50 rpm of agitation speed) mirrors to those used in the USP dissolution test 2 and test 4 (Mallinckrodt's dissolution method)

(b) (4)

(b) (4)

[34] Global Sumit – A208607 – 0001(2) dated 05/31/2016. **Module 2.7.1. RPT 15-03-ir-001-02R – Comparative Dissolution.** (Accessed on January 28, 2017)

(b) (4)

[redacted]

As mentioned earlier, during the development efforts by the Applicant, only USP test 1 and test 2 were official. Effective December 1, 2015, two additional tests (USP test 3 and test 4) became official. The initial development studies, exhibit batch release, and stability testing of the proposed methylphenidate HCl ER tablets USP (18mg, 27mg, 36mg, and 54mg) [redacted] This method was also used to demonstrate the dissolution similarity between lower strengths (18mg, 27mg, and 36mg) and the BE strength (54mg) to support the biowaiver request. However, the USP test 4 [(dissolution medium of 0.001 N HCl [redacted] is proposed for ongoing exhibit batch and future stability testing and commercial batch release post approval based on dissolution similarity between the above two methods for all strengths, successful verification of the USP test 4 method, and demonstration of equivalency between in-house and USP test 4 method for the proposed product (Discussed in detail below). The Applicant generated dissolution data with both the in-house and USP test 4 method for one batch of each strength (Figure 3) that indicates similarity ($f2$>50 tested by this reviewer (using data upto 8 hrs); $f2$ = 78.12, 81.83, 71.61, and 85.89 for 18mg, 27mg, 36mg, and 54mg respectively). The variability (%CV) in dissolution across time points and strengths by both dissolution methods is similar and is less than 10%. The above results along with demonstration of equivalency (discussed below) between two methods supports the adequacy of the USP test 4 dissolution method for the proposed generic methylphenidate HCl ER tablets.

[35] Global Summit – A208607 – 0001(2) dated 05/31/2016. Module 3.2.P.5.2. M32p52 Analytical Procedures. (Accessed on January 28, 2017)

However, it is noted that the drug product specification Table specifies [redacted] whereas, the analytical procedure for the control of drug product specifies 0.001 N HCl as the dissolution medium (USP test 4). The dissolution method development report also proposes to adopt the USP test 4 (0.001 N HCl) for future dissolution testing and the Applicant includes in the drug labeling the language [redacted] as required by USP.[1] Therefore, the Applicant was requested to update the drug product specification Table with the proposed dissolution method of USP test 4 (Refer Deficiency # 1 under "List of Deficiencies Dated Feb 7, 2017"). The Applicant adequately responded to the request[36] and updated the relevant sections of control of the drug product (M 2.3.P),[37] drug product specification table (M 3.2.P.5.1),[38] and analytical procedure (M 3.2.P.5.2).[39]

[redacted]

[36] Global Summit – A208607 – 0010(11) dated 03/20/2017. **Module 1.11.1. Quality Information Amendment – Reviewer Guide.** (Accessed on April 28, 2017)
[37] Global Summit – A208607 – 0010(11) dated 03/20/2017. **Module 2.3.P. Control of the Drug Product - PDF.** (Accessed on April 28, 2017)
[38] Global Summit – A208607 – 0010(11) dated 03/20/2017. **Module 3.2.P.5.1. Drug Product Specifications SPF-0003-rev-03.** (Accessed on April 28, 2017)
[39] Global Summit – A208607 – 0010(11) dated 03/20/2017. **Module 3.2.P.5.2. TMD-0007-version-03.** (Accessed on April 28, 2017)

(b) (4)

[redacted]

Dissolution Acceptance Criteria: The Applicant proposed dissolution specification time points of 1hr, 2hr, 6hr, and 10hr (Table 5) in accordance to the USP test 4. The strength independent dissolution acceptance criteria are proposed (Table 5). The proposed dissolution specifications are based on the observed data from the release and stability testing of the proposed methylphenidate HCl ER tablets, 54mg (in-house dissolution method). Since, the USP test 4 is proposed for quality control, the dissolution acceptance criterion based on the dissolution data generated by the proposed USP test 4 was recommended to the Applicant in the information request # 1(Table 6; Figure 4; Individual Data in Attachment – Table A3-A6; Refer Deficiency # 2 under "List of Deficiencies Dated Feb 7, 2017"). Since, the drug release from IR drug layer ([redacted] (b) (4) of the dose) is critical to obtain the first plasma concentration peak which is responsible for the onset of action, inclusion of 30 min (0.5 hr) time point for dissolution specification is relevant and necessary. Additionally, the time point of 0.5 hr is likely to better distinguish the release of drug from IR drug layer to the one from the ER matrix when compared to the time point of 1 hr. Therefore, the specification time point of 1 hr was replaced with 0.5 hr in the recommended dissolution acceptance criteria for the proposed methylphenidate HCl ER tablets.

Table 5. *Proposed* Dissolution Acceptance Criteria (% Dissolved of Label Claim) for the Proposed Generic Methylphenidate HCl ER Oral Tablets for Batch Release and Stability Testing[16]

Time (hr)	18mg, 27mg, 36mg, and 54mg
1	NLT [redacted] (b) (4) %
2	[redacted] (b) (4) %
6	NLT [redacted] (b) (4) %
10	NLT [redacted] %

Table 6. *Recommended* Dissolution Acceptance Criteria (% Dissolved of Label Claim) for the Proposed Generic Methylphenidate HCl ER Oral Tablets for Batch Release and Stability Testing (Based on USP test 4 and USP <711> Stage 2 Criteria)

The Applicant responded to the request on the recommended dissolution acceptance criteria for batch release and stability.[36] The Applicant accepted the recommended change in dissolution specification time point from 1hr to 0.5 hr and acceptance criteria (as per Table 6) and further proposed a range of 70%-90% for 6 hr time point versus the requested (b) (4)% dissolved. This is proposed based on the average (n=18) dissolution data for the biostrength batch SB69900301 (54mg) generated using the proposed USP test 4 method (n=12) and in-house method (n=6). The Applicant states that this batch was initially tested at product release (n=6, in-house method) and then tested again to demonstrate equivalency of in-house method to USP Test 4 (n=12, USP test 4). Therefore, the Applicant proposed the 6 hr limit of 70%-90% based on the overall average of n=18 ((b) (4)%; Table A7 of Attachment). The Applicant's proposal is adequate since both the proposed USP test 4 (0.001N HCl, (b) (4) and in-house method (b) (4) (b) (4) are demonstrated to be equivalent based on (1) dissolution similarity

between the two methods for all strengths (one batch tested for each strength; Table 4), (2) successful verification of the USP test 4 method (discussed below under "Dissolution Sample Analytical Method"), and (3) demonstration of equivalency between in-house and USP test 4 method for the proposed product (discussed below "Dissolution Sample Analytical Method"). The Applicant updated the relevant sections of the submission[37,38,40] to reflect the dissolution acceptance criteria showed in Table 7. The Applicant states that they intend "to petition the USP to include our ANDA approved dissolution test and acceptance criteria in the Methylphenidate Hydrochloride Extended-Release Tablets monograph."[36]

Table 7. Dissolution Acceptance Criteria (% Dissolved of Label Claim) for the Proposed Generic Methylphenidate HCl ER Oral Tablets for Batch Release and Stability Testing (USP test 4)

Time Points (hr)	USP39-NF34 S2	Proposed by the Applicant	Recommended by FDA in IR#1	Implemented by the Applicant in Response to IR#1*
0.5	-	(b) (4)		10% - 30%
1	20% - 40%			-
2	35% - 55%			28% - 48%
6	65% - 85%			70% - 90%
10	NLT 80%			NLT 85%
* Accepted by FDA				

A decreasing or increasing trend in dissolution of exhibit batches in accelerated, intermediate, and long term stability conditions for all strengths is not observed based on the data submitted in the sequence 0001(2) and the updated data submitted in the sequence 0010(11), and 0011(12). In response to the drug product reviewer's information request in IR # 2 letter on the drug product being out of specification for dissolution at 2hr and 6hr time points for several stability samples,[41] the Applicant provided the following to explain the above observation:

1. The dissolution data (n=6 units, S1 testing) were not out of specification as per the dissolution criteria proposed in the original ANDA submission [0001(2)].
2. The several observed dissolution data are out of specification (not meeting USP stage 1 criteria) according to the criteria proposed by FDA; however, this was recommended after the time of dissolution testing and hence not implemented when the batches tested.
3. Further, the Applicant rationalized statistically based on the dissolution data collected from exhibit batch stability lots that considering the criteria implemented based on FDA's recommendation, there is a greater than 99.99 probability that all strengths will meet

[40] Global Submit – A208607 – 0010(11) dated 03/20/2017. Module 3.2.P.5.6. Justification of Specifications. (Accessed on April 28, 2017)
[41] Global Submit – A208607 – 0011(12) dated 05/17/2017. Module 1.11.1. Quality Information Amendment. (Accessed on May 25, 2017)

stage 2 acceptance criteria at expiry with three out of the four strengths having >99 probability of meeting stage 1 acceptance criteria.

This reviewer agrees with the Applicant's response to the above. The above referenced statistical report[42] will be evaluated by the drug product reviewer and its acceptability is under drug product reviewer's purview.

Dissolution Sample Analytical Method: The Applicant employed in-house (b) (4)

(b) (4)

[redacted]

[42] Global Submit – A208607 – 0011(12) dated 05/17/2017. **Module 3.2.P.8.1. Risk Mitigation – Statistical Review of Exhibit Batch(es) Dissolution Results.** (Accessed on May 25, 2017)
[43] Global Submit – A208607 – 0001(2) dated 05/31/2016. **Module 3.2.P.5.3. QL-RPT-0356-rev-01 Dissolution.** (Accessed on January 31, 2017)
[44] Global Submit – A208607 – 0001(2) dated 05/31/2016. **Module 3.2.P.5.3. QL-RPT-0436 Related Substances.** (Accessed on February 01, 2017)

(b) (4)

[redacted]

Reviewer's Assessment: ***Adequate***

The proposed dissolution method (USP test 4) (b) (4) dissolution samples for finished product batch release and stability testing of the proposed methylphenidate HCl ER tablets is adequate. The Applicant adequately responded to the dissolution method and acceptance criteria related information requests (List of Deficiencies Dated Feb 7, 2017) for batch release and stability.

[45] Global Submit – A208607 – 0001(2) dated 05/31/2016. Module 3.2.P.5.3. RPT-00148-01 Dissolution by HPLC. (Accessed on February 01, 2017)

Clinical relevance of dissolution method & acceptance criteria (e.g., IVIVR, IVIVC, In Silico Modeling, small scale in vivo)

Reviewer's Assessment:

The Applicant proposed the USP dissolution test 4 [USP 2, 50 rpm, 500 mL of 0.001 N HCl (b) (4) (b) (4)] for *in vitro* dissolution testing of the proposed generic methylphenidate HCl ER oral tablets. No data were submitting linking the in vitro/in *vivo* data via IVIVC/IVIVR or *in silico* modeling. The dissolution profile of the proposed product (54mg) is generated on the batch that is bioequivalent to the RLD (54mg) as tested *in vivo* (Bioequivalence review adequate).

However, the in-house dissolution method (b) (4) (b) (4) (b) (4) This may also be concluded for the proposed USP test 4 dissolution method (USP 2, 50 rpm, 500mL of 0.001 N HCl, (b) (4) (b) (4) A detailed discussion on the discriminating ability and clinical relevance is made under the subsection "Assessment of Risk of Formulation Variables on Dissolution" of the section "Application of dissolution/IVIVC in QbD".

Application of dissolution/IVIVC in QbD[46]

The formulation of the proposed product (Table 9) is qualitatively different to that of the RLD with respect to excipients;[47,48] however, both products are bioequivalent based on *in vivo* BE fasted and fed studies. All strengths of the proposed generic methylphenidate HCl ER tablets are compositionally proportional (assessed by this reviewer; differences within SUPAC Level 2 for both release and non-release controlling excipients). The drug – excipient compatibility study supported the selection of the excipients. (b) (4) (b) (4)

[46] Global Submit – A208607 – 0001(2) dated 05/31/2016. Module 3.2.P.2. Pharmaceutical Development Report. (Accessed on February 02, 2017)
[47] Global Submit – A208607 – 0001(2) dated 05/31/2016. Module 1.12.12. Comparison of Generic to Reference Listed Drug. (Accessed on February 02, 2017)
[48] Global Submit – A208607 – 0001(2) dated 05/31/2016. Module 2.7.1. Background and Overview - PDF. (Accessed on February 02, 2017)

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Risk Assessment by FDA:

The initial risk ranking performed by Application Technical Lead (ATL) for dissolution is high (Attachment – Table A1 of Attachment). (b) (4) (b) (4) (b) (4) The Applicant implemented the recommended dissolution acceptance criteria for (b) (4) finished product batch release and stability testing and hence risk ranking for dissolution should be updated to low from a biopharmaceutics perspective .

Reviewer's Assessment: ***Adequate from biopharmaceutics perspective***

Dissolution is considered one of the CQAs that could be potentially impacted by formulation and process variables according to the risk assessment performed by the Applicant. The proposed (b) (4) (b) (4) The risk ranking for dissolution is updated due to low from a biopharmaceutics perspective.

MODIFIED RELEASE ORAL DRUG PRODUCTS –In-Vitro Alcohol Dose Dumping

Reviewer's Assessment: *Review of in vitro alcohol dose dumping study is under the purview of the Office of Bioequivalence (OB), Office of Generic Drugs (OGD).The study is found adequate by the OB, OGD.*[10]

In-Vitro Soft-food Interaction Study

Reviewer's Assessment: *Not Applicable*

In-Vitro Release Testing (IVRT) for Semi-Solid Products

Reviewer's Assessment: *Not Applicable.* The proposed product is an ER oral tablets.

In-Vitro Permeation Testing (IVPT) for Transdermal/Topical Products

Reviewer's Assessment: *Not Applicable.* The proposed product is an ER oral tablets.

In-Vitro Dissolution Testing for Abuse-deterrent Products

Reviewer's Assessment: *Not Applicable.*

In-Vitro BE Evaluation for Pulmonary Products

Reviewer's Assessment: *Not Applicable.* The proposed product is an ER oral tablets.

EXTENDED RELEASE DOSAGE FORMS –Extended Release Claim

Reviewer's Assessment: *Not Applicable.* The proposed product is a generic ER tablet referencing the RLD Concerta®.

Bridging of Formulations

Reviewer's Assessment: <u>Adequate from biopharmaceutics perspective</u>

The to-be-marketed methylphenidate HCl ER oral tablet formulation is the same as that of the formulation [54mg – Lot # SB69900300 (Bulk Lot #) / SB69900301 (Packaged Lot #)] used in pivotal BE study (Fasted *In Vivo* BE Study # 4002731, Fed *In Vivo* BE Study # 4002730). Therefore, the need for bridging data (e.g., dissolution profile comparisons/BE data) is not applicable.

Biowaiver Request

The submission contains *in vivo* single dose fasting and fed BE study performed for the proposed generic methylphenidate HCl ER oral tablets (54mg) comparing it to the RLD, Concerta® tablets (54mg). A waiver from conducting BE study is requested for the proposed lower strengths (18mg, 27mg, 36mg) based on *in vivo* bioequivalence between the proposed product and RLD on the highest strength, proportional similarity for the compositions and dissolution similarity of the formulation between the test strength with respect to test biostrength. The BE study and biowaiver request is found adequate by the Office of Bioequivalence (OB), OGD.[10,11]

Reviewer's Assessment:

The evaluation of biowaiver request is under the Office of Bioequivalence (OB), OGD's purview and is found adequate.

R Regional Information

Comparability Protocols

Reviewer's Assessment: *Not Applicable*

Post-Approval Commitments

Reviewer's Assessment: *Not Applicable*

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(b) (4)

Table A3. Individual Dissolution Data of the Proposed Methylphenidate HCl ER Oral Tablets, 18mg (Lot # SB51300301) (Proposed USP Test 4)

Appendix 1: Table 8
Results for CorePharma Methylphenidate HCl ER Tablets, USP 18 mg Lot # SB51300301 under CorePharma and USP Dissolution Test 4 Conditions

%Dissolved

Tablet	CorePharma								Test 4							
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
1	(b) (4)															
2																
3																
4																
5																
6																
7																
8																
9																
10																
11																
12																
Mean	19	27	41	69	87	97	100	101	18	26	39	64	85	95	99	102
Min	(b) (4)															
Max																
%RSD	7.1	7.2	6.2	4.7	3.1	2.3	2.2	2.1	8.5	7.0	6.3	3.9	3.1	2.6	2.3	2.5

Table A4. Individual Dissolution Data of the Proposed Methylphenidate HCl ER Oral Tablets, 27mg (Lot # SB51400301) (Proposed USP Test 4)

Appendix 1: Table 9
Results for CorePharma Methylphenidate HCl ER Tablets, USP 27 mg Lot # SB51400301under CorePharma and USP Dissolution Test 4 Conditions

%Dissolved

Tablet	CorePharma								Test 4							
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
1	(b) (4)															
2																
3																
4																
5																
6																
7																
8																
9																
10																
11																
12																
Mean	20	28	41	67	86	97	100	101	16	26	40	67	85	95	100	101
Min	(b) (4)															
Max																
%RSD	5.8	4.9	4.7	3.0	2.5	2.2	2.1	2.2	14.1	6.3	6.5	3.9	2.7	1.6	1.4	1.5

Table A5. Individual Dissolution Data of the Proposed Methylphenidate HCl ER Oral Tablets, 36mg (Lot # SB51500301) (Proposed USP Test 4)

Appendix 1: Table 10
Results for CorePharma Methylphenidate HCl ER Tablets, USP 36 mg Lot # SB51500301under CorePharma and USP Dissolution Test 4 Conditions

%Dissolved

Tablet	CorePharma								Test 4							
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
1																(b) (4)
2																
3																
4																
5																
6																
7																
8																
9																
10																
11																
12																
Mean	20	26	40	65	83	93	97	97	13	23	37	64	81	91	97	98
Min																(b) (4)
Max																
%RSD	3.8	6.1	6.0	3.5	2.6	2.3	2.1	1.8	22.6	4.0	4.0	4.5	3.8	3.2	2.7	2.4

Table A6. Individual Dissolution Data of the Proposed Methylphenidate HCl ER Oral Tablets, 54mg (Lot # SB69900301) (Proposed USP Test 4)

Appendix 1: Table 11
Results for CorePharma Methylphenidate HCl ER Tablets, USP 54 mg Lot # SB69900301 under CorePharma and USP Dissolution Test 4 Conditions

%Dissolved

Tablet	CorePharma								Test 4							
	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr	0.5 hr	1 hr	2 hr	4 hr	6 hr	8 hr	10 hr	12 hr
1	(b) (4)															
2																
3																
4																
5																
6																
7																
8																
9																
10																
11																
12																
Mean	21	26	39	63	81	92	97	98	20	25	38	63	79	89	96	98
Min	(b) (4)															
Max																
%RSD	6.3	5.2	4.6	2.9	2.2	2.0	2.3	2.5	6.6	5.0	3.9	3.4	2.7	2.9	3.0	3.0

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Sandra Suarez

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Poonam Delvadia

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PROCESS

Product Background:

ANDA: 208607

Drug Product Name / Strength: Methylphenidate Hydrochloride Extended Release (b) (4) Tablets, 18 mg, 27 mg, 36 mg, 54 mg

Route of Administration: Oral

Applicant Name: Core Pharma

Review Summary: The drug product Methylphenidate Hydrochloride Extended Release (b) (4) tablets, 18 mg, 27 mg, 36 mg, 54 mg will be manufactured at (b) (4) (b) (4)

List Submissions being reviewed (table):

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000 (1) ORIG-1: Original ANDA submission	*04/18/2016*	*All*
0001 (2) ORIG-1: Original ANDA submission	05/31/2016	*All*
0010 (11): ORIG-1: Original ANDA submission	03/20/2017	*All*
0012 (13): ORIG-1: Quality response	06/12/2017	*All*

Highlight Key Outstanding Issues from Last Cycle: NA.

Concise Description Outstanding Issues Remaining: NA
ANDA is recommended for approval from Process perspective

P.3 Manufacture

(b) (4)

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Iwona
Weidlich

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Arwa
El Hagrasy

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FACILITIES

Product Background: Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65. First Generic. RLD: NDA – 21121.

NDA/ANDA: ANDA-208607-ORIG-1

Drug Product Name / Strength: Methylphenidate Hydrochloride Extended-Release Tablets, USP / 18 mg, 27 mg, 36 mg and 54 mg

Route of Administration: Oral

Applicant Name: CorePharma, LLC

Review Summary: All facilities associated with the manufacturing, testing and packaging of Methylphenidate Hydrochloride Extended-Release Tablets, USP under pending ANDA-208607-ORIG-1 are recommended for approval.

List Submissions being reviewed (table): ANDA-208607-ORIG-1

Highlight Key Outstanding Issues from Last Cycle: None

Concise Description Outstanding Issues Remaining: None

3.2.S.2 Manufacture

Summary of Facility Information:

(b) (4)

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Zhihao Peter Qiu

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Viviana Matta

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Date: 5/31/2017 03:10:17PM
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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208607Orig1s000

BIOEQUIVALENCE REVIEW(s)

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	208607			
Drug Product Name	Methylphenidate Hydrochloride Extended-Release Tablets USP			
Strength(s)	18 mg, 27 mg, 36 mg and 54 mg			
Applicant Name	CorePharma, LLC			
Applicant Address	215 Wood Avenue Middlesex, New Jersey 08846 USA			
Applicant's Point of Contact and Mailing Address	Kimberly D. Ernst 100 Somerset Corporate Blvd. Suite 3000 Bridgewater, New Jersey 08807 USA			
Contact's Telephone Number	732-667-6009			
Contact's Fax Number	732-805-5643			
Contact's Email Address	kimberly.ernst@impaxlabs.com			
Original Submission Date(s)	04/18/2016 05/31/2016 (Response to the filing comments)			
Submission Date(s) of Amendment(s) Under Review	N/A			
Reviewer	Sung-Yong Hwang, Ph.D.			
Secondary Reviewer	Suman Dandamudi, Ph.D.			
Tertiary Reviewer	Ke Ren, Ph.D.			
Study Number(s)	ARL/13/061	ARL/13/062	ARL/13/547	ARL/13/548
Study Type(s)	Fasting (pilot)	Fed (pilot)	Fasting (failed extra study)	Fed (failed extra study)
Strength(s)	1 x 54 mg	1 x 54 mg	1 x 54 mg	1 x 54 mg
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd.			
Clinical Site Address	A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai -400 709, Maharashtra, INDIA.			
Analytical Site	(b) (4)			
Analytical Site Address				
Study Number(s)	ARL/14/694		ARL/14/695	
Study Type(s)	Fasting (pivotal)		Fed (pivotal)	

Strength(s)	1 x 54 mg	1 x 54 mg
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd.	
Clinical Site Address	A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai -400 709, Maharashtra, INDIA.	
Analytical Site	(b) (4)	
Analytical Site Address		
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete** ☐ **N/A (Waiver)**	**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection** ☒ **Complete**
Waiver	☒ **Granted** ☐ **Tentatively granted** ☐ **Not granted** ☐ **N/A**	
QC Dissolution	☒ **Pending** ☐ **Adequate** ☐ **Inadequate**	
Formulation	☒ **Adequate** ☐ **Inadequate**	
Will Response to CR Result in a Reformulation?	☐ **Possibly** ☒ **No** ☐ **N/A**	
Deficiency Classification	☐ **Major** ☐ **Minor** ☒ **N/A (review is adequate)**	
Overall Review Result	☒ **Adequate** ☐ **Inadequate**	
Revised/New Draft Guidance Generated as Part of Current Review	☐ **YES** ☒ **NO**	

Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1, 2	**Fasting**	**54 mg**	☒ **Adequate** ☐ **Inadequate**
1, 2	**Fed**	**54 mg**	☒ **Adequate** ☐ **Inadequate**
1, 2	**Waivers**	**18 mg, 27 mg and 36 mg**	☒ **Adequate** ☐ **Inadequate**

ADDENDUM: Review of a Consult Response

1 EXECUTIVE SUMMARY

This is an addendum to a previous bioequivalence (BE) review[1] to include the review of a consult response from the Division of Quantitative Methods and Modelling (DQMM) in

[1] GDRP, ANDA 208607, Bioequivalence Discipline Review, Sungyong Hwang, A208607N000DB_N04182016.doc, Date Completed: 11/29/2016.

Office of Research and Standards (ORS) for expert opinion on the fed BE study (No. ARL/14/695) in CorePharma's ANDA 208607 (Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg).

The reference listed drug (RLD) product is Janssen Pharmaceuticals Inc.'s Concerta® (methylphenidate HCl) Extended-Release Tablets, 54 mg (NDA 021121, approved on December 8, 2000). It is indicated for the treatment of attention deficit hyperactivity disorder (ADHD) in children 6 years of age and older, adolescent, and adults up to the age of 65.

In the original application dated 04/18/2016, the firm submitted the results of fasting and fed BE studies comparing its test product, Methylphenidate Hydrochloride Extended-Release Tablets USP, 54 mg, to the corresponding RLD product, Concerta® (methylphenidate HCl) Extended Release Tablets, 54 mg. The application also includes waiver requests for the lower strengths, 18 mg, 27 mg and 36 mg of the test product. Each of the BE studies was designed as a single-dose, four-period, two-sequence, replicate crossover study in healthy male and female subjects as per the current revised draft guidance on Methylphenidate Hydrochloride Extended Release Tablets (Revised November 2014)[2].

The 90% confidence intervals (CIs) for all the pharmacokinetic (PK) parameters including the partial AUC (pAUC) metrics were within the acceptable BE limits of 80.00%-125.00% for both fasting and fed BE studies. In addition, the upper 95% confidence bounds for the subject-by-formulation interaction variance (SbF), $H_{\sigma_D^2}$ for all the PK parameters of the fasting study were below the recommended allowance (0.03) provided in the current product guidance for Methylphenidate Hydrochloride Extended-Release Tablets. Thus the fasting BE study (No. ARL/14/694) was deemed acceptable[1]. However, for the fed BE study (No. ARL/14/695), the value of $H_{\sigma_D^2}$ exceeds the allowance of 0.03 for the PK parameters of C_{max} and $pAUC_{4\text{-}8}$[1]. Therefore, the application was deemed inadequate and a consult to the ORS was sent to determine the acceptability of the fed study[3].

The ORS consult response concluded the results of the CorePharma's fed study (No. ARL/14/695) be acceptable for BE establishment[4]. Per ORS, this conclusion was drawn based on the following reasons:

1) The CorePharma's fed BE study passed the narrow therapeutic index (NTI) drugs BE criteria. Therefore, acceptance of this study inspite of failing to meet SbF

[2] Draft guidance on Methylphenidate Hydrochloride (Recommended Sep 2012; Revised Nov 2014) http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320007.pdf

[3] GDRP, ANDA 208607, Bioequivalence Discipline Review, A208607N000DB_C10132016.doc, Date Completed: 11/29/2016.

[4] GDRP, ANDA 208607, Consult Review for ANDA 208607_Final.docx, Andrew Babiskin, Date Completed: 01/09/2017.

requirement for all PK parameters will not have adverse impact on safety or efficacy of CorePharma's drug product. In addition, as long as Cmax passes the BE limit 80.00% -125.00% requirement, it does not raise additional concerns if the upper bound goes beyond the SbF threshold.

2) The ANDA 76772/76655 submitted by Watson/Actavis, is a case similar to the current ANDA, where the fasting BE study had SbF failure on its AUC_{3-7} and C_{max}: The value of σ_D^2 for AUC_{3-7} (0.05098) and C_{max} (0.05539) for the fasting study for ANDA 76772/76655, is significantly higher than that of the associated PK metrics for the current ANDA (AUC_{4-8}= 0.03063; C_{max}=0.03441). The Watson studies were yet found to be adequate and got approved.

3) The metrics of AUC_{4-8} and C_{max} are considered as "low-risk" metrics. These two metrics were not indicated as a source of concern for the complaints about generic Concerta that triggered the Concerta BE guidance revision. These metrics were also not identified as directly needing additional control in the tracked safety issue (TSI).

For more details on this conclusion and scientific evaluation of the fed BE study data in drawing this conclusion, please see Section 6.1 Attachments of this review for the ORS Science Staff consult response.

Based on the above information, the Division of Bioequivalence III (DBIII) considers the fed BE study (No. ARL/14/695) to be acceptable.

Per the previous BE review of the current ANDA[2], the OSIS status of the clinical and analytical sites for the current ANDA is considered complete.

As a result, the BE portion of the application is **adequate.**

2 TABLE OF CONTENTS

3 REVIEW OF CONSULT RESPONSE

Consult request:
CorePharma, LLC submitted ANDA 208607 seeking the approval of a generic version of Methylphenidate Hydrochloride (HCl) Extended Release Tablets, 18 mg, 27 mg, 36 mg, 54 mg and 72 mg. The reference listed drug (RLD) is Concerta® (methylphenidate hydrochloride) Extended-Release Tablets, 54 mg, manufactured by Janssen Pharms (NDA 021121). The reference product is also available in 18 mg, 27 mg and 36 mg strengths.

In the original submission dated April 18, 2016, the firm submitted the results of fasting and fed bioequivalence (BE) studies comparing the test product, Methylphenidate Hydrochloride Extended Release Tablets, 54 mg to the corresponding reference product, Janssen Pharmaceuticals, Inc.'s Concerta® (methylphenidate hydrochloride) Extended Release Tablets, 54 mg. The firm conducted the BE studies as per the current revised draft guidance on Methylphenidate Hydrochloride Extended Release Tablets (Revised November 2014)[5].

Issues:
The BE review can be found at the following link in the Generic Drug Review Platform (GDRP):
GDRP, ANDA 208607, Bioequivalence Discipline Review, Bioequivalence Primary Review, Sungyong Hwang, A208607N000DB_N04182016.docx
http://panorama.fda.gov/document/preview?versionID=57ffe4460097e2c47e42a774945386b8&ID=57ffe4440097e2bf87ab95284a05dba9

The 90% confidence intervals for all the pharmacokinetic (PK) parameters including the partial AUC metrics are within the acceptable BE limits of 80.00%-125.00% for both fasting and fed BE studies. In addition, the fasting BE study met the BE requirement for subject-by-formulation interaction variance for all the PK parameters. Thus the fasting BE study (No. ARL/14/694) is acceptable. However, for the fed BE study (No. ARL/14/695) the 95% upper confidence bound for subject-by-formulation interaction variance exceeds 0.03 for the PK parameters, Cmax and $pAUC_{4-8}$.

*The firm concluded the study outcome based on the **point estimate** of subject-by-formulation interaction variance, σ2D. Per firm's statistical report (please see attachment #2, page 45), the 95% upper bound for subject by formulation interaction variance exceed 0.03 for the PK parameters, Cmax (0.0347) and $pAUC_{4-8}$ (0.0305). According to current product-specific BE recommendations for Methylphenidate Hydrochloride Extended Release Tablets, the **95% upper confidence bound for subject-by-formulation interaction variance** is recommended for ensuring the switchability between test and reference products.*

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[5] http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320007.pdf

Please note that the firm submitted a control correspondence (#49819; submitted on February 26, 2015) regarding the statistical analysis for subject-by-formulation interaction variance. However, the Agency only responded that the subject-by-formulation interaction variance for each PK metric should be less than or equal to 0.03[6].

Based on the above information, the Division of Bioequivalence (DBIII) seeks confirmation from the Division of Quantitative Method and Modeling for whether the fed BE study (No. ARL/14/695) should be considered unacceptable, due to the failure to meet the BE requirement for subject-by-formulation interaction variance.

ORS response to the DBIII consult request:

Based on an extensive analysis of the fed, fully-replicated CorePharma BE study, we concluded that the BE results acceptable. After receiving post-market complaints for two Concerta generics (by Mallinckrodt and Kudco) and initiating a TSI, OGD convened a working group that resulted in the revising of the BE guidance for generic products referencing Concerta. Since a number of complaints centered on the lack of duration of efficacy, particularly after 7 hours, additional pAUC metrics were included in the guidance to assess MPH concentrations in the associated time periods. There were also complaints related to early onset from the generics and the SbF was included in the guidance primarily as a way of controlling the variance for the early pAUCs. The detailed history and summaries of the revision could be found in the Concerta BE guidance revision memo[7] *and the review of ANDA 76772/76655.*[8]

The ANDA 76772/76655 submitted by Watson/Actavis, is a case similar to the CorePharma case, where the BE studies had SbF failure on its fasting AUC_{3-7} and C_{max}. Additionally, the 95% upper confidence bonds of the SbF interaction variance, are higher than that for CorePharma – 0.05098 for AUC_{3-7} and 0.05539 for C_{max}. In Watson's case, the two problematic metrics would be able to pass full IBE and NTI criteria and it was never the intention of the Concerta guidance to place criteria more stringent than that for NTI. In addition, the review concluded that C_{max} and AUC_{3-7} were not metrics of primary concern during the TSI and were not identified as needing additional level of control. As a result, the BE studies for Watson were found to be adequate, regardless of the SbF result.

In BE revision discussions, C_{max} andAUC_{4-8} (and its associated fasting metric of AUC_{3-7}) were not included as metrics needing additional control (i.e., variance control and/or point estimate restriction). In fact, the original Mallinckrodt study of two-way crossover

[6] http://panorama fda.gov/project/view?ID=54ef889f0008ec424e7bafe2029247ba
[7] Concerta guidance internal, "Memo: Revision of the Draft Bioequivalence Guidance for Methylphenidate Hydrochloride Extended-Release Tablets", http://panorama.fda.gov/project/view?ID=53ff812b000871179208c9f0461b1dc7
[8] Babiskin, Andrew. *et.al.* "OGD Science Staff Consult Review: Response to DBIII Request ANDA 076772 ORS Consult Request from DBIII", http://panorama.fda.gov/issue/view?ID=55ce50bc00103d3c5ce4943a05b43ce8

fasting state had a similar case with lower bound close to the threshold, and a significant amount of individuals are observed to be outside 80-125% for C_{max}.[9] Furthermore, in the other submission of the Concerta generics by Actavis (ANDA 76772/76655) as mentioned above, its C_{max} for fasting state actually had higher SbF upper confidence ($H_{\sigma_D^2}$=0.05539), yet still got approved. This means that for C_{max}, as long as these metrics pass the BE limit 80-125% requirement, it does not raise additional concerns if the upper bound goes beyond the SbF threshold. It should be noted that since the Concerta guidance revision, Kudco conducted new fully-replicate BE studies under fasting and fed conditions and ORS sponsored its own fasting fully-replicate BE study comparing the Mallinckrodt product to Concerta. For the Kudco studies, all metrics had $H_{\sigma_D^2}$ values below 0.03. For the Mallinckrodt study, only AUC_{7-12} had an upper bound value above 0.03 ($H_{\sigma_D^2}$=0.04782). These results demonstrates that for the complaints associated with the Mallinckrodt and Kudco products, they are not probably due to SbF issues with C_{max} and the middle pAUCs.

*<u>Recommendation:</u> **DQMM recommends that the CorePharma fed study ARL/14/695 be found acceptable.** While the estimated 95% upper confidence bound for the subject-by-formulation interaction variance for AUC_{4-8} and C_{max} in the fed state is greater than the recommended allowance of 0.03, we find the fed study still be acceptable for the following reasons:*

1. *The fed study passes full NTI criteria for AUC_{4-8}, and only the variance comparison test for C_{max}. Even though C_{max} does not pass the tighter BE limit due to its high T/R point estimate, results still indicate that C_{max} has very tight 90% CI interval.*
2. *The $H_{\sigma_D^2}$ values above 0.03 for C_{max} and AUC_{4-8} are significant less than the $H_{\sigma_D^2}$ values that were ultimately found acceptable for the same associated metrics in the Watson product (ANDA 76772/76655).*
3. *The metrics of AUC_{4-8} and C_{max} are "low-risk" metrics since they were neither associated with the complaints for Mallinckrodt and Kudco generics triggering the TSI, nor were they identified as directly needing additional control in the TSI.*

Reviewer's Comments:

- Per the current Individual Product Bioequivalence Recommendation for Methylphenidate Extended Release Tablets[2], to ensure the switchability between Concerta® and generic products, a subject-by-formulation test for each PK metric is recommended in addition to the establishment of average BE based on the PK metrics. In order to pass this test, the value of 95% upper confidence bound for subject-by-formulation interaction variance (SbF), $H_{\sigma_D^2}$ should not exceed the

[9] See the previously mentioned ANDA 76772/76655 review

recommended allowance of 0.03 (the regulatory cut-off value per the draft guidance).

- For the fed BE study (No. ARL/14/695), the 90% CIs for the least squares geometric means of all the PK parameters including the pAUC metrics were within the acceptable BE criteria of 80.00%-125.00%. However, **the $H_{\sigma_D^2}$ values for C_{max} and $pAUC_{4-8}$ exceed the allowance of 0.03**[1]. Thus the DBIII has submitted consult request to ORS regarding the firm's failure to meet the BE requirement for SbF for the fed BE study[3].

- In the current ORS consult response to the DBIII[4], ORS recommended the CorePharma's fed BE study (No. ARL/14/695) be acceptable based on the following reasons:

  1. The fed study passes full NTI criteria for AUC_{4-8}, and only the variance comparison test for C_{max}. Even though C_{max} does not pass the tighter BE limit due to its high T/R point estimate, results still indicate that C_{max} has very tight 90% CI interval.

  2. The $H_{\sigma_D^2}$ values above 0.03 for C_{max} and AUC_{4-8} are significant less than the $H_{\sigma_D^2}$ values that were ultimately found acceptable for the same associated metrics in the Watson product (ANDA 76772/76655).

  3. The metrics of AUC_{4-8} and C_{max} are "low-risk" metrics since they were neither associated with the complaints for Mallinckrodt and Kudco generics triggering the TSI, nor were they identified as directly needing additional control in the TSI.

- Based on the following considerations, the reviewer agrees with the above recommendation of ORS on accepting the CorePharma's fed BE study, inspite of the fact that the fed BE study failed to meet 95% upper confidence bound for subject-by-formulation interaction variance (SbF), $H_{\sigma_D^2}$ for two PK metrics, C_{max} and AUC_{4-8} :

  1) Applying the Reference Scaled Average Bioequivalence (RSABE) approach that was recommended for NTI drugs for the fed BE study of the current drug product. The BE guidance for NTI products includes a test for comparison of the test and reference product within-subject variability. Specifically, the upper 90% confidence bound of s_{WT}/s_{WR} must be less than 2.5. The CorePharma's fed BE study (No. ARL/14/695) passed the NTI drugs BE criteria. Therefore, acceptance of this study inspite of failing to meet SbF requirement for all PK parameters will not have adverse impact on safety or efficacy of CorePharma's drug product. In addition, as long as Cmax passes

the BE limit of 80.00%-125.00% requirement, it does not raise additional concerns if the upper bound goes beyond the SbF threshold.

2) The ANDA 76772/76655 submitted by Watson/Actavis, is a case similar to the current ANDA, where the fasting BE study had SbF failure for its AUC_{3-7} and C_{max}: The value of $\frac{H}{\sigma_D^2}$ for AUC_{3-7} (0.05098) and C_{max} (0.05539) for the fasting study for ANDA 76772/76655, is significantly higher than that of the associated PK metrics for the current ANDA (AUC_{4-8}= 0.03063; C_{max}=0.03441). Yet, the Watson studies were found to be adequate and got approved.

3) The metrics of AUC_{4-8} and C_{max} are considered as "low-risk" metrics, since these two metrics were not indicated as a source of concern for the complaints about generic Concerta that triggered the Concerta BE guidance revision. These metrics were also not identified as directly needing additional control in the TSI.

- Based on the above information, the fed BE study (No. ARL/14/695) is now considered **adequate**.

4 DEFICIENCY COMMENT

None

5 RECOMMENDATION

1. The Division of Bioequivalence III (DBIII) accepts the fasting BE study (Study No. ARL/14/694) conducted by CorePharma, LLC on its Methylphenidate Hydrochloride Extended- Release Tablets USP, 54 mg (lot # SB69900301) comparing it to Janssen Pharmaceuticals Inc.'s Concerta® (methylphenidate HCl) Extended-Release Tablets, 54 mg (lot # 13KG402).

2. The DBIII accepts the fed BE study (Study No. ARL/14/695) conducted by CorePharma, LLC on its Methylphenidate Hydrochloride Extended- Release Tablets USP, 54 mg (lot # SB69900301) comparing it to Janssen Pharmaceuticals Inc.'s Concerta® (methylphenidate HCl) Extended-Release Tablets, 54 mg (lot # 13KG402).

3. The formulations for the test product, 18 mg, 27 mg and 36 mg strengths are proportionally similar to the 54 mg strength of the test product which underwent BE testing. The dissolution testing also demonstrated dissolution similarities among all the strengths of the test product. Therefore, the DBIII deems the 18 mg, 27 mg and 36 mg strengths of the test product, Methylphenidate Hydrochloride

Extended-Release Tablets, bioequivalent to their corresponding strengths of the reference product under the 21 CFR 320.24(b)(6).

6 APPENDIX

6.1 Attachments[10]

Office of Generic Drugs
DQMM/ORS/OGD CONSULT REVIEW

To:	Sung-Yong Hwang, Ph.D Through Nilufer M. Tampal, Ph.D Director, Division of Bioequivalence III Office of Generic Drugs Center for Drug Evaluation and Research
Re:	DBIII Request for Consultation: ANDA 208607
Consult No:	NA
Drug Product:	Methylphenidate HCl ER Tablets 18 mg, 27 mg, 36 mg, and 54 mg
Sponsor:	CorePharma, LLC
Original Submission:	04/18/2016
Date of Consult Request:	11/20/2016
Date of Review:	01/05/2017
Consultant:	Lili Pan, Ph.D., DQMM/ORS/OGD
Through:	Andrew Babiskin, Ph.D., DQMM/ORS/OGD Liang Zhao, Ph.D., Director, DQMM/ORS/OGD

Reason for Consultation

CorePharma, LLC submitted ANDA 208607 seeking the approval for 18mg, 36mg, 54mg, and 72mg Methylphenidate (MPH) Hydrochloride (HCl) Extended Release (ER) Tablets, referencing Janssen Pharmaceuticals, Inc.'s Concerta (MPH HCl) ER Tablets (NDA 021121). In the submission dated April 18, 2016, the firm submitted bioequivalence (BE) studies with results of fasting and fed comparing the test product MPH HCl ER Tablets, 54mg, to the corresponding reference product, Janssen Pharmaceuticals, Inc's Concerta ER Tablets, 54mg. The BE studies were completed following the current revised draft guidance (revised November 2014) on MPH HCl ER Tablets.

[10] GDRP, ANDA 208607, Consult Review for ANDA 208607_Final.docx, Andrew Babiskin, Date Completed: 01/09/2017

The 90% confidence intervals (CI) for all the five pharmacokinetic (PK) parameters - three partial AUC ($AUC_{0\text{-}T1}$, $AUC_{T1\text{-}T2}$, $AUC_{T2\text{-}T3}$) metrics in addition to the traditional ($AUC_{0\text{-}\infty}$ and C_{max}) metrics - are within the acceptable BE limits of 80%-125% for both fasting and fed BE studies. In addition, the fasting BE studies also met the additional assessment for subject-by-formulation (SbF) interaction variance component (σ_D^2), for all the five PK metrics. Hence, the fasting BE study is acceptable.

However the fed BE study (No. ARL-14695) is questionable since the upper 95% confidence bound for the SbF interaction variance component σ_D^2, $H_{\sigma_D^2}$, exceeds 0.03 for the PK metrics of C_{max} and $AUC_{4\text{-}8}$, from both the reviewer and the firm's calculations.

Based on the above information, the DBIII seeks ORS's inputs on the acceptability of the fed BE study due to the failure to meet the BE requirement for the SbF interaction variance.

Executive Summary

In the submitted fasting and fed BE studies from CorePharma comparing their proposed generic product to Concerta, the studies passed all the currently recommended five BE metrics in the average BE (ABE) evaluation, all of which were associated with tight 90% CIs. However, in the SbF evaluation, the fed state failed in C_{max} and $AUC_{4\text{-}8}$ metrics with values right above the value 0.03 (the recommended allowance) for $H_{\sigma_D^2}$, while most of the remaining metrics of both fed and fasting states were far below this allowance. In the working group to revise the BE guidance, these two metrics were not indicated as a source of concern for the complaints about generic Concerta that triggered the Concerta BE guidance revision. In fact, later fully replicate studies conducted with these problematic products did not show evidence of a SbF issue with C_{max} and the middle pAUC. As a final point, Watson/Actavis (ANDA 76772/76655) submitted fully replicate studies against Concerta, where the $H_{\sigma_D^2}$ values for C_{max} and $AUC_{3\text{-}7}$ in the fasting state were above 0.03 and far higher than the value observed from CorePharma for C_{max} and $AUC_{4\text{-}8}$ in the fed state. The Watson studies were found to be adequate based upon similar rationale as above. With all these considerations, DQMM recommends that the results of CorePharma fully-replicated studies be found acceptable.

Summary of BE Guidance for MPH ER Tablets and SbF Criteria

In November 2014, FDA released a revised BE guidance on Methylphenidate HCl ER Tablet.[11] The revision was done to solve the Tracked Safety Issue (TSI) in response to

the lack of efficacy found in post-market reporting for the approved Concerta generics by Kudco (ANDA 091695) and Mallinckrodt (ANDA 202608). In the new BE guidance, the *in vivo* BE studies are recommended with evaluation of the test-to-reference (T/R) ratio and subject-by-formulation (SbF) interaction variance (σ_D^2) of: (1) $AUC_{0-\infty}$, AUC_{0-3}, AUC_{3-7}, AUC_{7-12}, and C_{max} for fasting conditions; and (2) $AUC_{0-\infty}$, AUC_{0-4}, AUC_{4-8}, AUC_{8-12}, and C_{max} for fed conditions.

For the BE studies under both fasting and fed conditions, the acceptability criteria for T/R ratio is that the 90% CI falls within the standard BE limits of 80-125%. For the SbF evaluation, the 95% upper confidence bound of σ_D^2 ($^H\sigma_D^2$) is calculated and "as per APPENDIX A in the FDA 2001 bioequivalence guidance, the recommended allowance for σ_D^2 is 0.03". It does not clearly state that whether the test allowance is for point estimate or the upper bound of σ_D^2.

In fact, σ_D^2 is a component from the test of IBE in the 2001 BE guidance.[12] The recommended allowance 0.03 is "associated with the percentage of individuals whose average T to R ratios lie outside 80%-125%." When σ_D=0.1741, ~20% of the individuals would have their average ratios outside80-125%.[13] A thorough comparison of σ_D measures *vs.* proportion of individuals outside 80-125% was provided by Hauck, *et.al.* in 2000. [14]In the full aggregate IBE test, σ_D^2 is one of the three major components. The determination of IBE limit is based on the consideration of average BE criterion and the addition of variance terms to the individual BE criterion:

$$\theta_I = \frac{(ln1.25)^2 + \varepsilon_I}{\sigma_{W_0}^2}$$

Here ε_I considers both σ_D^2 and the difference of within-subject variabilities ($\sigma_{WT}^2 - \sigma_{WR}^2$). The recommended allowance of ε_I is 0.05, with 0.03 for σ_D^2 and 0.02 for ($\sigma_{WT}^2 - \sigma_{WR}^2$). The 0.03 allowance for σ_D^2 is equivalent to 20% of individuals outside BE limits. Therefore, a test product could still pass the IBE test even though the

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[11] Draft Guidance on Methylphenidate Hydrochloride (RLD: Concerta, N21121) http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm320007.pdf

[12] Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001, http://www fda.gov/downloads/Drugs/.../Guidances/ucm070244.pdf

[13] Chen, Mei-Ling, and Lawrence J. Lesko. "Individual Bioequivalence Revisited." Clinical pharmacokinetics 40.10 (2001): 701-706.

[14] Hauck, Walter W. *et.al.* "Subject-by-Formulation Interaction in Bioequivalence: Conceptual and Statistical Issues." Pharmaceutical research 17.4 (2000): 375-380.

corresponding BE metrics fail in SbF test (σ_D^2 >0.03), if they have small T/R ratios (tight 90% CI windows), or if their within-test and within-reference variability differences are small (($\sigma_{WT}^2 - \sigma_{WR}^2$) < 0.02). That is to say, for the IBE criteria it allows >20% of individuals outside the BE limits (σ_D^2 >0.03), while in the Concerta BE guidance it strictly requires <20% of the individuals outside the BE limits (σ_D^2 <0.03).

Summary of DBIII Review of ANDA 208607

CorePharma, LLC submitted in their application ANDA 208607 the results of BE studies comparing their generic version of MPH HCl ER Tablets, 54 mg, to the corresponding reference product, Janssen Pharmaceutical Inc.'s Concerta ER Tablets, 54 mg. The application includes waiver requests for the lower strengths, 18 mg, 27 mg, and 36 mg of the test product.

(b) (4)

(b) (4) The *in vivo* BE studies were done under both fasting and fed states in healthy male and female subjects, conducted as a single-dose, four-period, two-sequence, replicated crossover study, as per the current revised draft guidance on MPH HCl ER Tablets referencing Concerta. Table 1 provides the results of the ABE studies for both fasting and fed states and Figure 1 provides the mean PK curves under both study conditions. Since the within-reference standard deviation (S_{WR}) are all within a range of 0.14~0.19 and well below the 0.294 regulatory limit for the highly-variable drugs (HVD), reference-scaled ABE (RSABE) for HVDs does not apply and the 90% CI must be between 80-125% for the PK metric evaluation.

Table 1. ABE results for studies ARL/14/694 (fasting) and ARL/14/695 (fed). The results are reviewer-calculated and provided by DBIII. The BE calculations were performed in Phoenix. *PE* represents the point estimate, *LL* and *UL* represent the lower and upper limits of the 90% CI of the metrics respectively.

Metric	*PE*	*LL*	*UL*
Fasting			
$AUC_{0-\infty}$	94.36	91.72	97.08
AUC_{0-3}	104.48	100.75	108.35
AUC_{3-7}	112.73	108.92	116.68
AUC_{7-12}	86.75	83.94	89.65
C_{max}	101.68	97.73	105.78
Fed			

$AUC_{0-\infty}$	97.22	94.34	100.20
AUC_{0-4}	98.30	94.49	102.26
AUC_{4-8}	107.26	102.56	112.18
AUC_{8-12}	91.02	87.71	94.46
C_{max}	116.90	111.32	122.76

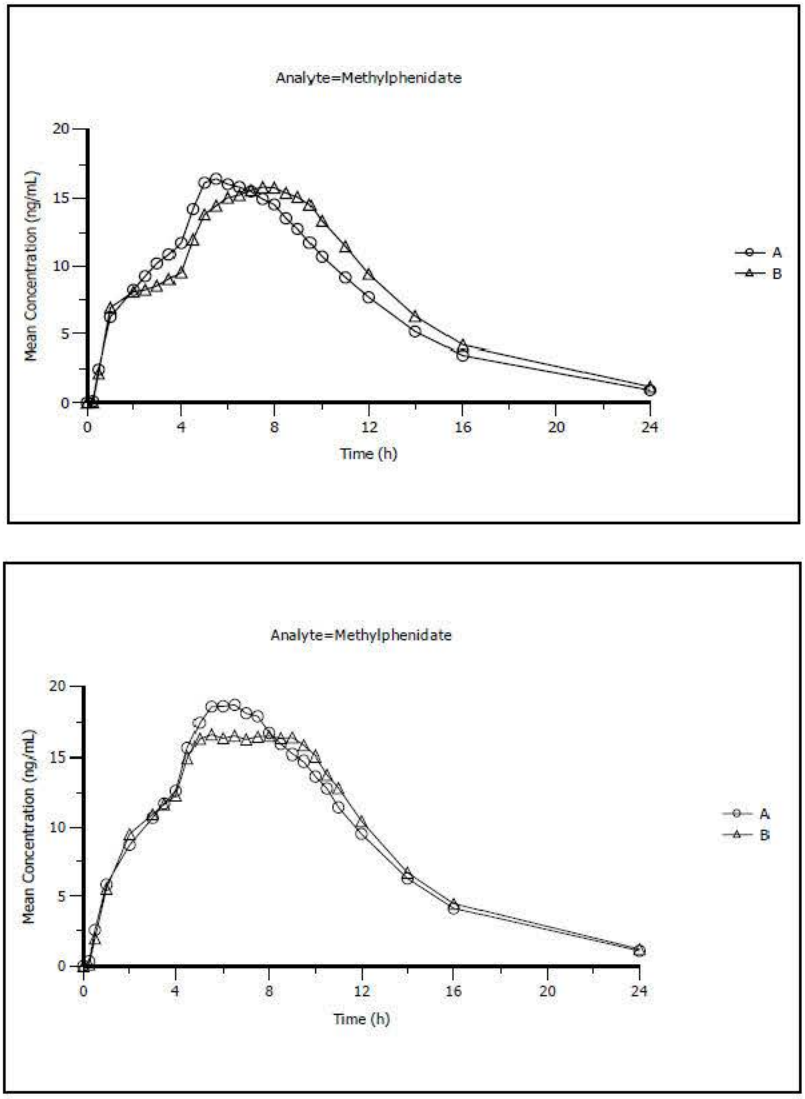


Figure 1. Mean MPH concentrations versus time for CorePharma/test formulation (A) and Concerta/reference formulation (B) in the fasting (upper panel) and fed (lower panel) states.

The SbF results are given in Table 2 for both fasting and fed studies. The within-reference standard deviation s_{WR}, within-test standard deviation s_{WT}, *SbF* interaction variance component σ_D^2, and its 95% upper confidence bound $H_{\sigma_D^2}$ are provided.

Table 2. *SbF* results for fasting (ARL/14/694) and fed (ARL/14/695) studies. The results are reviewer calculated and provided by DBIII. The SbF calculations are performed in SAS. DBIII results were confirmed by DQMM's independent analysis.

Metric	s_{WR}	s_{WT}	σ_D^2	$H_{\sigma_D^2}$
Fasting				
$AUC_{0-\infty}$	0.168373	0.099611	-0.00595	0.000867117
AUC_{0-3}	0.164283	0.143203	0.003565	0.016008448
AUC_{3-7}	0.152035	0.164159	-0.00167	0.009294078
AUC_{7-12}	0.187577	0.11179	-0.00284	0.007315087
C_{max}	0.16211	0.193185	-0.00083	0.013626058
Fed				
$AUC_{0-\infty}$	0.150267	0.151495	-0.00254	0.005990668
AUC_{0-4}	0.15843	0.18801	0.009424	0.025238303
AUC_{4-8}	0.142807	0.24123	0.010484	0.030631957
AUC_{8-12}	0.162272	0.202141	-0.00061	0.013096282
C_{max}	0.154211	0.272251	0.010253	0.034414719

In the fasting studies, $H_{\sigma_D^2}$ for all five metrics are below the recommended 0.03 allowance. However in the fed studies, AUC_{4-8} and C_{max} are borderline above 0.03; however, the point estimates of σ_D^2 for all metrics fall below 0.03. According to current BE guidance for MPH HCl ER Tablets, the σ_D^2 evaluation is recommended for ensuring the switchability between test and reference products. Therefore, the SbF failures initiated the consultation request from DBIII to DQMM. In the consultation, it is noted that the firm provided different values for each parameter, although the results also show failures on AUC_{4-8} (0.0305) and C_{max} (0.0347) based on the point estimate of σ_D^2 per firm's statistical reports.

ORS Response

Question: Based on the above information, the DBIII seeks ORS confirmation from DQMM for whether the fed BE study (No. ARL/14/695) should be considered unacceptable, due to the failure to meet the BE requirement for SbF interaction variance.

Based on an extensive analysis of the fed, fully-replicated CorePharma BE study, we concluded that the BE results acceptable. After receiving post-market

complaints for two Concerta generics (by Mallinckrodt and Kudco) and initiating a TSI, OGD convened a working group that resulted in the revising of the BE guidance for generic products referencing Concerta. Since a number of complaints centered on the lack of duration of efficacy, particularly after 7 hours, additional pAUC metrics were included in the guidance to assess MPH concentrations in the associated time periods. There were also complaints related to early onset from the generics and the SbF was included in the guidance primarily as a way of controlling the variance for the early pAUCs. The detailed history and summaries of the revision could be found in the Concerta BE guidance revision memo[15] and the review of ANDA 76772/76655.[16]

The ANDA 76772/76655 submitted by Watson/Actavis, is a case similar to the CorePharma case, where the BE studies had SbF failure on its fasting AUC_{3-7} and C_{max}. Additionally, the 95% upper confidence bonds of the SbF interaction variance, are higher than that for CorePharma – 0.05098 for AUC_{3-7} and 0.05539 for C_{max}. In Watson's case, the two problematic metrics would be able to pass full IBE and NTI criteria and it was never the intention of the Concerta guidance to place criteria more stringent than that for NTI. In addition, the review concluded that C_{max} and AUC_{3-7} were not metrics of primary concern during the TSI and were not identified as needing additional level of control. As a result, the BE studies for Watson were found to be adequate, regardless of the SbF result.

In BE revision discussions, C_{max} andAUC_{4-8} (and its associated fasting metric of AUC_{3-7}) were not included as metrics needing additional control (i.e., variance control and/or point estimate restriction). In fact, the original Mallinckrodt study of two-way crossover fasting state had a similar case with lower bound close to the threshold, and a significant amount of individuals are observed to be outside 80-125% for C_{max}.[17] Furthermore, in the other submission of the Concerta generics by Actavis (ANDA 76772/76655) as mentioned above, its C_{max} for fasting state actually had higher SbF upper confidence ($H_{\sigma_D^2}$=0.05539), yet still got approved. This means that for C_{max}, as long as these metrics pass the BE limit 80-125% requirement, it does not raise additional concerns if the upper bound goes beyond the SbF threshold. It should be noted that since the Concerta guidance revision, Kudco conducted new fully-replicate BE studies under fasting and fed conditions and ORS sponsored its own fasting fully-replicate BE study comparing the Mallinckrodt product to Concerta. For the Kudco studies, all metrics had

[15] Concerta guidance internal, "Memo: Revision of the Draft Bioequivalence Guidance for Methylphenidate Hydrochloride Extended-Release Tablets", http://panorama.fda.gov/project/view?ID=53ff812b000871179208c9f0461b1dc7

[16] Babiskin, Andrew. *et.al.* "OGD Science Staff Consult Review: Response to DBIII Request ANDA 076772 ORS Consult Request from DBIII", http://panorama.fda.gov/issue/view?ID=55ce50bc00103d3c5ce4943a05b43ce8

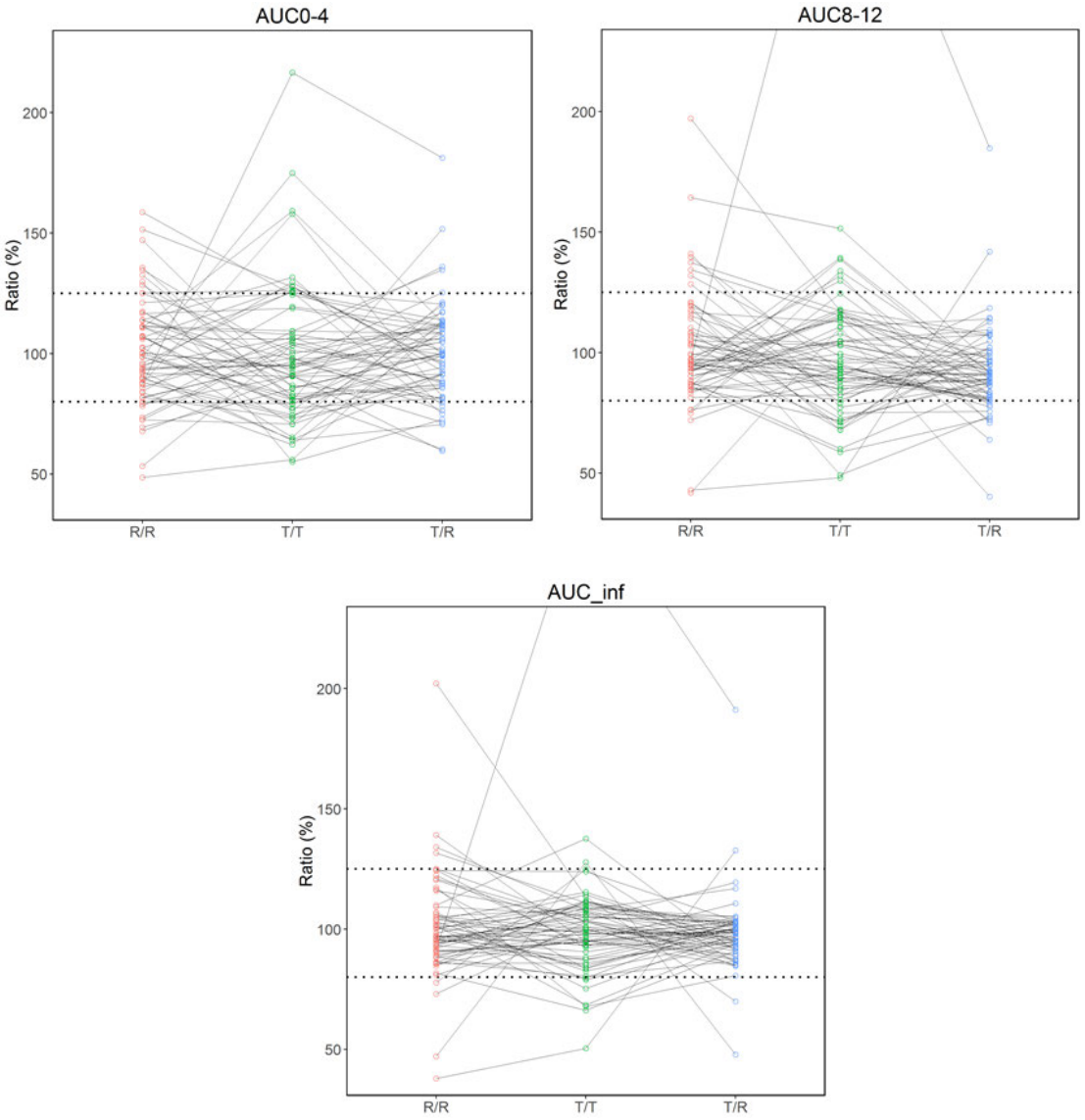
[17] See the previously mentioned ANDA 76772/76655 review

$H_{\sigma_D^2}$ values below 0.03. For the Mallinckrodt study, only $AUC_{7\text{-}12}$ had an upper bound value above 0.03 ($H_{\sigma_D^2}$=0.04782). These results demonstrates that for the complaints associated with the Mallinckrodt and Kudco products, they are not probably due to SbF issues with C_{max} and the middle pAUCs.

Recommendation: **DQMM recommends that the CorePharma fed study ARL/14/695 be found acceptable.** While the estimated 95% upper confidence bound for the subject-by-formulation interaction variance for $AUC_{4\text{-}8}$ and C_{max} in the fed state is greater than the recommended allowance of 0.03, we find the fed study still be acceptable for the following reasons:

4. The fed study passes full NTI criteria for $AUC_{4\text{-}8}$, and only the variance comparison test for C_{max}. Even though C_{max} does not pass the tighter BE limit due to its high T/R point estimate, results still indicate that C_{max} has very tight 90% CI interval.
5. The $H_{\sigma_D^2}$ values above 0.03 for C_{max} and $AUC_{4\text{-}8}$ are significant less than the $H_{\sigma_D^2}$ values that were ultimately found acceptable for the same associated metrics in the Watson product (ANDA 76772/76655).
6. The metrics of $AUC_{4\text{-}8}$ and C_{max} are "low-risk" metrics since they were neither associated with the complaints for Mallinckrodt and Kudco generics triggering the TSI, nor were they identified as directly needing additional control in the TSI.

Appendix A. R/R, T/T, and T/R scatterplots for $AUC_{0\text{-}4}$, $AUC_{8\text{-}12}$, and $AUC_{0\text{-}\infty}$ (AUC_inf) in fed, fully-replicated CorePharma BE study (ARL/14/695). Lines connect the ratios with the same individual.


AUC0-4
AUC8-12
AUC_inf
Ratio (%)
200
150
100
50
R/R
T/T
T/R

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 208607

APPLICANT CorePharma, LLC

DRUG PRODUCT: Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg

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

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if additional concerns raised by chemistry, manufacturing and controls, microbiology, labeling, other scientific or regulatory issues or inspectional results arise in the future. Please be advised that these concerns may result in the need for additional bioequivalence information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

6.2 Outcome Page

Completed Assignment for 208607 ID: 30009

Reviewer: Hwang, Sung-Yong **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg (Addendum, consult res. review)

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
30009	4/18/2016	BIO	Consult Review (For Consults to Other Office) [1]	1	1
30009	4/18/2016	Parallel	Review of the Consult Response and Formal Consult to DB [1]	1	1
30009	1/12/2017	BIOQUALITY	Quality Assessment [1-5]	4.5	4.5
				Total:	6.5

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	208607			
Drug Product Name	Methylphenidate Hydrochloride Extended-Release Tablets USP			
Strength(s)	18 mg, 27 mg, 36 mg and 54 mg			
Applicant Name	CorePharma, LLC			
Applicant Address	215 Wood Avenue Middlesex, New Jersey 08846 USA			
Applicant's Point of Contact and Mailing Address	Kimberly D. Ernst 100 Somerset Corporate Blvd. Suite 3000 Bridgewater, New Jersey 08807 USA			
Contact's Telephone Number	732-667-6009			
Contact's Fax Number	732-805-5643			
Contact's Email Address	kimberly.ernst@impaxlabs.com			
Original Submission Date(s)	04/18/2016 05/31/2016 (Response to the filing comments)			
Submission Date(s) of Amendment(s) Under Review	N/A			
Reviewer	Sung-Yong Hwang, Ph.D.			
Secondary Reviewer	Suman Dandamudi, Ph.D.			
Tertiary Reviewer	Ke Ren, Ph.D.			
Study Number(s)	ARL/13/061	ARL/13/062	ARL/13/547	ARL/13/548
Study Type(s)	Fasting (pilot)	Fed (pilot)	Fasting (failed extra study)	Fed (failed extra study)
Strength(s)	1 x 54 mg	1 x 54 mg	1 x 54 mg	1 x 54 mg
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd.			
Clinical Site Address	A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai -400 709, Maharashtra, INDIA.			
Analytical Site	(b) (4)			
Analytical Site Address				
Study Number(s)	ARL/14/694		ARL/14/695	
Study Type(s)	Fasting (pivotal)		Fed (pivotal)	

Strength(s)	1 x 54 mg	1 x 54 mg
Clinical Site	Accutest Research Laboratories (I) Pvt. Ltd.	
Clinical Site Address	A-31, M.I.D.C., T.T.C., Industrial Area, Khairane, Navi Mumbai -400 709, Maharashtra, INDIA.	
Analytical Site	(b) (4)	
Analytical Site Address		
OSIS status	**Backlog, Year 1 and Year 2 ANDAs** **☐ Pending** **☐ Complete** **☐ N/A (Waiver)**	**Post October 1, 2014 ANDAs** **☐ To Be Determined by OSIS** **☐ Pending For Cause Inspection** **☒ Complete**
Waiver	**☐ Granted ☐ Tentatively granted ☒ Not granted ☐ N/A**	
QC Dissolution	**☒ Pending ☐ Adequate ☐ Inadequate**	
Formulation	**☒ Adequate ☐ Inadequate**	
Will Response to CR Result in a Reformulation?	**☐ Possibly ☒ No ☐ N/A**	
Deficiency Classification	**☐ Major** **☐ Minor** **☒ N/A (pending consult response from ORS)**	
Overall Review Result	**☐ Adequate ☒ Inadequate (pending consult response from ORS)**	
Revised/New Draft Guidance Generated as Part of Current Review	**☐ YES ☒ NO**	

Bioequivalence study tracking/supporting document #	**Study/test type**	**Strength**	**Review Result**
1, 2	**Fasting**	**54 mg**	**☒ Adequate ☐ Inadequate**
1, 2	**Fed**	**54 mg**	**☐ Adequate ☒ Inadequate**
1, 2	**Waivers**	**18 mg, 27 mg and 36 mg**	**☐ Adequate ☒ Inadequate**

1 EXECUTIVE SUMMARY

This application contains the results of fasting and fed bioequivalence (BE) studies comparing a test product, CorePharma, LLC's Methylphenidate Hydrochloride Extended-Release Tablets USP, 54 mg, to the corresponding reference product, Janssen Pharmaceuticals Inc.'s Concerta® (methylphenidate HCl) Extended Release Tablets, 54 mg. The application includes waiver requests for the lower strengths, 18 mg, 27 mg and

36 mg of the test product. Each of the BE studies was designed as a single-dose, four-period, two-sequence, replicate crossover study in healthy male and female subjects. The results are summarized in the tables below.

Fasting study-Reviewer Calculated

Methylphenidate HCl (No of subjects completed=58) Dose (1 x 54 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study (4002731, ARL/14/694)							
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
Cmax (ng/mL)	17.16	58	16.87	58	101.68	97.73	105.78
AUC0-3 (hr *ng/mL)	18.24	58	17.45	58	104.48	100.75	108.35
AUC3-7 (hr *ng/mL)	54.43	58	48.28	58	112.73	108.92	116.68
AUC7-12 (hr *ng/mL)	56.14	58	64.72	58	86.75	83.94	89.65
AUC0-∞ (hr *ng/mL)	171.95	58	182.23	58	94.36	91.72	97.08

Fasting study: Subject by Formulation Interaction Variance-Reviewer Calculated

Fasting Bioequivalence Study No. ARL/14/694					
Pharmacokinetic Parameter (s)	**sigmaWT**	**sigmaWR**	**sigmaD2**	**SigmaD2upper***	**Study Outcome**
AUC0-inf	0.099611	0.168373	-0.00595	0.000867117	Pass
AUC0-3	0.143203	0.164283	0.003565	0.016008448	Pass
AUC3-7	0.164159	0.152035	-0.00167	0.009294078	Pass
AUC7-12	0.11179	0.187577	-0.00284	0.007315087	Pass
Cmax	0.193185	0.16211	-0.00083	0.013626058	Pass

* SigmaD2upper = 95% upper confidence bound

Fed study-Reviewer Calculated

Methylphenidate HCl (No of subjects completed=70) Dose (1 x 54 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (4002730, ARL/14/695)							
Parameter	Test	N	RLD	N	Ratio	90% C.I.	
Cmax (ng/mL)	20.99	70	17.96	70	116.90	111.32	122.76
AUC0-4 (hr *ng/mL)	29.29	70	29.80	70	98.30	94.49	102.26
AUC4-8 (hr *ng/mL)	65.08	70	60.68	70	107.26	102.56	112.18
AUC8-12 (hr *ng/mL)	49.20	70	54.05	70	91.02	87.71	94.46
AUC0-∞ (hr *ng/mL)	193.34	70	198.86	70	97.22	94.34	100.20

Fed study: Subject by Formulation Interaction Variance-Reviewer Calculated

Fed Bioequivalence Study No. ARL/14/695					
Pharmacokinetic Parameter (s)	**sigmaWT**	**sigmaWR**	**sigmaD2**	**SigmaD2upper***	**Study Outcome**
AUC0-inf	0.151495	0.150267	-0.00254	0.005990668	Pass
AUC0-4	0.18801	0.15843	0.009424	0.025238303	Pass
AUC4-8	0.24123	0.142807	0.010484	0.030631957	Fail
AUC8-12	0.202141	0.162272	-0.00061	0.013096282	Pass
Cmax	0.272251	0.154211	0.010253	0.034414719	Fail

* SigmaD2upper = 95% upper confidence bound

The 90% confidence intervals for all the pharmacokinetic (PK) parameters including the partial AUC metrics are within the acceptable BE criteria of 80.00%-125.00% for both fasting and fed BE studies. In addition, the fasting BE study also met the BE requirement for subject by formulation interaction variance for all the PK parameters. Thus the fasting BE study (No. ARL/14/694) is acceptable.

However, the fed BE study (No. ARL/14/695) is unacceptable due to the PK parameters, pAUC4-8 and Cmax failing to meet the BE requirement for subject by formulation interaction variance (exceed 0.03). The Office of Research and Standards (ORS) has previously conducted the extensive research on the BE methods for this current drug product, and also prepared the currently posted draft guidance on the Methylphenidate Hydrochloride Extended Release Tablets. Thus Division of Bioequivalence III (DBIII) will consult with the ORS for an opinion regarding the unacceptability of the fed BE study due to the failure of Cmax and $pAUC_{4-8}$ to meet the BE requirement for subject by formulation interaction variance.

The firm also submitted the results of two pilot BE studies (fasting study No. ARL/13/061; fed study No. ARL/13/062). Each of these pilot studies was designed as a single-dose, four-period, four-sequence crossover study and conducted with three different test lots (Test A, B, and C lot). The pilot BE studies failed to meet the BE requirements listed in the current BE guidance (please refer to Section 4.4.1 Additional Studies for details). Since the formulations for all three test lots used in the pilot studies are not considered the same as that of bio-lot used in the pivotal BE studies, the reviewer did not evaluate these pilot BE studies in the current review.

Additionally, the firm also submitted the results of two extra BE studies (fasting study No. ARL/13/547; fed study No. ARL/13/548). Each of these extra studies was designed as a single-dose, three-period, six-sequence crossover study and conducted with two different test lots (Test A and B lot). The formulation of the Test B lot is the same as that of bio-lot used in the pivotal BE studies. Whereas the extra BE studies conducted with

Test A lot failed to meet the BE requirement listed in the current BE guidance, the extra BE studies conducted with Test B lot met the BE requirements (please refer to Section 4.4.1 Additional Studies for details). Since the formulation for the Test A lot used in the extra studies is not considered the same as that of bio-lot used in the pivotal BE studies, The reviewer did not evaluate the extra BE studies in the current review.

The dissolution testing is pending review. The dissolution testing will be reviewed separately by the biopharmaceutics quality reviewer in the Office of New Drug Products (ONDP) for establishing the quality control method and specifications for batch release.

The firm provided the comparative dissolution data of the test and reference products in three additional pH media (pH 1.2, 4.5 and 6.8 buffers). The firm's dissolution data showed no evidence of dose dumping.

The firm also submitted data for in vitro alcohol dose-dumping testing using various concentrations of ethanol (5, 20 and 40%) in the dissolution medium. The firm's dissolution data showed that % drug release between the test and reference products are similar in 40% ethanol at 2 hrs. However, it is noted by the reviewer that in 20% alcohol, the mean % difference between with and without alcohol for all strengths of the test product is higher than that of the corresponding reference product. However, the reviewer considers it acceptable for the following reasons:

- The mean % difference between the 20% alcohol and without alcohol between the test and reference product is less than 10%.
- The mean % difference for all strengths of test product in 20% alcohol is less than 18% of the maximum mean % difference observed for all strengths of the reference product in 40% alcohol.

Therefore, the alcohol dose dumping results of the test product is acceptable.

The formulations for the test product, 18 mg, 27 mg, and 36 mg strengths are proportionally similar to the 54 mg strength of the test product which underwent BE testing. The dissolution testing also demonstrated dissolution similarities among all the strengths of the test product. However, at this time the lower strengths, 18 mg, 27 mg, and 36 mg of the test product, **are not considered acceptable** for the waiver request pending consult response from ORS regarding the unacceptability of the fed BE study due to the failure to meet the BE requirement for subject by formulation interaction variance for Cmax and $pAUC_{4-8}$.

Office of Study Integrity and Surveillance (OSIS) Inspection:

Since the current ANDA is a GDUFA year 4 applications, the final inspection status of clinical and analytical sites will be determined by the OSIS. However, the Division of Generic Drug Bioequivalence (DGDBE) within the OSIS recommends accepting data without on-site inspection of both the clinical and analytical sites[1]. The rationale for this

[1] GDRP for ANDA 208607: Bioanalytical and clinical PK/PD sites,

decision is noted as follows: OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI). In addition, the study submitted in the current ANDA does not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer.

The BE portion of the application is **inadequate** pending consult response from ORS.

NOTE TO REGULATORY PROJECT MANAGER (RPM): The review is pending consult response from ORS.

http://panorama.fda.gov/task/view?ID=5717ab6a005c9582e3f3056531804344

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3 SUBMISSION SUMMARY

3.1 Drug Product Information[2]

Test Product	Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg
Reference Product	Concerta®(methylphenidate HCl) Extended-Release Tablets, 54 mg*
RLD Manufacturer	Janssen Pharmaceuticals Inc.
NDA No.	021121
RLD Approval Date	December 8, 2000 (54 mg) August, 1, 2000 (18 mg and 36 mg) April 1, 2002 (27 mg)

*Also available in 18 mg, 27 mg and 36 mg strengths

3.2 PK/PD Information[3]

Most recent RLD label (provide embedded document) Please check if an NG tube study is needed.	RLD label (Concerta).pdf An NG tube study is not needed as per the RLD label.
Indication	CONCERTA® is a CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65.
Boxed warning	CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence, with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underling disorder that may require follow-up.
Bioavailability	Methylphenidate is readily absorbed. Following oral administration of CONCERTA®, plasma methylphenidate concentrations increase rapidly, reaching an initial maximum at about 1 hour, followed by gradual ascending concentrations over the next 5 to 9 hours, after which a gradual decrease begins.
Food Effect	There were no differences in either the pharmacokinetics or the pharmacodynamic performance of CONCERTA® when administered after a high-fat breakfast. There is no evidence of dose dumping in the presence or absence of

[2] Electronic Orange Book, Search word: Concerta, N021121, Last accessed: 10/13/2016.
[3] Drugs@FDA, Search word: Concerta, NDA# 021121, RLD label approved date: 04/17/2015, Last accessed: 10/13/2016.

	food.
Tmax	Mean times to reach peak plasma concentrations across all doses of CONCERTA® occurred between 6 and 10 hours.
Metabolism	In humans, methylphenidate is metabolized primarily by de-esterification to PPAA, which has little or no pharmacologic activity. In adults the metabolism of CONCERTA® once daily as evaluated by metabolism to PPAA is similar to that of methylphenidate three times daily. The metabolism of single and repeated once-daily doses of CONCERTA® is similar.
Excretion	After oral dosing of radiolabeled methylphenidate in humans, about 90% of the radioactivity was recovered in urine. The main urinary metabolite was PPAA, accounting for approximately 80% of the dose.
Half-life	The half-life of methylphenidate in adults and adolescents following oral administration of CONCERTA® was approximately 3.5 hours.
Maximum Daily Dose	72 mg
Drug Specific Issues	**WARNING: DRUG DEPENDENCE** CONCERTA® should be given cautiously to patients with a history of drug dependence or alcoholism. Chronic abusive use can lead to marked tolerance and psychological dependence with varying degrees of abnormal behavior. Frank psychotic episodes can occur, especially with parenteral abuse. Careful supervision is required during withdrawal from abusive use since severe depression may occur. Withdrawal following chronic therapeutic use may unmask symptoms of the underlying disorder that may require follow-up.

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance	 Draft Guidance on Methylphenidate Hydı	
Summary of OGD or DB History	Approved ANDAs:	Yes, multiple[4]
	Pending ANDAs:	Yes, multiple[4]
	Controls:	Yes, Multiple[5] (CC# 49819 from current applicant)
	Protocols:	Yes, Multiple[6] (not from current applicant)

[4] DARRTS and GDRP, Application search for "methylphenidate", Last accessed: 10/11/2016.
[5] OGD Division of Bioequivalence Controls Documents Tracking and GDRP, Last accessed: 10/11/2016.
[6] OGD Division of Bioequivalence Protocols Tracking, Last accessed: 10/11/2016.

	Pending Citizen Petitions and other legal and regulatory issues: If yes, please comment.	☒ Yes ☐ No The drug product is listed in the OGD Policy Alert list (CP and TSI)[7].

3.4 Pre-Study Bioanalytical Method Validation (ARL/14/694 and ARL/14/695)

Information Requested	Data
Bioanalytical method validation report location	m 5.3.1.2.4
Analyte	Methylphenidate
Internal standard (IS)	Methylphenidate-D_3
Method description	(b) (4) Liquid-liquid extraction; (b) (4) LC-MS-MS; (b) (4)
Limit of quantitation	0.500 ng/mL
Average recovery of drug (%)	Ave- 104.21 %, %CV-7.86[#] HQC 101.94% (1.85%[#]) MQC 105.66% (2.10%[#]) LQC 105.04% (14.98%[#])
Average recovery of IS (%)	Ave-104.05%, %CV-2.99[#]
Standard curve concentrations (ng/mL)	0.500 to 50.0
QC concentrations (ng/mL)	1.50, 10.00, 40.0[##]
QC Intraday precision range (%)	1.2 to 3.1
QC Intraday accuracy range (%)	112.7 (LQC) to 114.8 (HQC) 94.2 (LLOQ)
QC Interday precision range (%)	4.2 to 5.1
QC Interday accuracy range (%)	104.7 to 106.0
Bench-top stability (hrs)	4 hours @ room temperature; 12 hours on ice
Stock stability (days)	203 days @ 4 °C; 22 hours @ room temperature
Processed stability (hrs)	73 hours @ room temperature
Freeze-thaw stability (cycles)	5 cycles @ room temperature; 5 cycles on ice
Long-term storage stability (days)	91 days @ -20 °C
Dilution integrity	250 ng/mL diluted 10-fold (Accuracy- 102.4%, %CV: 1.8)
Selectivity	No interfering peaks noted in blank plasma samples

[#] Average recovery and %CV calculated by the reviewer

[##] As per the firm's method validation report, the QCs considered for intraday and inter-day accuracy range were 1.50, 10 and 40 ng/ml. However, in the above summary table, the firm provided the QC concentrations as 1.5, 8.0 and 40 ng/ml[8]. The reviewer considers this as a typographical error and the firm will not be asked for the clarification

[7] DLRS policy updates in the link http://sharepoint fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx, search for "Methylphenidate", Last accessed: 10/11/2016.
[8] ANDA 208607, EDR 2, 05/31/2016, M.5.3.1.4, Fasting (and Fed) Bioanalytical Study-Method-Validation-Report, Pages 17 & 18 of 263.

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No (b) (4)
Is the same anticoagulant used in the pre-method validation study and BE sample analysis? **If not, was cross validation study conducted?**	☒ Yes ☐ No
Does the duration of the each of the LTSS stability parameters support the sample preparation/assay duration and clinical study sample storage temperature?	☒ Yes ☐ No
Was the % recovery consistent across QC concentrations?	☒ Yes ☐ No
Was the pre-study validation of the bioanalytical method used for the pivotal bioequivalence studies acceptable?	☒ Yes ☐ No

Comments on the Pre-Study Method Validation:

- The long-term storage stability data of 91 days at -20°C are sufficient to cover the maximum storage period of the fasting (65 days at -15 °C to -35 °C) and fed (52 days at -15 °C to -35 °C) BE study samples.

- The firm used K_2-EDTA as anticoagulant for both pre-study method validation and BE study samples.

- The pre-study method validation is **adequate**.

3.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Fasting study (ARL/14/694)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. M/F) Type Age: Mean (Range)	Mean Parameters (± SD)								Study Report Location
					Cmax (ng/mL)	Tmax (h)*	AUC0-3 (h*ng/mL)	AUC3-7 (h*ng/mL)	AUC7-12 (h*ng/mL)	AUC∞ (h*ng/mL)	T1/2 (h)	Kel (h^{-1})	
4002731 ARL/ 14/694	A Randomized, Balanced, Open Label, Two-Treatment, Four-Period, Two-Sequence, Single Dose, Crossover, Fully Replicated Bioequivalence Study of Test Formulation of Methylphenidate HCl Extended-Release Tablets USP, 54 mg, CorePharma, LLC, versus Reference Product Concerta® (Methylphenidate HCl) Extended-Release Tablets, 54 mg, in Normal, Healthy, Adult, Male and Female Human Subjects under Fasting Conditions	A randomized, balanced, open label, two-treatment, four-period, two-sequence, single dose, fully replicated design, fasted crossover study	Test (T): Methyl-phenidate HCl Dose = 1 x 54 mg Extended-Release Tablet Oral [Lot #: SB69900301] Reference (R): Concerta® Dose = 1 x 54 mg Extended-Release Tablet Oral [Lot #: 13KG402]	58 healthy male (n=52) and female (n=6) subjects Mean age = 28.53 yr (20-39)	T: 18.1 ± 6.86 R: 17.6 ± 5.00	T: 6.00 (4.50-9.50) R: 7.50 (4.50-10.0)	T: 18.94 ± 5.383 R: 18.29 ± 5.483	T: 56.95 ± 18.41 R: 50.50 ± 14.50	T: 58.55 ± 17.64 R: 68.29 ± 21.03	T: 179.5 ± 55.61 R: 192.1 ± 59.65	T: 3.97 ± 0.81 R: 4.01 ± 0.67	Test 0.1822 ± 0.0384 Ref 0.1782 ± 0.0322	Module 5.3.1.2

* Median (range)

Fed study (ARL/14/695)

Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Dosage Form, Route) [Product ID]	Subjects (No. M/F) Type Age: Mean (Range)	Mean Parameters (± SD)								Study Report Location
					Cmax (ng/mL)	Tmax (h)*	AUC0-4 (h*ng/mL)	AUC4-8 (h*ng/mL)	AUC8-12 (h*ng/mL)	AUC∞ (h*ng/mL)	T1/2 (h)	Kel (h^{-1})	
4002730 ARL/ 14/695	A Randomized, Balanced, Open Label, Two-Treatment, Four-Period, Two-Sequence, Single Dose, Crossover, Fully Replicated Bioequivalence Study of Test Formulation of Methylphenidate HCl Extended-Release Tablets USP, 54 mg, CorePharma, LLC, versus Reference Product Concerta® (Methylphenidate HCl) Extended-Release Tablets, 54 mg, in Normal, Healthy, Adult, Male and Female Human Subjects under Fed Conditions	A randomized, balanced, open label, two-treatment, four-period, two-sequence, single dose, , fully replicated design, fed crossover study	Test (T): Methyl-phenidate HCl Dose = 1 x 54 mg Extended-Release Tablet Oral [Lot #: SB69900301] Reference (R): Concerta® Dose = 1 x 54 mg Extended-Release Tablet Oral [Lot #: 13KG402]	70 healthy male (n=66) and female (n=4) subjects Mean age= 28.97 yr (19-43)	T: 22.5 ± 10.0 R: 19.0 ± 7.46	T: 6.50 (1.00-12.00) R: 7.00 (4.50-11.0)	T: 31.17 ± 13.64 R: 31.51 ± 12.36	T: 69.75 ± 29.81 R: 63.76 ± 23.61	T: 53.58 ± 30.58 R: 57.57 ± 24.62	T: 208.5 ± 118.3 R: 211.7 ± 98.92	T: 3.73 ± 0.65 R: 3.92 ± 0.65	Test: 0.1920 ± 0.0372 Ref: 0.1821 ± 0.0350	Module 5.3.1.2

* Median (range)

3.6 OSIS Status

Since the current ANDA is a GDUFA year 4 applications, the final inspection status of clinical and analytical sites will be determined by the OSIS. However, the Division of Generic Drug Bioequivalence (DGDBE) within the OSIS recommends accepting data without on-site inspection of both the clinical and analytical sites[9].

[9] GDRP for ANDA 208607: Bioanalytical and clinical PK/PD sites, http://panorama.fda.gov/task/view?ID=5717ab6a005c9582e3f3056531804344

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-dose Fasting Bioequivalence Study (pivotal)

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	**ARL/14/694**			
Study Title	A Randomized, Balanced, Open Label, Two-Treatment, Four-Period, Two-Sequence, Single Dose, Crossover, Fully Replicated Bioequivalence Study of Test Formulation of Methylphenidate HCl Extended-Release Tablets USP, 54 mg, CorePharma, LLC, versus Reference Product Concerta® (Methylphenidate HCl) Extended-Release Tablets, 54 mg, in Normal, Healthy, Adult, Male and Female Human Subjects under Fasting Conditions			
Study Type	☒In Vivo BE	☐In Vitro BE	☐Permeability	☐Other
Submission Location: Study Report	Module 5.3.1.2			
Validation Report	Module 5.3.1.4			
Bioanalytical Report	Module 5.3.1.4			
Clinical Site (Name, Address, Phone #, Fax #)	Accutest Research Laboratories (I) Pvt. Ltd. A-31, M.I.D.C, TTC Industrial Area Khairane, Navi Mumbai -400 709 Maharashtra, India Phone: 91.22.2778.0718/19/21 Fax: 91.22.2778.0720			
Principal Clinical Investigator (Name, Email)	Vivekananda Murthi, MBBS Vivekanand.Murthy@accutestindia.com			
Dosing Dates	Period 1: 25 December 2014 Period 2: 06 January 2015 Period 3: 14 January 2015 Period 4: 21 January 2015			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)			
Analysis Dates	06 February 2015 to 28 February 2015			
Principal Analytical Investigator (Name, Email)	(b) (4)			

Sample Storage: (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	(a) 65 days (b) -15 °C to -35 °C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	91 days @ -20 °C
LTSS Data Location	Module 5.3.1.4; Validation Report; [redacted] (b) (4) First Amendment to Report; Method Validation Tables, Table 10: Long Term Stability for Methylphenidate Extracted from Human EDTA Plasma; Page # 121 of 263

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	**A**	**B**
Product/Brand Name	Methylphenidate Hydrochloride Extended-Release Tablets, USP	CONCERTA® (Methylphenidate HCl) Extended-Release Tablets
Manufacturer	[redacted] (b) (4) Manufactured for: CorePharma, LLC 215 Wood Avenue Middlesex, NJ 08846	Manufactured by: Janssen-Cilag Manufacturing, LLC, Gurabo, PR 00778 or Alza Corp. Vacaville, CA 95688 Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560
Lot No.	SB69900301	13KG402
Manufacture Date	09/04/2014	N/A
Expiration Date	N/A	07/2015
Strength	54 mg	54 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	[redacted] (b) (4)	
Production Batch Size		
Potency	97.3%	101.5%
Content Uniformity (mean, SD)	96.3% (1.27)	N/A
Dose Administered	1 x 54 mg Tablet	1 x 54 mg Tablet
Route of Administration	Oral	Oral

Are the test and reference products expired at the time of study?	☐ Yes ☒ No

If Yes, please comment	
Is same bio-batch used in the dissolution and all BE studies? **If No, please comment**	☒ Yes ☐ No
Is the bio-batch size at least the recommended minimum of 100K or 10% of the production batch (whichever is greater) for oral solid dosage form? **If No, please comment**	☒ Yes ☐ No ☐ N/A
Is difference of the potency values for the Test and RLD within 5%? **If No, please comment**	☒ Yes ☐ No ☐ N/A

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 60 Dosed: • Period I: 60 • Period II: 57 • Period III: 57 • Period IV: 56 Completed: 54 (all 4 periods) Samples Analyzed: 58* Statistically Analyzed: 58*
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	12 days between Period I and II 8 days between Period II and III 7 days between Period III and IV
Randomization	☒ Yes ☐ No
Blood Sampling Times	A total of 26 blood samples (4 mL per sample) were collected from each subject. Blood samples were collected in K2-EDTA vacutainers at pre dose (within 01.00 hr prior to dosing), 0.25, 0.50, 1.00, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 9.50, 10.00, 11.00, 12.00, 14.00, 16.00, and 24.00 hours post-dose within 2 minutes of scheduled sampling time.
IRB/IEC Approval	☒ Yes Date: 11/29/2014 ☐ No
Informed Consent	☒ Yes Date: 11/29/2014 ☐ No
Length of Fasting	At least 10 hours of overnight fast and 4 hours post dose
Length of Confinement	At least 34.5 hours (at least 10.50 hours prior to dosing until 24 hours post- dose in each study period)
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A
Safety Monitoring	☒ Yes ☐ No

* Subject Nos. (b) (6) had completed at least two study periods and thus were included in the statistical PK analyses as per study protocol.

Comments on Study Design:

- As per the RLD labeling, the half-life of methylphenidate in adults and adolescents following oral administration of CONCERTA® was approximately 3.5 hours. Therefore, the firm's sampling schedule up to 24 hours and at least 7 days of washout period between each period in fasting study are adequate.

- The study design is **adequate**.

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. ARL/14/694			
		Treatment Groups	
		Test A N=58	Reference B N=58
Age (years)	Mean ± SD	28.53 ± 04.47	28.53 ± 04.47
	Range	20-39	20-39
Age Groups	< 18	Nil	Nil
	18 – 40	58 (100.00 %)	58 (100.00 %)
	41 – 64	Nil	Nil
	65 – 75	Nil	Nil
	> 75	Nil	Nil
Sex	Male	52 (89.66 %)	52 (89.66 %)
	Female	06 (10.34 %)	06 (10.34 %)
Race	Asian	58 (100.00 %)	58 (100.00 %)
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic	Nil	Nil
	Other	Nil	Nil
BMI	Mean ± SD	23.99 ± 02.47	23.99 ± 02.47
	Range	18.93 - 27.94	18.93 - 27.94
Other Factors		N/A	N/A

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.1.2.2 Dropout Information

Study No. ARL/14/694				
Subject No	**Reason for dropout/replacement***	**Period(s)***	**Replaced?**	**Replaced with**
(b) (6)	Subject was dropped out only from Period II as subject did not report to study center. Randomization was ABAB.	II	No	NA
	Subject was withdrawn due to adverse event in period IV after 14.00 hrs of dosing. Randomization was ABAB.	IV	No	NA
	Subject dropped out only from Period III and IV as subject did not report to study center. Randomization was ABAB.	III, IV	No	NA
	Subject was withdrawn due to adverse event before dosing of Period IV. Randomization was BABA.	IV	No	NA
	Subject dropped out from Period II, III and IV as subject did not report to study center. No samples analyzed. Randomization was BABA.	II, III, IV	No	NA
	Subject dropped out from Period II, III and IV as subject did not report to study center. No samples analyzed. Randomization was BABA.	II, III, IV	No	NA

* Missed study period(s).

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No ☐ N/A

4.1.1.2.3 Study Adverse Events

Body System/ Adverse Event	**Reported Incidence by Treatment Groups**	
	Fasting Bioequivalence Study Study No. ARL/14/694	
	Test Product A N=114	**Reference Product B N=116**
Digestive System		
Pain in abdomen	01 (0.88 %)	--
Lymphatic System		
Hot flushes	--	01 (0.86 %)
High blood pressure	--	01 (0.86 %)
Central Nervous System		
Headache	--	01 (0.86 %)

Giddiness	01 (0.88 %)	01 (0.86 %)
Anxiety	--	01 (0.86 %)
Body as a whole		
Fever	--	02 (1.72 %)
Total	**02 (01.75 %)**	**07 (06.03 %)**

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
No emesis reported					

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☐ Yes ☒ No (See comments below)
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.1.2.4 Protocol Deviations

Study No. ARL/14/694		
Type	**Subjects (Test A)**	**Subjects (Reference B)**
Blood Time Point Deviation	(b) (6)	

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time	☒ Actual ☐ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results:

1. Dropouts:
   - A total of 6 dropouts were reported. The subject Nos. (b) (6) were dropped out from the study.
   - Subject No. (b) (6) was withdrawn after administration of test product as the subject did not report to study center.
   - Subject Nos (b) (6) were withdrawn after administration of reference product as the subjects did not report to study center.
   - Subject Nos (b) (6) were withdrawn due to adverse event (fever and giddiness, respectively) after administration of reference product.
   - The reviewer agrees with the firm's dropouts.

2. Adverse Events (AEs):
   - A total of 9 AEs were reported for 4 subjects (subject Nos. (b) (6)). Two AEs occurred after administration of test product and 7 AEs occurred after administration of reference product (please refer to the table of Study Adverse Event above for details). All AEs were considered mild to moderate in intensity.
   - Subject No. (b) (6) who experienced AE of fever was resolved with medication (Calpol Tablet, 500 mg). This subject was dropped out from the study.
   - Subject No. (b) (6) who experienced AE of giddiness was resolved without medication. This subject was dropped out from the study.
   - Other 7AEs were resolved without medication.
   - No deaths and serious AEs were reported during the entire duration of the study.
   - Based on evaluation of AEs, clinical laboratory evaluation and vital signs examination, it was concluded that both the test and reference products were well tolerated and were found to be safe.

3. Protocol deviations**:** All of the protocol deviations were related to deviation in blood sample collection time**.** Since the actual time points were used in PK analysis, therefore, these deviations did not compromise the integrity of the study.

4. The firm's handling of dropouts, adverse events and protocol deviations are **acceptable**.

4.1.1.3 Bioanalytical Results

4.1.1.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

SOP No.	Effective Date of SOP	SOP Title
(b) (4)		Biological Fluid Assay – Study Sample Analysis

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. ARL/14/694 Methylphenidate								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.500	1.00	2.00	4.00	20.0	30.0	45.0	50.0
Inter day Precision (%CV)	2.2	4.0	2.9	2.5	1.6	1.6	1.8	2.1
Inter day Accuracy (%Actual)	99.6	101.0	99.0	100.0	99.5	100.7	98.2	101.8
Linearity (R^2 value)	0.9942 to 0.9999							
Linearity Range (ng/mL)	0.500 to 50.0							
Sensitivity/LOQ (ng/mL)	0.500							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	1.50	8.00	20.0	40.0
Inter day Precision (%CV)	4.4	4.1	3.6	4.0
Inter day Accuracy (%Actual)	98.0	96.4	97.5	95.5

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

Reviewer's Comments:

- Human blank plasma containing K_2-EDTA was used as biological matrix.
- **Incurred Sample Reanalysis (ISR):** A total of 446 samples (10% of first 3000 samples plus 5% of remaining samples) were reanalyzed to evaluate incurred sample reproducibility (b) (4) Biological Fluid Assay – Study Sample Analysis, (b) (4)). Out of 446 samples, 435 samples (97.53%) met the acceptance criteria (the difference between the original and repeat values should be within ±20.0% for 67% of the total incurred samples analyzed). Therefore, the ISR is acceptable.

4.1.1.3.3 Reanalysis of Study Samples

Study No. ARL/14/694								
Methylphenidate								
Reason why assay was repeated	Number of samples reanalyzed				Number of recalculated values used after reanalysis			
	Actual number		% of total assays		Actual number		% of total assays	
	T	R	T	R	T	R	T	R
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Above the Limit of Quantitation	1	0	0.03	0.00	1	0	0.03	0.00
High Internal Standard	0	1	0.00	0.03	0	1	0.00	0.03
Low Internal Standard	4	8	0.13	0.27	4	8	0.13	0.27
No Peak(s) Present	11	13	0.37	0.44	11	13	0.37	0.44
Poor Chromatography	2	1	0.07	0.03	2	1	0.07	0.03
Total	**18**	**23**	**0.60**	**0.78**	**18**	**23**	**0.60**	**0.78**

Total number of samples analyzed = 5902

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Reviewer's Comments on Reanalysis of Study Samples:

The firm reassayed the study samples based on the following [redacted] (b) (4) Biological Fluid Assay – Study Sample Analysis, [redacted] (b) (4). A total of 41 out of 5902 samples (0.70%, 18 test and 23 reference products) were reassayed in fasting study. The reassayed samples were further investigated as below:

Above the Limit of Quantitation (ALQ): One sample (test product) was reassayed under this code as the concentration of the sample was above the limit of quantitation (ULOQ, 50 ng/mL). The sample was diluted with dilution factor of 10 and reanalyzed in a subsequent run. Dilution QCs were included in the sample run. The reviewer has verified that the firm followed selection of repeat sample and the reassayed value was at least 85% of ULOQ. The firm also reported the final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

High Internal Standard (HIS): One sample (reference product) was reassayed under this code as the internal standard (IS) area was greater than or equal to 175% of the mean of the non-zero IS response for the run. The sample was repeated in singlet. The reviewer has verified that the firm followed selection of repeat sample and reporting final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

Low Internal Standard (LIS): A total of 12 samples (4 test and 8 reference products) were reassayed under this code as the IS area was less than or equal to 50% of the mean of the non-zero IS response for the run. The samples were repeated in singlet. The reviewer has verified that the firm followed selection of repeat sample and reporting final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

No Peak(s) Present (NP): A total of 24 samples (11 test and 13 reference products) were reassayed under this code as no peaks was detected. The samples were repeated in singlet. It is noted by the reviewer that no peak was observed in samples of many subjects at different time points. Based on the reviewer's evaluation that all samples with no peak had no peak for the corresponding IS as well, the reviewer considers it acceptable. The reviewer checked the chromatograms and raw data and has verified that the firm followed selection of repeat sample and reporting final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

Poor Chromatography (PC): A total of 3 samples (2 test and 1 reference product) were reassayed under this code. The samples were repeated in singlet. The reviewer checked the chromatograms of original and repeated samples and has verified that the firm followed selection of repeat sample and reporting final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

Comments on Bioanalytical Results: The reanalysis of study samples in fasting study is **adequate**.

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters - Reviewer Calculated using Phoenix WinNonlin software

Fasting Bioequivalence Study No. ARL/14/694									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-3 (hr *ng/mL)	18.94	28.42	9.00	36.09	18.29	29.97	9.63	38.08	1.04
AUC3-7 (hr *ng/mL)	56.95	32.33	27.75	144.19	50.50	28.71	21.57	95.97	1.13
AUC7-12 (hr *ng/mL)	58.55	30.13	26.75	115.68	68.29	30.79	20.61	124.16	0.86
AUC∞ (hr *ng/mL)	179.48	30.98	86.69	382.52	192.05	31.06	83.01	379.37	0.93
Cmax (ng/mL)	18.09	37.93	7.68	61.27	17.62	28.37	8.36	30.78	1.03
Tmax* (hr)	6.00	-	4.50	9.50	7.50	-	4.50	10.00	0.80
Kel (hr^{-1})	0.18	21.05	0.10	0.29	0.18	18.06	0.12	0.28	1.00
T1/2 (hr)	3.97	20.36	2.36	6.74	4.01	16.69	2.50	5.88	0.99

[#] Tmax values are presented as median, range.

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Methylphenidate HCl (No of subjects completed=58) Dose (1 x 54 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study (4002731, ARL/14/694)							
Parameter	Test	N	RLD	N	Ratio	90% C.I.	
Cmax (ng/mL)	17.1553	58	16.8722	58	101.68	97.73	105.78
AUC0-3 (hr *ng/mL)	18.2354	58	17.4532	58	104.48	100.75	108.35
AUC3-7 (hr *ng/mL)	54.4274	58	48.2797	58	112.73	108.92	116.68
AUC7-12 (hr *ng/mL)	56.1426	58	64.7174	58	86.75	83.94	89.65
AUC∞ (hr *ng/mL)	171.9476	58	182.2264	58	94.36	91.72	97.08

Subject-by-Formulation Interaction Variance Assessment of the Natural Log-Transformed Systemic Exposure Parameters of Methylphenidate -Firm Calculated

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	σ^2_D [a]	Method Used	Outcome
Cmax (ng/mL)	101.68	97.73	105.78	0.0260	0.1612	N/A	-0.0018	ANOVA	BE
AUC0-3 (hr *ng/mL)	104.48	100.75	108.35	0.0267	0.1635	N/A	0.0030	ANOVA	BE
AUC3-7 (hr *ng/mL)	112.73	108.92	116.68	0.0230	0.1517	N/A	-0.0021	ANOVA	BE
AUC7-12 (hr *ng/mL)	86.75	83.94	89.65	0.0346	0.1860	N/A	-0.0023	ANOVA	BE
AUC∞ (hr *ng/mL)	94.36	91.72	97.08	0.0278	0.1668	N/A	-0.0056	ANOVA	BE

As per the firm: [a] = Subject-by-formulation interaction variance. Reference is made to the Controlled Correspondence (CC) # 49819 enclosed in this section for ease of review. In response to the CC, the OGD stated that the subject-by-formulation interaction variance for each PK metric should be less than or equal to 0.03.

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated using Phoenix WinNonlin software

Methylphenidate HCl (No of subjects completed=58) Dose (1 x 54 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study (4002731, ARL/14/694)							
Parameter	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**	
Cmax (ng/mL)	17.16	58	16.87	58	101.68	97.73	105.78
AUC0-3 (hr *ng/mL)	18.24	58	17.45	58	104.48	100.75	108.35
AUC3-7 (hr *ng/mL)	54.43	58	48.28	58	112.73	108.92	116.68
AUC7-12 (hr *ng/mL)	56.14	58	64.72	58	86.75	83.94	89.65
AUC∞ (hr *ng/mL)	171.95	58	182.23	58	94.36	91.72	97.08

Subject by Formulation Interaction Variance-- Reviewer Calculated

Fasting Bioequivalence Study No. ARL/14/694					
Pharmacokinetic Parameter (s)	**sigmaWT**	**sigmaWR**	**sigmaD2**	**SigmaD2upper***	**Study Outcome**
AUC0-inf	0.099611	0.168373	-0.00595	0.000867117	Pass
AUC0-3	0.143203	0.164283	0.003565	0.016008448	Pass
AUC3-7	0.164159	0.152035	-0.00167	0.009294078	Pass
AUC7-12	0.11179	0.187577	-0.00284	0.007315087	Pass
Cmax	0.193185	0.16211	-0.00083	0.013626058	Pass

* SigmaD2upper = 95% upper confidence bound

4.1.1.4.4 Additional Information for the Study

Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)**	☒ Yes (please see comment below) ☐ No
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed)**	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? **If yes, please comment**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Comments on PK results:

- According to current product-specific BE recommendations for Methylphenidate Hydrochloride Extended Release Tablets[10], for the fasting BE study, the 90% confidence intervals (CIs) for the geometric mean test/reference ratios of the following pharmacokinetic (PK) parameters AUC_{0-3}, AUC_{3-7}, AUC_{7-12}, $AUC_{0-\infty}$ and C_{max}, should fall within the limits of 80.00-125.00%.

- In addition, to ensure the switchability between the Concerta® and generic products, a subject-by-formulation test for each above PK metric is also

[10] Draft guidance on Methylphenidate Hydrochloride (Recommended Sep 2012; Revised Nov 2014) http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320007.pdf

recommended for the demonstration of BE. The 95% upper confidence bound for subject by formulation variance of each PK parameter should not exceed 0.03.

- It is noted that there is a difference of 1.5 hr in median Tmax between test (6 hr, range 4.5-9.5 hr) and reference (7.5 hr, range 4.5-10 hr) products. The T/R ratio of median Tmax is 0.8. As per the RLD labeling, range of Tmax is 6 to 10 hours. However, as per the Office of the Clinical Pharmacology (OCP) review of NDA 021121, the range of Tmax observed was 1-10 hr when Concerta of 54 mg strength was given to healthy subjects once daily in a dose escalation study[11]. Thus, the median Tmax of the test product is within the Tmax range of RLD product.

- Further, the firm performed Wilcoxon Signed Rank Test comparing Tmax values of test and reference products. Based on the firm's clinical report, the difference between the Tmax values was found to be significant[12]. However, as per DB policy, the parameter Tmax is evaluated for similarity but not subjected to any statistical evaluation.

- Since the values of within-subject standard deviation (sWR) for all log-transformed PK parameters are < 0.294, the average bioequivalence method was used for PK analysis in fasting study as per the protocol. The reviewer utilized Phoenix WinNonlin software in conducting the statistical PK analyses.

- The 90% CIs for the least squares geometric means of all the PK parameters including partial AUC metrics calculated by the reviewer agree with the firm's calculation and meet the criteria for BE.

- The firm concluded the study outcome based on the point estimate of subject-by-formulation interaction variance (SbF). However, according to current product-specific BE recommendations for Methylphenidate Hydrochloride Extended Release Tablets, the 95% upper confidence bound for SbF is recommended for determination of SbF. The 95% upper confidence bounds for SbF for all PK metrics calculated by the reviewer do not exceed 0.03 and meet the criteria for BE requirement for SbF.

4.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Acceptable

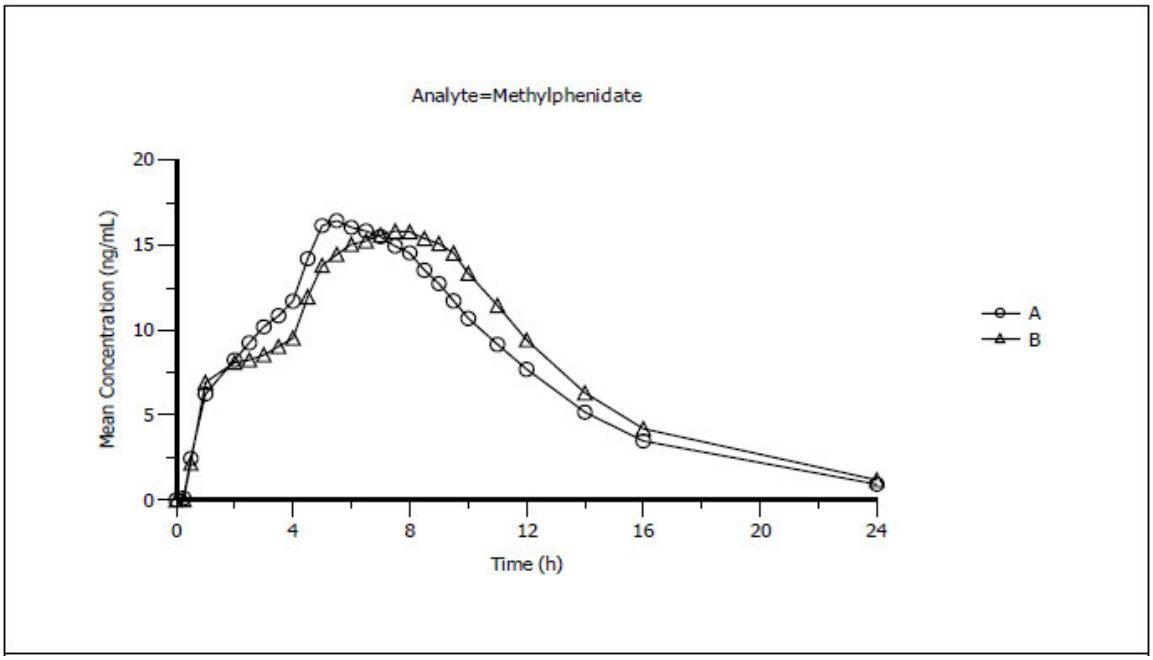
[11] DARRTS, NDA 021121, REV-CLIN-PHARM-01 (General Review), Kofi A Kumi date 05/09/2008 (page 9 of 113).
[12] ANDA 208607, EDR 2, 05/31/2016, M 5.3.1.2. Statistical Methods Interim Analysis Plan, Fasting Bioequivalence Study-Statistical Analyses, page 81 of 84.

Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study

(Firm-Submitted Data)

Time (h)	Treatment A: Test Formulation n	Mean (ng/mL)	SD (ng/mL)	CV (%)	Treatment B: Reference Product (Concerta) n	Mean (ng/mL)	SD (ng/mL)	CV (%)
0.00	114	0.00	0.00	NC	113	0.00	0.00	NC
0.25	114	0.103	0.328	317.18	113	0.0266	0.150	564.26
0.50	114	2.43	1.76	72.40	113	2.15	1.56	72.61
1.00	114	6.23	2.30	36.94	113	6.91	3.04	44.05
2.00	114	8.23	2.37	28.76	113	8.09	2.30	28.46
2.50	114	9.23	2.67	28.94	113	8.23	2.37	28.78
3.00	114	10.2	2.97	29.14	113	8.52	2.60	30.56
3.50	114	10.8	3.18	29.39	113	9.03	2.76	30.63
4.00	114	11.7	3.56	30.49	113	9.51	2.95	30.99
4.50	114	14.2	4.87	34.35	113	11.9	3.72	31.14
5.00	114	16.1	5.76	35.75	113	13.8	4.20	30.46
5.50	114	16.4	6.89	41.96	113	14.4	4.38	30.32
6.00	114	16.0	5.97	37.30	113	15.0	4.61	30.65
6.50	114	15.8	5.43	34.32	113	15.2	4.67	30.64
7.00	114	15.5	5.08	32.79	113	15.6	4.56	29.27
7.50	114	14.9	4.72	31.62	113	15.8	4.99	31.60
8.00	114	14.5	4.53	31.17	113	15.8	5.13	32.54
8.50	114	13.5	4.24	31.38	113	15.4	5.08	33.01
9.00	114	12.7	4.13	32.47	113	15.1	4.92	32.64
9.50	114	11.7	3.58	30.59	113	14.5	4.65	32.05
10.00	114	10.7	3.47	32.53	113	13.3	4.43	33.28
11.00	114	9.14	3.03	33.20	113	11.4	3.82	33.43
12.00	114	7.68	2.60	33.81	113	9.40	3.20	34.04
14.00	114	5.16	2.00	38.69	113	6.30	2.30	36.56
16.00	114	3.46	1.55	44.83	113	4.19	1.77	42.35
24.00	114	0.918	0.703	76.58	113	1.17	0.700	59.66

Figure 1. Mean Plasma Concentrations, Single-Dose Fasting Bioequivalence Study (Firm-Submitted Plot)



4.1.2 Single-dose Fed Bioequivalence Study (pivotal)

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	**ARL/14/695**
Study Title	A Randomized, Balanced, Open Label, Two-Treatment, Four-Period, Two-Sequence, Single Dose, Crossover, Fully Replicated Bioequivalence Study of Test Formulation of Methylphenidate HCl Extended-Release Tablets USP, 54 mg, CorePharma, LLC, versus Reference Product Concerta® (Methylphenidate HCl) Extended-Release Tablets, 54 mg, in Normal, Healthy, Adult, Male and Female Human Subjects under Fed Conditions
Study Type	☒In Vivo BE ☐In Vitro BE ☐Permeability ☐Other
Submission Location: Study Report	Module 5.3.1.2
Validation Report	Module 5.3.1.4
Bioanalytical Report	Module 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Accutest Research Laboratories (I) Pvt. Ltd. A-31, M.I.D.C, TTC Industrial Area Khairane, Navi Mumbai -400 709 Maharashtra, India Phone: 91.22.2278.0718/19/21 Fax: 91.22.2778.0720
Principal Clinical Investigator (Name, Email)	Vivekananda Murthi, MBBS Vivekanand.Murthy@accutestindia.com
Dosing Dates	Period 1: 14 December 2014 Period 2: 23 December 2014 Period 3: 31 December 2014 Period 4: 08 January 2015
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)
Analysis Dates	20 January 2015 to 04 February 2015
Principal Analytical Investigator (Name, Email)	(b) (4)
Sample Storage: (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	(a) 52 days (b) -15 °C to -35 °C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	91 days @ -20 °C

LTSS Data Location	Module 5.3.1.4; Validation Report; (b) (4) First Amendment to Report; Method Validation Tables, Table 10: Long Term Stability for Methylphenidate Extracted from Human EDTA Plasma; Page # 121 of 263

4.1.2.1.2 Product Information

Product information is the same as the fasting study.

4.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 72 Dosed: • Period I: 72 • Period II: 70 • Period III: 68 • Period IV: 65 Completed: 65 (all 4 periods) Samples Analyzed: 70* Statistically Analyzed: 70*
No. of Sequences	2
No. of Periods	4
No. of Treatments	2
No. of Groups	1
Washout Period	9 days between Period I and II 8 days between Period II and III 9 days between Period III and IV
Randomization	☒ Yes ☐ No
Blood Sampling Times	A total of 26 blood samples (4 mL per sample) were collected from each subject. Blood samples were collected in K2-EDTA vacutainers at pre dose (within 01.00 hr prior to dosing), 0.25, 0.50, 1.00, 2.00, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 6.50, 7.00, 7.50, 8.00, 8.50, 9.00, 9.50, 10.00, 10.50, 11.00, 12.00, 14.00, 16.00 and 24.00 hrs post-dose within 2 minutes of scheduled sampling time.
IRB/IEC Approval	☒ Yes Date: 11/29/2014 ☐ No
Informed Consent	☒ Yes Date: 11/29/2014 ☐ No
Length of Fasting	At least 10 hours of overnight fast and 4 hours post dose
Length of Confinement	At least 34.5 hours (at least 10.50 hours prior to dosing until 24 hours post- dose in each study period)
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☒ Yes ☐ No ☐ N/A
Safety Monitoring	☒ Yes ☐ No

* Subject Nos (b) (6) had completed at least two study periods and thus were included in the statistical PK analyses as per study protocol.

Standard FDA Meal Used?	☐ Yes	☑ No			
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study					
Ingredients	**Amount**	**Energy (kcal)**	**Protein (kcal)**	**Fat (kcal)**	**Carbohydrate (kcal)**
White bread	45g	123.2	15.6	3.6	104
Butter	20g	180	0	180	0
Hash brown Potatoes	~65 g	203.2	10	93.6	99.6
Chicken	35 g	81.3	40.8	36.9	3.6
Corn flour 5g	5 g	20	0	0	20
Eggs	~110 g	189.8	58.4	131.4	0
Whole milk	240g	156.9	31.6	80.1	45.2
Sugar	10g	40	0	0	40
TOTAL		**994.4**	**156.4**	**525.6**	**312.4**
PERCENTAGE		**--**	**15.73**	**52.86**	**31.42**

Comments on Study Design:

- As per the RLD labeling, the half-life of methylphenidate in adults and adolescents following oral administration of CONCERTA® was approximately 3.5 hours. There were no differences in either the pharmacokinetics or the pharmacodynamic performance of CONCERTA® when administered after a high-fat breakfast. Therefore, the firm's sampling schedule up to 24 hours and at least 8 days of washout period between each period in fed study are adequate.

- The study design is **adequate**.

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Study No. ARL/14/695			
		Treatment Groups	
		Test A N=70	**Reference B N=70**
Age (years)	Mean ± SD	28.97 ± 05.89	28.97 ± 05.89
	Range	19-43	19-43
Age Groups	< 18	Nil	Nil
	18 – 40	68 (97.14 %)	68 (97.14 %)
	41 – 64	02 (2.86 %)	02 (2.86 %)
	65 – 75	Nil	Nil

	> 75	Nil	Nil
Sex	Male	66 (94.29 %)	66 (94.29 %)
	Female	04 (05.71 %)	04 (05.71 %)
Race	Asian	70 (100.00 %)	70 (100.00 %)
	Black	Nil	Nil
	Caucasian	Nil	Nil
	Hispanic	Nil	Nil
	Other	Nil	Nil
BMI	Mean ± SD	23.65 ± 02.38	23.65 ± 02.38
	Range	18.73 - 27.99	18.73 - 27.99
Other Factors		N/A	N/A

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation? If no, please comment.	☒ Yes ☐ No

4.1.2.2.2 Dropout Information

Study No. ARL/14/695				
Subject No	**Reason for dropout**	**Period(s)***	**Replaced?**	**Replaced with**
(b) (4)	Subject was withdrawn due to adverse event in washout of Period III. Randomization was BABA.	IV	No	NA
	Subject was withdrawn due to adverse event in washout of Period II. Randomization was BABA.	III, IV	No	NA
	Subject dropped out as he did not report to center for Period IV. Randomization was BABA.	IV	No	NA
	Subject was withdrawn due to adverse event in washout of Period II. Randomization was BABA.	III, IV	No	NA
	Subject dropped out as she did not report to center for Period IV. Randomization was BABA.	IV	No	NA
	Subject dropped out as she did not report to centre for period II, III & IV. Randomization was ABAB.	II, III & IV	No	NA
	Subject dropped out as she did not report to centre for period II, III & IV. Randomization was BABA.	II, III & IV	No	NA

* Missed study period(s).

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

4.1.2.2.3 Study Adverse Events

Body System/ Adverse Event	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study Study No. ARL/14/695	
	Test Product A N=136	Reference Product B N=139
Gastro Intestinal Tract		
Bleeding per rectum	01 (0.74%)	--
Central Nervous System		
Headache	01 (0.74%)	01 (0.72%)
Giddiness	--	03 (02.16%)
Anxiety	01 (0.74%)	--
Integumentary System		
Boils around umbilicus	--	01 (0.72%)
Trauma to the right eyelid	01 (0.74%)	--
Auditory System		
Left Earache	--	01 (0.72%)
Total	**04 (02.94%)**	**06 (04.32%)**

Subjects Experiencing Emesis (Include in eCTD)

Subject Number	Test/ Reference	Period	Time and Date of dosing	Time and Date of emesis	Duration Between Dosing and Start of Emesis (hours)
No emesis reported					

Were subjects who experienced vomiting included in statistical analysis?	☐ Yes ☐ No ☒ N/A
If yes, does the time of emesis exceed two times the median Tmax value (immediate release products) or the labeled dosing interval (modified release products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☐ Yes ☒ No (See comments below)
Are there any serious adverse events or death?	☐ Yes ☒ No
If yes, then if the study conducted in US, are they reported to the OGD Safety Committee?	☐ Yes ☐ No ☒ N/A
Are there any other safety concerns based on the adverse event profile?	☐ Yes ☒ No

4.1.2.2.4 Protocol Deviations

Study No. ARL/14/695		
Type	**Subjects (Test A)**	**Subjects (Reference B)**
Blood Time Point Deviation	(b) (6)	

If the firm used nominal time points, the sampling time deviations (if any) > 5% and 90% CI of any PK parameters is border line, please reanalyze data using actual sampling time	☒ Actual ☒ Nominal

Is the dropout/withdrawal/exclusion of subjects and protocol deviations as per the criteria mentioned in the IRB approved study protocol?	☒ Yes ☐ No

Comments on Clinical Results:

1. Dropouts:
   - A total of 7 dropouts were reported. The subject Nos. (b) (6) (b) (6) were dropped out from the study.
   - Subject No. (b) (6) was withdrawn after administration of test product as the subject did not report to study center.
   - Subject Nos (b) (6) were withdrawn after administration of reference product as the subjects did not report to study center.
   - Subject Nos. (b) (6) was withdrawn due to adverse event (Boils around umbilicus) after administration of reference product.
   - Subject Nos. (b) (6) were withdrawn due to adverse event (Trauma to the right eyelid and Bleeding per rectum, respectively) after administration of test product.
   - The reviewer agrees with the firm's dropouts.

2. Adverse Events (AEs):
   - A total of 10 AEs were reported for 10 subjects (b) (6), (b) (6)). Four AEs occurred after administration of test product and 6 AEs occurred after administration of reference product (please refer to the table of Study Adverse Event above for details). All AEs were considered mild to moderate in intensity.
   - Subject No. (b) (6) who experienced AE of boils around umbilicus was resolved with medication (Combiflam, 400 mg/325 mg, Zifi 200, 200 mg and Omee, 20 mg). This subject was dropped out from the study.
   - Subject No. (b) (6) who experienced AE of Trauma to the right eyelid was resolved with medication (Combiflam, 400 mg/325 mg, Zifi 200, 200 mg and Omee, 20 mg). This subject was dropped out from the study.
   - Subject No. (b) (6) who experienced AE of bleeding per rectum was resolved with medication (Omee, 20 mg). This subject was dropped out from the study.

- Other 7AEs were resolved without medication.
- No deaths and serious AEs were reported during the entire duration of the study.
- Based on evaluation of AEs, clinical laboratory evaluation and vital signs examination, it was concluded that both the test and reference products were well tolerated and were found to be safe.

3. Protocol deviations**:** All of the protocol deviations were related to deviation in blood sample collection time**.** Since the actual time points were used in PK analysis, therefore, these deviations did not compromise the integrity of the study.

4. The firm's handling of dropouts, adverse events and protocol deviations are **acceptable**.

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Same as the SOPs from the fasting study.

4.1.2.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. ARL/14/695 Methylphenidate								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.500	1.00	2.00	4.00	20.0	30.0	45.0	50.0
Inter day Precision (%CV)	2.2	4.1	3.6	2.9	1.9	2.0	2.6	2.1
Inter day Accuracy (%Actual)	99.8	101.0	100.0	98.7	99.0	100.3	98.9	102.2
Linearity (R^2 value)	0.9939 to 0.9999							
Linearity Range (ng/mL)	0.500 to 50.0							
Sensitivity/LOQ (ng/mL)	0.500							

Parameter	**Quality Control Samples**			
Concentration (ng/mL)	1.50	8.00	20.0	40.0
Inter day Precision (%CV)	5.8	4.2	3.7	5.0
Inter day Accuracy (%Actual)	98.7	96.6	98.5	96.3

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes, comment below or consult TL/tertiary reviewer for additional actions	☐ Yes ☒ No
Were 20% of chromatograms included?	☒ Yes ☐ No

Were chromatograms serially or randomly selected?	☒ serially ☐ randomly
Any interfering peaks in chromatogram?	☐ Yes ☒ No
Were the chromatograms submitted by the firm acceptable?	☒ Yes ☐ No
Were 100% raw analytical data, including failed runs, provided?	☒ Yes ☐ No

Reviewer's Comments:

- Human blank plasma containing K_2-EDTA was used as biological matrix.
- **Incurred Sample Reanalysis (ISR):** A total of 505 samples (10% of first 3000 samples plus 5% of remaining samples) were reanalyzed to evaluate incurred sample reproducibility (b) (4) Biological Fluid Assay – Study Sample Analysis, (b) (4). Out of evaluable 503 samples, 492 samples (97.81%) met the acceptance criteria (the difference between the original and repeat values should be within ±20.0% for 67% of the total incurred samples analyzed). Therefore, the ISR is acceptable.

4.1.2.3.3 Reanalysis of Study Samples

Study No. ARL/14/695								
Methylphenidate								
Reason why assay was repeated	**Number of samples reanalyzed**				**Number of recalculated values used after reanalysis**			
	Actual number		**% of total assays**		**Actual number**		**% of total assays**	
	T	**R**	**T**	**R**	**T**	**R**	**T**	**R**
Pharmacokinetic	0	0	0.00	0.00	0	0	0.00	0.00
Above the Limit of Quantitation	20	15	0.56	0.41	20	15	0.56	0.41
High Internal Standard	1	8	0.03	0.22	1	8	0.03	0.22
Low Internal Standard	10	2	0.28	0.05	10	2	0.28	0.05
No Peak(s) Present	7	7	0.20	0.19	7	7	0.20	0.19
Poor Chromatography	16	18	0.45	0.49	16	18	0.45	0.49
Total	**54**	**50**	**1.52**	**1.37**	**54**	**50**	**1.52**	**1.37**

Total number of samples analyzed = 7098

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☒ Yes ☐ No
If no, is recalculation of PK parameters necessary?	☐ Yes ☐ No ☒ N/A
Did recalculation of PK parameters change the study outcome?	☐ Yes ☐ No ☒ N/A
Are the PK parameters of reanalysis still within the acceptance limits for the 90% CI?	☐ Yes ☐ No ☒ N/A

Reviewer's Comments on Reanalysis of Study Samples: The firm reassayed the study samples based on the following SOP: (b) (4), Biological Fluid Assay – Study Sample

Analysis, [redacted]. A total of 104 out of 7098 samples (1.47%, 54 test and 50 reference products) were reassayed in fed study. The reassayed samples were further investigated as below:

Above the Limit of Quantitation (ALQ): A total of 35 samples (20 test and 15 reference products) were reassayed under this code as the concentration of the sample was above the limit of quantitation (ULOQ, 50 ng/mL). These samples were diluted with dilution factor of 10 and reanalyzed in subsequent runs. Dilution QCs were included in the sample runs. The reviewer has verified that the firm followed selection of repeat sample and the reassayed value was at least 85% of ULOQ. The firm also reported the final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

High Internal Standard (HIS): A total of 9 samples (1 test and 8 reference products) were reassayed under this code as the internal standard (IS) area was greater than or equal to 175% of the mean of the non-zero IS response for the run. The samples were repeated in singlet. The reviewer has verified that the firm followed selection of repeat sample and reporting final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

Low Internal Standard (LIS): A total of 12 samples (10 test and 2 reference products) were reassayed under this code as the IS area was less than or equal to 50% of the mean of the non-zero IS response for the run. The samples were repeated in singlet. The reviewer has verified that the firm followed selection of repeat sample and reporting final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

No Peak(s) Present (NP): A total of 14 samples (7 each test and reference products) were reassayed under this code as no peaks was detected. The samples were repeated in singlet. It is noted by the reviewer that no peak was observed in samples of many subjects at different time points. Based on the reviewer's evaluation that all samples with no peak had no peak for the corresponding IS as well, the reviewer considers it acceptable. The reviewer checked the chromatograms and raw data and has verified that the firm followed selection of repeat sample and reporting final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

Poor Chromatography (PC): A total of 34 samples (16 test and 18 reference products) were reassayed under this code. The samples were repeated in singlet. The reviewer checked the chromatograms of original and repeated samples and has verified that the firm followed selection of repeat sample and reporting final value per the SOP. Therefore, the reviewer considers the firm's reassay under this code acceptable.

Comments on Bioanalytical Results: The reanalysis of study samples in fed study is **adequate**.

4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters –Reviewer Calculated using Phoenix WinNonlin software

Fed Bioequivalence Study No. ARL/14/695									
Parameter (units)	Test				Reference				T/R
	Mean	%CV	Min	Max	Mean	% CV	Min	Max	
AUC0-4 (hr *ng/mL)	31.17	43.76	13.48	131.51	31.51	39.24	14.21	121.42	0.99
AUC4-8 (hr *ng/mL)	69.75	42.74	20.25	274.98	63.76	37.03	28.68	222.45	1.09
AUC8-12 (hr *ng/mL)	53.58	57.07	14.02	321.47	57.57	42.76	24.05	234.65	0.93
AUC∞ (hr *ng/mL)	208.46	56.74	77.47	1283.40	211.71	46.72	100.74	1054.28	0.98
Cmax (ng/mL)	22.49	44.51	6.94	99.83	18.96	39.32	8.23	73.67	1.19
Tmax* (hr)	6.50	-	1.00	12.00	7.00	-	4.50	11.00	0.93
Kel (hr^{-1})	0.19	19.36	0.12	0.34	0.18	19.21	0.10	0.32	1.06
T1/2 (hr)	3.73	17.50	2.02	5.90	3.92	16.68	2.16	7.05	0.95

[#] Tmax values are presented as median, range.

4.1.2.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Methylphenidate HCl (No of subjects completed=70) Dose (1 x 54 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (4002730, ARL/14/695)							
Parameter	Test	N	RLD	N	Ratio	90% C.I.	
Cmax (ng/mL)	20.9932	70	17.9581	70	116.90	111.32	122.76
AUC0-4 (hr *ng/mL)	29.2895	70	29.7970	70	98.30	94.49	102.26
AUC4-8 (hr *ng/mL)	65.0814	70	60.6755	70	107.26	102.56	112.18
AUC8-12 (hr *ng/mL)	49.1990	70	54.0537	70	91.02	87.71	94.46
AUC∞ (hr *ng/mL)	193.3395	70	198.8586	70	97.22	94.34	100.20

Subject-by-Formulation Interaction Variance Assessment of the Natural Log-Transformed Systemic Exposure Parameters of Methylphenidate -Firm Calculated

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	s2wr	sWR	Criteria Bound	σ^2_D [a]	Method Used	Outcome
Cmax (ng/mL)	116.90	111.32	122.76	0.0232	0.1523	N/A	0.0105	ANOVA	BE
AUC0-4 (hr *ng/mL)	98.30	94.49	102.26	0.0260	0.1613	N/A	0.0090	ANOVA	BE
AUC4-8 (hr *ng/mL)	107.26	102.56	112.18	0.0206	0.1434	N/A	0.0104	ANOVA	BE
AUC8-12 (hr *ng/mL)	91.02	87.71	94.46	0.0269	0.1640	N/A	-0.0009	ANOVA	BE
AUC∞ (hr *ng/mL)	97.22	94.34	100.20	0.0228	0.1510	N/A	-0.0026	ANOVA	BE

As per the firm: [a] = Subject-by-formulation interaction variance. Reference is made to the Controlled Correspondence (CC) # 49819 enclosed in this section for ease of review. In response to the CC, the OGD stated that the subject-by-formulation interaction variance for each PK metric should be less than or equal to 0.03.
N/A = Not applicable

4.1.2.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated using Phoenix WinNonlin software

Methylphenidate HCl (No of subjects completed=70) Dose (1 x 54 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (4002730, ARL/14/695)							
Parameter	Test	N	RLD	N	Ratio	90% C.I.	
Cmax (ng/mL)	20.99	70	17.96	70	116.90	111.32	122.76
AUC0-4 (hr *ng/mL)	29.29	70	29.80	70	98.30	94.49	102.26
AUC4-8 (hr *ng/mL)	65.08	70	60.68	70	107.26	102.56	112.18
AUC8-12 (hr *ng/mL)	49.20	70	54.05	70	91.02	87.71	94.46
AUC∞ (hr *ng/mL)	193.34	70	198.86	70	97.22	94.34	100.20

Subject by Formulation Interaction Variance-- Reviewer Calculated

Fed Bioequivalence Study No. ARL/14/695					
Pharmacokinetic Parameter (s)	**sigmaWT**	**sigmaWR**	**sigmaD2**	**SigmaD2upper***	**Study Outcome**
AUC0-inf	0.151495	0.150267	-0.00254	0.005990668	Pass
AUC0-4	0.18801	0.15843	0.009424	0.025238303	Pass
AUC4-8	0.24123	0.142807	0.010484	**0.030631957**	**Fail**
AUC8-12	0.202141	0.162272	-0.00061	0.013096282	Pass
Cmax	0.272251	0.154211	0.010253	**0.034414719**	**Fail**

* SigmaD2upper = 95% upper confidence bound

4.1.2.4.4 Additional Information for the Study

Is there a Tmax difference between Test and Reference? **If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference)**	☒ Yes (slight difference) ☐ No
Were the subjects dosed in groups? **If yes, was the statistical analysis proper? Is reanalysis by reviewer necessary?**	☐ Yes ☒ No
Are there measurable drug concentrations at 0 hr? **If yes, please comment (and take necessary action, if needed)**	☐ Yes ☒ No
Are there first measurable drug concentration as Cmax? **If yes, please comment**	☐ Yes ☒ No
Are there Cmax at the first time point? **If yes, is the study (sample) design adequate?**	☐ Yes ☒ No

Comments on PK results:

- According to current product-specific BE recommendations for Methylphenidate Hydrochloride Extended Release Tablets[13], for the fed BE study, the 90% CIs for the geometric mean test/reference ratios of the following PK parameters AUC_{0-4}, AUC_{4-8}, AUC_{8-12}, $AUC_{0-\infty}$ and C_{max}, should fall within the limits of 80.00-125.00%.

- In addition, to ensure the switchability between the Concerta® and generic products, a subject-by-formulation test for each above PK metric is also

[13] Draft guidance on Methylphenidate Hydrochloride (Recommended Sep 2012; Revised Nov 2014) http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM320007.pdf

recommended for the demonstration of BE. The 95% upper confidence bound for subject by formulation variance of each PK parameter should not exceed 0.03.

- Since the values of within-subject standard deviation (sWR) for all log-transformed PK parameters are < 0.294, the average bioequivalence method was used for PK analysis in fed study as per the study protocol. The reviewer utilized Phoenix WinNonlin software in conducting the statistical PK analyses.

- The 90% CIs for the least squares geometric means of all the PK parameters including partial AUC metrics calculated by the reviewer agree with the firm's calculation and meet the criteria for BE.

- The firm concluded the study outcome based on the point estimate of subject-by-formulation interaction variance (SbF). However, according to current product-specific bioequivalence recommendations for Methylphenidate Hydrochloride Extended Release Tablets, the 95% upper confidence bound for SbF is recommended for determination of SbF. Based on the reviewer's calculation above, the 95% upper confidence bounds for SbF of two PK parameters, $pAUC_{4-8}$ and C_{max} exceed 0.03 and failed to meet the BE requirement for SbF. In addition, per firm's statistical report[14], the 95% upper confidence bounds for SbF exceed 0.03 for the PK parameters, Cmax (0.0347) and $pAUC_{4-8}$ (0.0305).

- Please note that the firm submitted a control correspondence (#49819; submitted on February 26, 2015) regarding the statistical analysis for SbF. However, the Agency only responded that *the subject-by-formulation interaction variance for each PK metric should be less than or equal to 0.03*[15].

- Thus the fed BE study (No. ARL/14/695) is **unacceptable** due to the failure of the PK parameters, $pAUC_{4-8}$ and C_{max} to meet the switchability requirement for SbF. A similar issue was observed for fasting study in another in-house application of the same drug product (ANDA 076772) and had been previously consulted to the Office of Research and Standards (ORS). The ORS recommended the fasting study be acceptable for BE establishment for the following reasons:

  - The SbF is not required for establishing the BE of generic products.
  - The fasting BE study passed the narrow therapeutic index (NTI) drugs BE criteria, therefore, acceptance of this study in spite of failing to meet SbF requirement for all PK parameters will not have adverse impact on safety or efficacy of the test drug product.
  - The fasting BE study failed to meet allowance for the upper 95% confidence bound for $\hat{\sigma}_D^2$, $H_{\hat{\sigma}_D^2}$ of 0.03 for those metrics (Cmax and AUC3-7) which are

[14] DARRTS, ANDA 208607, EDR2, 05/31/2016, Module 5 Clinical Study Reports, Fed Bioequivalence Study-Statistical Analysis, Page 45 of 84.
[15] http://panorama.fda.gov/project/view?ID=54ef889f0008ec424e7bafe2029247ba

considered "low risk" metrics as determined in tracked safety issue (TSI) for this drug product.

- **The ORS has previously conducted the extensive research on the BE methods for this current drug product, and also prepared the currently posted draft guidance on the Methylphenidate Hydrochloride Extended Release Tablets. Thus Division of Bioequivalence III (DBIII) will consult with the ORS for an opinion regarding the unacceptability of the fed BE study due to the failure of Cmax and $pAUC_{4-8}$ to meet the BE requirement for subject by formulation interaction variance.**

4.1.2.5 Overall Comment

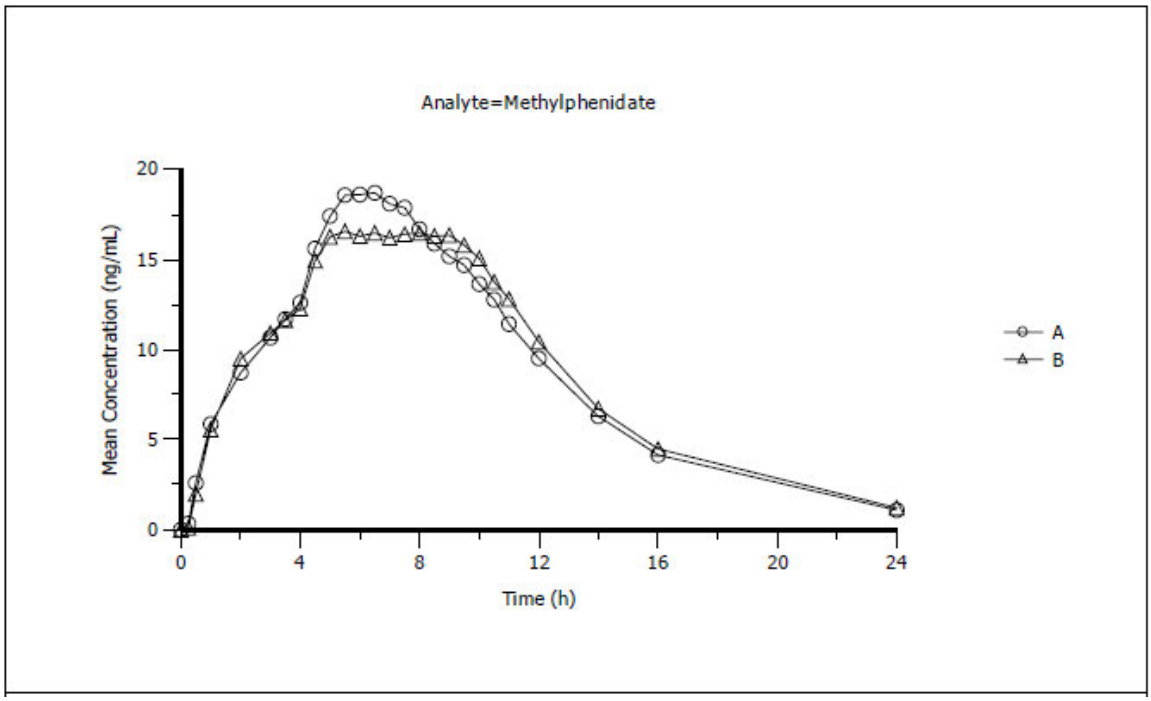
Was the Fed bioequivalence study acceptable? Inadequate

Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study

(Firm-Submitted Data)

Time (h)	Treatment A: Test Formulation n	Mean (ng/mL)	SD (ng/mL)	CV (%)	Treatment B: Reference Product (Concerta) n	Mean (ng/mL)	SD (ng/mL)	CV (%)
0.00	135	0.00	0.00	NC	138	0.00	0.00	NC
0.25	135	0.349	0.778	222.72	138	0.111	0.358	323.25
0.50	135	2.60	2.51	96.74	138	1.99	2.43	122.27
1.00	135	5.86	3.33	56.77	138	5.57	3.41	61.22
2.00	135	8.72	4.02	46.11	138	9.49	3.86	40.64
3.00	135	10.7	5.20	48.80	138	10.9	4.55	41.69
3.50	135	11.7	5.82	49.75	138	11.6	4.84	41.64
4.00	135	12.6	6.24	49.53	138	12.3	4.96	40.44
4.50	135	15.6	6.95	44.54	138	14.9	5.61	37.56
5.00	135	17.4	7.40	42.48	138	16.3	5.83	35.84
5.50	135	18.6	7.89	42.47	138	16.6	6.13	37.00
6.00	135	18.6	8.16	43.87	138	16.3	6.18	37.92
6.50	135	18.7	8.60	45.98	138	16.5	6.39	38.78
7.00	135	18.1	8.76	48.40	138	16.2	6.26	38.59
7.50	135	17.9	8.73	48.82	138	16.4	6.55	39.91
8.00	135	16.7	8.14	48.79	138	16.5	6.89	41.86
8.50	135	15.9	9.14	57.54	138	16.3	6.35	38.96
9.00	135	15.2	8.28	54.52	138	16.4	7.15	43.71
9.50	135	14.7	8.86	60.31	138	15.8	7.42	47.00
10.00	135	13.6	8.34	61.12	138	15.1	6.50	43.13
10.50	135	12.8	8.03	62.81	138	13.8	6.04	43.91
11.00	135	11.4	7.02	61.49	138	12.8	5.88	45.88
12.00	135	9.51	6.55	68.89	138	10.4	5.27	50.48
14.00	135	6.30	5.20	82.60	138	6.73	3.85	57.15
16.00	135	4.15	3.97	95.60	138	4.48	3.05	68.01
24.00	135	1.09	1.53	139.85	138	1.22	1.28	105.14

Figure 2. Mean Plasma Concentrations, Single-Dose Fed Bioequivalence Study (Firm-Submitted Plot)



4.2.2 Formulation data for extra studies (Study No. ARL/13/547 and ARL/13/548)[17]

Ingredient	Amount (mg) / 54 mg Tablet		Amount (%) / Tablet	
	Test A: Lot SB69800501	Test B: Lot SB69900301*	Test A: Lot SB69800501	Test B: Lot SB69900301
Methylphenidate Hydrochloride, USP	54.00	54.00	(b) (4)	
Lactose Monohydrate, NF, (b) (4) (b) (4) (b) (4)	(b) (4)			
Magnesium Stearate, NF, (b) (4) (b) (4)				
Ethylcellulose (b) (4)				
Hypromellose, USP (b) (4)				
Triethyl Citrate, NF				
Povidone , USP (b) (4) (b) (4)				
Tablet Weight (mg)				

[17] ANDA 208607, EDR 2, 05/31/2016, M.2.7. Clinical Summary, Clinical Summary ARL/13/547 and 548 Old Guidance –Word.

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Comments on Formulation:

- Based on the MDD of this drug product (72 mg/day), the reviewer calculated the maximum daily intake of all the inactive ingredients. All the inactive ingredients of the test product fall within acceptable limits listed in the FDA's Inactive Ingredient Guidance (IIG) limits and/or in FDA approved oral dosage formulations.

- The total quantity of elemental iron in Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg as per maximum daily dose is well within the 5 mg limit of Elemental Iron per day as per 21 CFR 73.1200 (c).

- The test product is formulated such that it has dose similar extended release core tablets for all strengths. 18 mg is dose proportional to 27 mg whereas 36 mg and 54 mg are dose proportional.

- In order to determine the formulation proportionality, the amounts of the inactive ingredients between all strengths were compared separately for immediate release (IR) and extended release (ER) portions of the test product. (b) (4) t (b) (4) (b) (4) These ingredients in IR portion are not evaluated for dose proportionality. For ER portion, the rate controlling excipients in the formulation were evaluated separately from non-rate controlling excipients for dose proportionality. Based on the above tables, (b) (4)

- The formulations are **adequate**.

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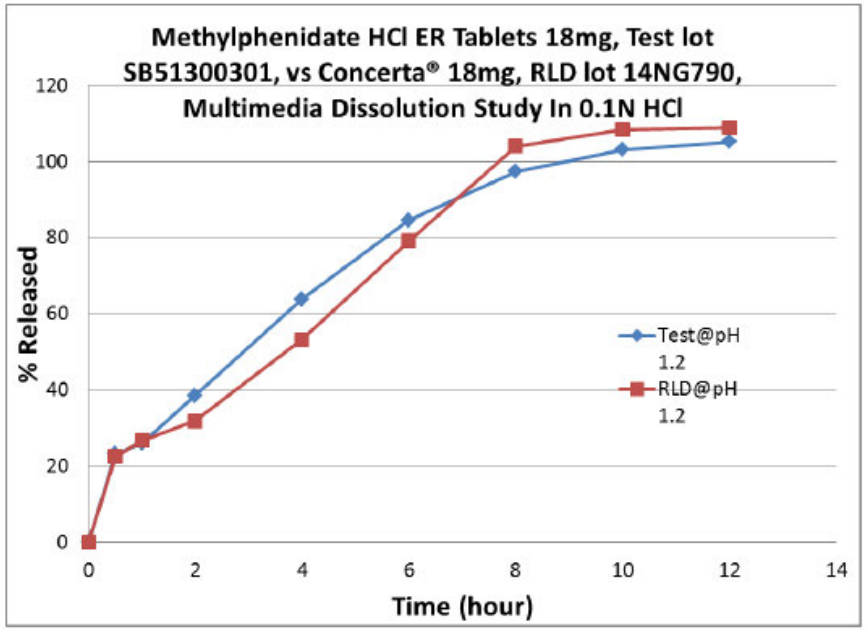
4.3.1.3 Test vs RLD products, 18 mg and 27 mg in multi-media (pH 1.2)

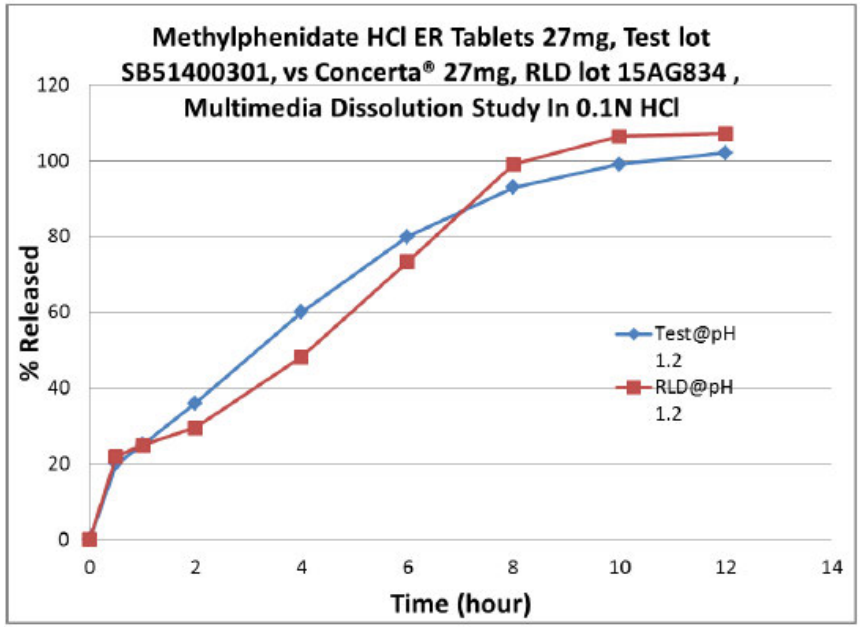
Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid (pH 1.2)**
	Volume:	**500 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications*	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (hours) 0.5	1	2	4	6	8	10	12	Study Report Location
Report #: 15-03-IR-002-01R	06/26/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		23	26	39	64	85	97	103	105	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.2	5.9	5.6	4.2	3.2	2.4	2.4	2.4	
	04/08/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		22	27	32	53	79	104	108	109	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.7	5.9	4.8	3.2	2.8	3.0	2.3	2.3	
	07/30/15 & 07/31/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		20	25	36	60	80	93	99	102	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		6.8	5.5	6.3	4.8	3.9	3.2	3.0	2.8	
	04/20/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		22	25	29	48	73	99	106	107	
					Range	Min	(b) (4)								
						Max									
					% RSD		3.5	3.2	3.4	3.4	4.1	3.4	1.8	1.6	

F2 value – Reviewer calculated

F2 Metric Test vs RLD pH 1.2 medium (6 time points: 0.5, 1, 2, 4, 6 and 8 hrs)	
18 mg vs 18 mg	59.0
27 mg vs 27 mg	58.0





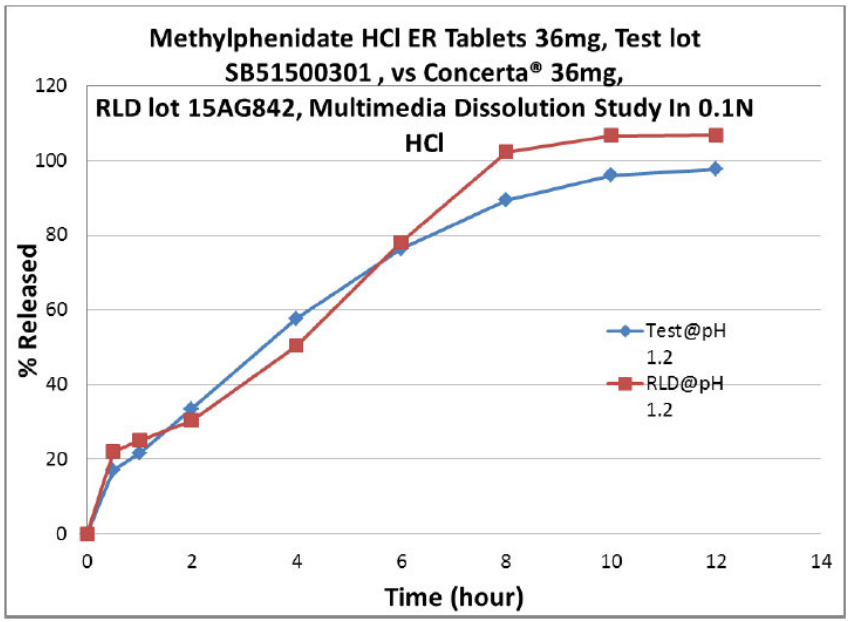
4.3.1.4 Test vs RLD products, 36 mg and 54 mg in multi-media (pH 1.2)

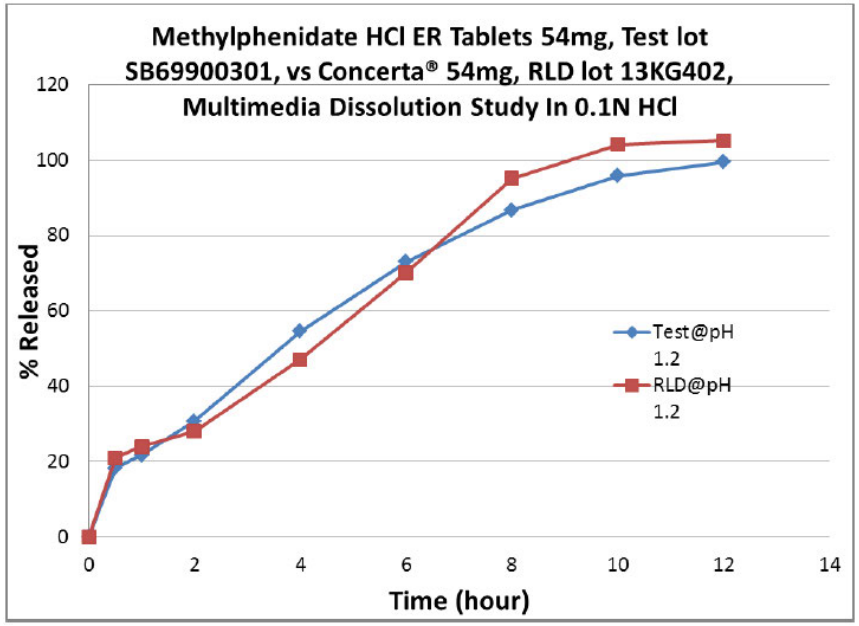
Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid (pH 1.2)**
	Volume:	**500 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 0.5	1	2	4	6	8	10	12	Study Report Location
Report #: 15-03-IR-002-01R	07/21/15 & 07/23/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean	17	22	33	58	76	89	96	98	Module 2.7
					Range Min	(b) (4)								
					Range Max									
					% RSD	3.2	3.9	5.1	4.7	4.2	3.7	2.6	1.8	
	04/20/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean	22	25	30	50	78	102	107	107	
					Range Min	(b) (4)								
					Range Max									
					% RSD	6.3	5.4	5.0	4.9	5.0	2.9	2.0	1.9	
	04/02/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean	18	22	31	54	73	87	96	99	
					Range Min	(b) (4)								
					Range Max									
					% RSD	6.5	6.7	7.6	5.9	4.8	3.8	3.2	2.5	
	03/25/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean	21	24	28	47	70	95	104	105	
					Range Min	(b) (4)								
					Range Max									
					% RSD	5.4	5.0	3.8	4.4	4.9	5.2	2.0	2.2	

F2 value – Reviewer calculated

F2 Metric Test vs RLD pH 1.2 medium (6 time points: 0.5, 1, 2, 4, 6 and 8 hrs)	
36 mg vs 36 mg	58.0
54 mg vs 54 mg	65.1





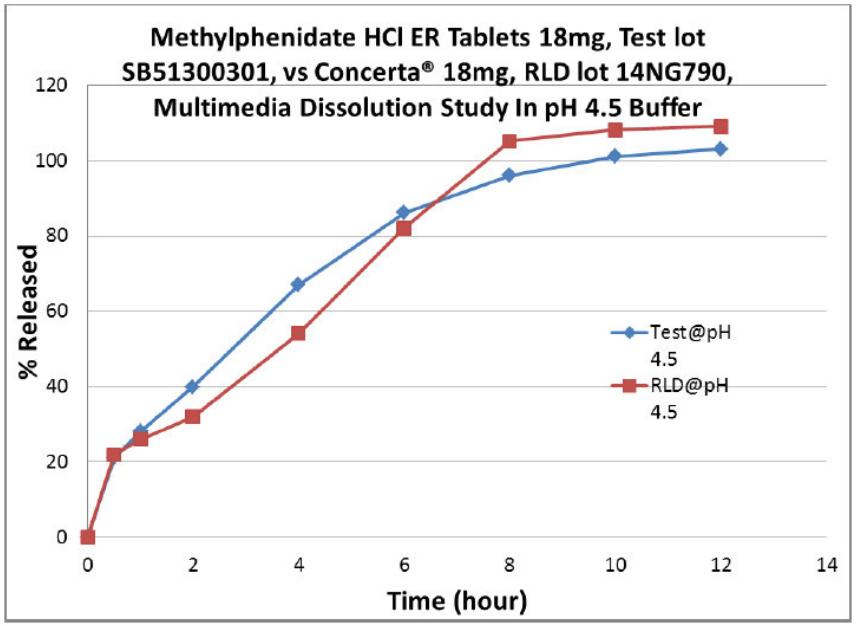
4.3.1.5 Test vs RLD products, 18 mg and 27 mg in multi-media (pH 4.5)

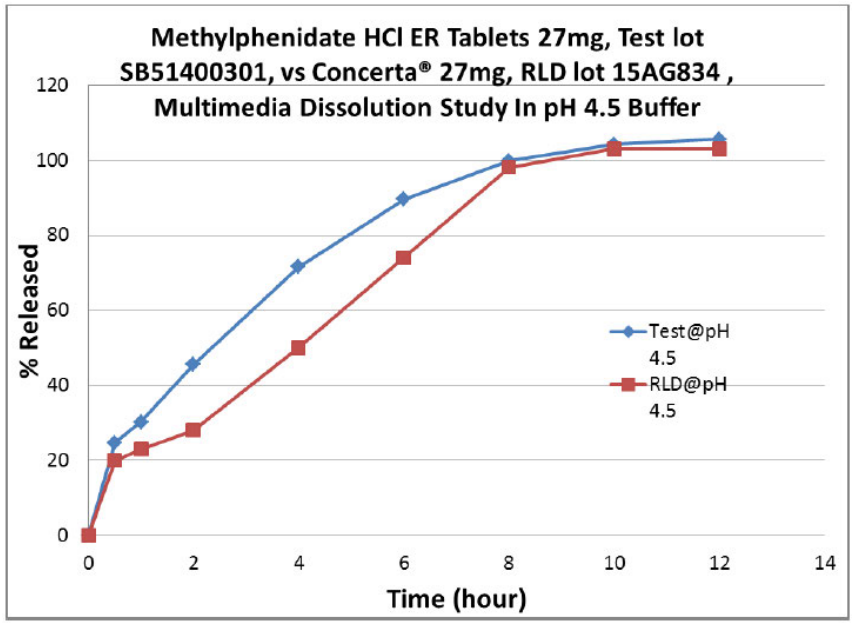
Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**pH 4.5** (b) (4)
	Volume:	**500 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (hours) 0.5	1	2	4	6	8	10	12	Study Report Location
Report #: 15-03-IR-002-01R	06/29/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		21	28	40	67	86	96	101	103	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		5.2	5.6	6.5	3.9	2.8	1.8	1.4	1.3	
	04/24/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		22	26	32	54	82	105	108	109	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.4	5.7	4.7	3.2	3.3	2.8	3.1	3.2	
	07/08/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		25	30	46	72	90	100	104	105	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.1	5.4	4.9	3.7	3.1	2.8	2.7	2.6	
	04/23/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		20	23	28	50	74	98	103	103	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.7	6.0	5.0	4.5	4.3	2.7	2.8	2.8	

F2 value – Reviewer calculated

F2 Metric Test vs RLD pH 4.5 medium (6 time points: 0.5, 1, 2, 4, 6 and 8 hrs)	
18 mg vs 18 mg	56.1
27 mg vs 27 mg	43.0





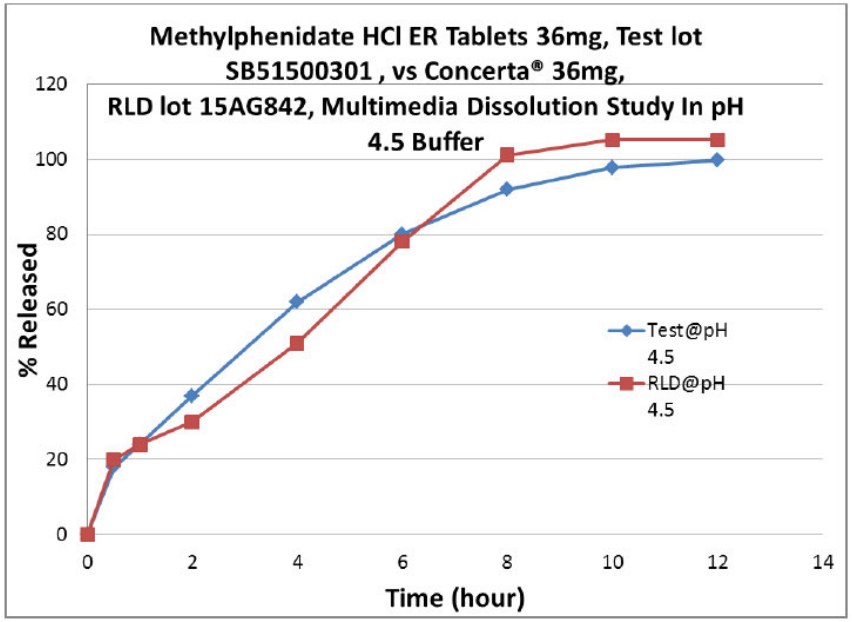
4.3.1.6 Test vs RLD products, 36 mg and 54 mg in multi-media (pH 4.5)

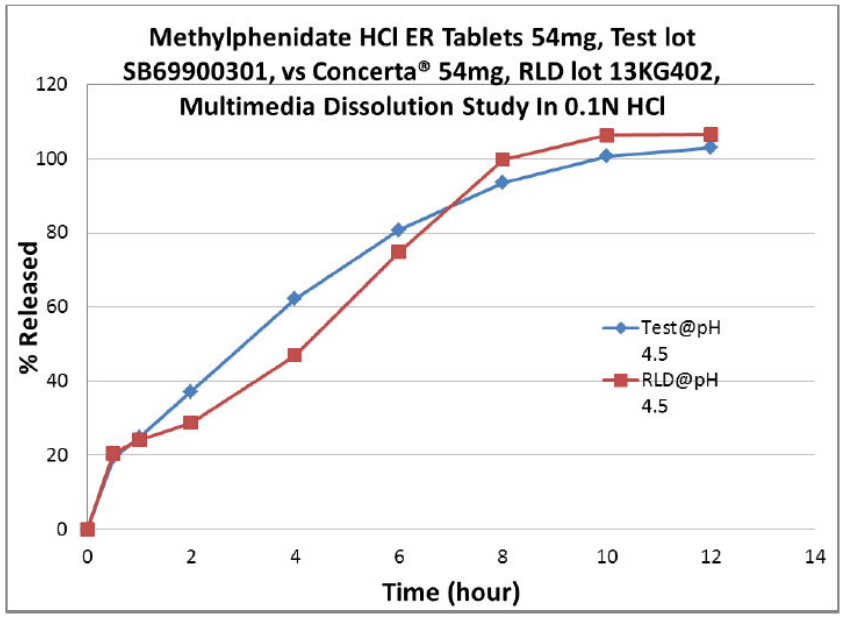
Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**pH 4.5** (b) (4)
	Volume:	**500 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 0.5	1	2	4	6	8	10	12	Study Report Location
Report #: 15-03-IR-002-01R	07/27/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean	18	24	37	62	80	92	98	100	Module 2.7
					Range Min	(b) (4)								
					Range Max									
					% RSD	4.3	4.2	4.9	3.8	3.0	2.5	2.3	2.3	
	04/22/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean	20	24	30	51	78	101	105	105	
					Range Min	(b) (4)								
					Range Max									
					% RSD	6.7	6.1	6.3	6.0	5.3	2.6	1.6	1.7	
	04/08/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean	19	25	37	62	81	93	100	103	
					Range Min	(b) (4)								
					Range Max									
					% RSD	5.6	5.4	4.5	3.7	2.9	2.5	2.0	1.9	
	03/25/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean	21	24	29	47	75	100	106	106	
					Range Min	(b) (4)								
					Range Max									
					% RSD	5.8	5.6	5.8	6.4	5.9	4.5	2.3	2.2	

F2 value – Reviewer calculated

F2 Metric Test vs RLD pH 4.5 medium (6 time points: 0.5, 1, 2, 4, 6 and 8 hrs)	
36 mg vs 36 mg	59.0
54 mg vs 54 mg	55.0





In the above profile graph for 54 mg strength in pH 4.5 buffer, the firm labeled "Multimedia Dissolution Study in 0.1N HCl". After checking the dissolution data, the reviewer considers it as a typographical error and confirms and the firm will not be asked for the clarification.

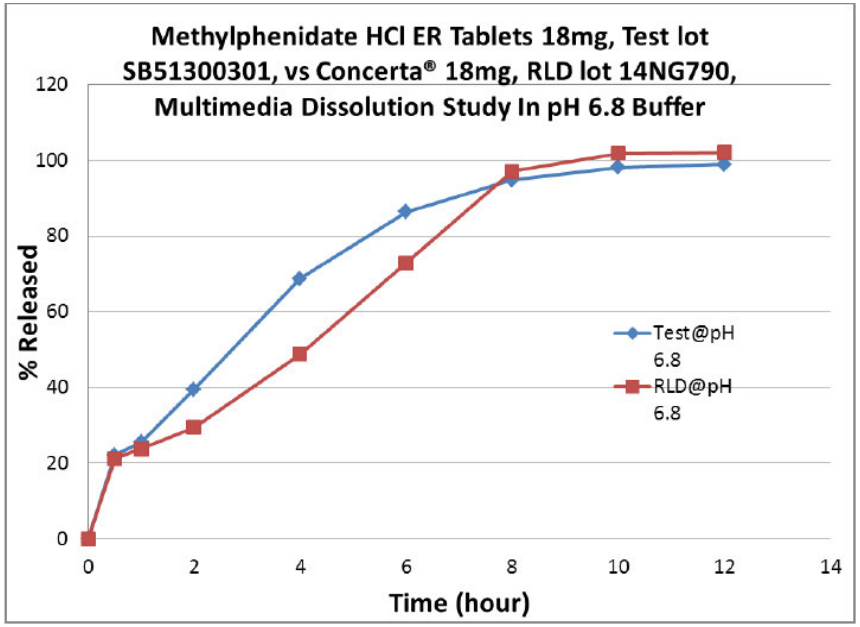
4.3.1.7 Test vs RLD products, 18 mg and 27 mg in multi-media (pH 6.8)

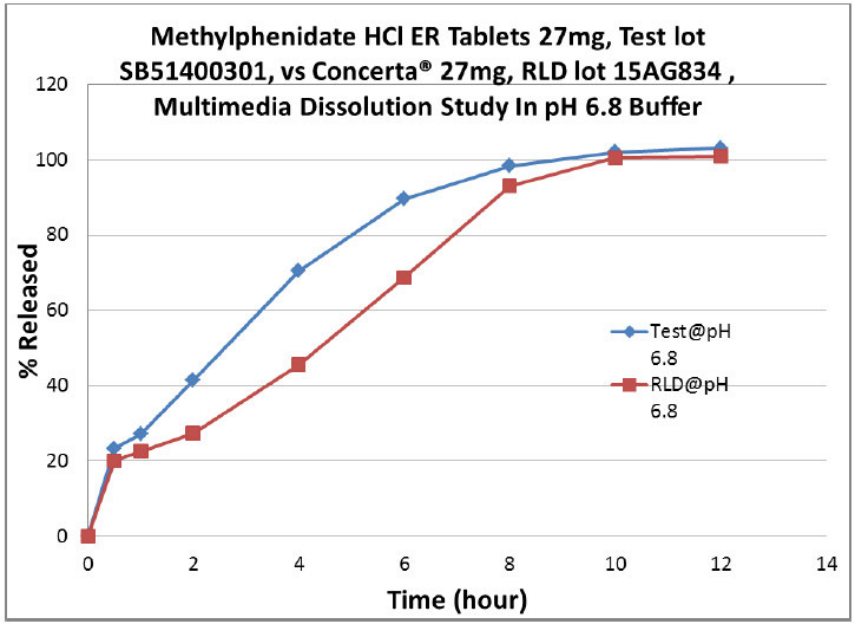
Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**pH 6.8** (b) (4)
	Volume:	**500 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (hours) 0.5	1	2	4	6	8	10	12	Study Report Location
Report #: 15-03-IR-002-01R	06/30/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean	22	25	39	69	86	95	98	99	Module 2.7
					Range Min	(b) (4)								
					Range Max									
					% RSD	9.7	10.0	8.9	6.9	4.9	4.4	3.6	3.1	
	04/13/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean	21	24	29	49	73	97	102	102	
					Range Min	(b) (4)								
					Range Max									
					% RSD	6.6	6.0	5.2	4.1	3.8	3.1	2.8	2.7	
	07/06/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean	23	27	41	70	90	98	102	103	
					Range Min	(b) (4)								
					Range Max									
					% RSD	5.3	4.9	4.7	4.6	4.7	3.9	3.2	3.0	
	04/15/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean	20	23	27	46	69	93	100	101	
					Range Min	(b) (4)								
					Range Max									
					% RSD	7.8	7.6	6.1	4.3	4.1	3.3	2.3	2.2	

F2 value – Reviewer calculated

F2 Metric Test vs RLD pH 6.8 medium (6 time points: 0.5, 1, 2, 4, 6 and 8 hrs)	
18 mg vs 18 mg	49.0
27 mg vs 27 mg	42.0





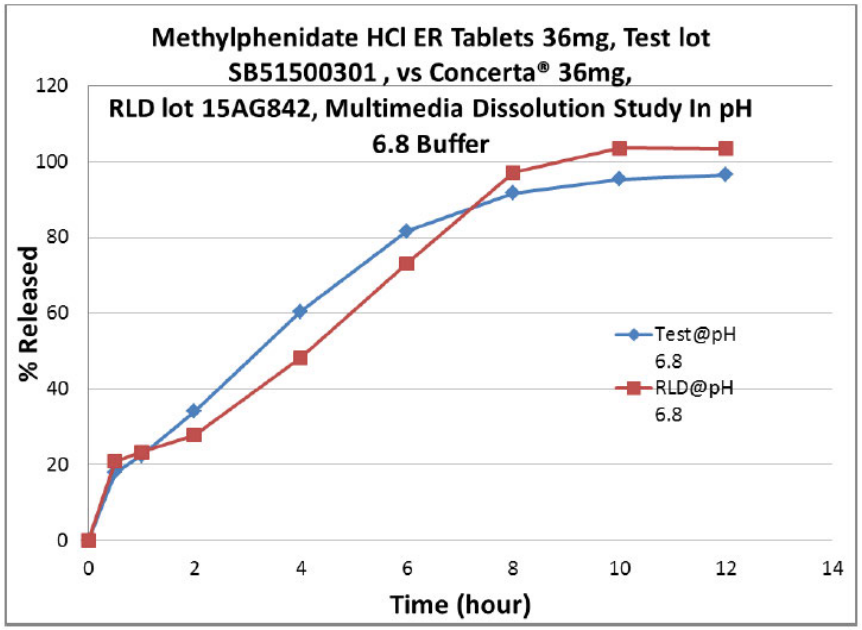
4.3.1.8 Test vs RLD products, 36 mg and 54 mg in multi-media (pH 6.8)

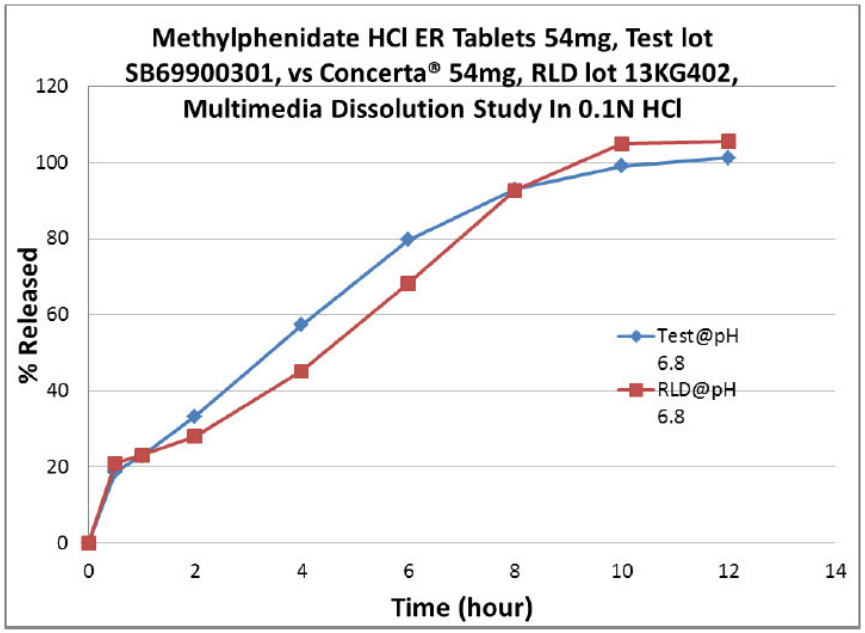
Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**pH 6.8** (b) (4)
	Volume:	**500 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (hours) 0.5	1	2	4	6	8	10	12	Study Report Location
Report #: 15-03-IR-002-01R	07/21/15 & 07/23/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		18	22	34	60	82	92	95	96	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		4.7	4.1	3.9	3.6	4.4	3.2	2.7	2.6	
	04/17/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		21	23	28	48	73	97	103	103	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.3	5.9	4.9	3.0	2.9	2.0	1.5	1.6	
	04/07/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		19	23	33	57	80	93	99	101	
					Range	Min	(b) (4)								
						Max									
					% RSD		9.7	9.0	7.2	5.9	4.5	4.0	3.2	2.9	
	03/30/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		21	23	28	45	68	93	105	105	
					Range	Min	(b) (4)								
						Max									
					% RSD		4.9	5.4	5.5	4.9	3.4	3.1	2.2	2.5	

F2 value – Reviewer calculated

F2 Metric Test vs RLD pH 6.8 medium (6 time points: 0.5, 1, 2, 4, 6 and 8 hrs)	
36 mg vs 36 mg	58.0
54 mg vs 54 mg	57.0





In the above profile graph for 54 mg strength in pH 6.8 buffer, the firm labeled "Multimedia Dissolution Study in 0.1N HCl". After checking the dissolution data, the reviewer considers it as a typographical error and confirms and the firm will not be asked for the clarification.

4.3.1.9 Test vs RLD products, 18 mg and 27 mg in 0.1 N HCl with 0% Alcohol

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1N Hydrochloric acid**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	06/25/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		20	22	23	24	27	30	33	36	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		6.5	5.9	5.3	3.8	4.5	5.0	5.3	5.5	
	04/28/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		24	25	25	25	26	27	29	30	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.1	6.0	5.8	5.5	5.3	5.0	4.7	4.5	
	07/28/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		20	23	24	26	28	31	34	38	
					Range	Min	(b) (4)								
						Max									
					% RSD		3.5	2.9	2.8	2.8	3.1	3.0	3.5	2.7	
	05/06/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		23	23	24	24	25	26	27	29	
					Range	Min	(b) (4)								
						Max									
					% RSD		4.9	5.2	5.1	5.2	5.1	5.2	5.2	5.2	

4.3.1.10 Test vs RLD products, 36 mg and 54 mg in 0.1 N HCl with 0% Alcohol

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1N Hydrochloric acid**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	08/04/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		17	19	20	22	25	29	32	36	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		2.9	2.4	2.4	3.0	3.0	3.3	3.3	3.1	
	05/18/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		18	22	23	24	24	26	27	29	
					Range	Min	(b) (4)								
						Max									
					% RSD		5.4	6.5	6.1	5.9	5.5	5.2	4.9	4.7	
	04/07/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		20	21	21	22	25	27	30	33	
					Range	Min	(b) (4)								
						Max									
					% RSD		9.7	9.9	10.6	11.4	11.4	11.0	10.7	10.3	
	03/27/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		19	23	24	24	25	26	27	28	
					Range	Min	(b) (4)								
						Max									
					% RSD		7.4	7.2	7.1	6.9	6.6	6.3	5.7	5.4	

4.3.1.11 Test vs RLD products, 18 mg and 27 mg in 0.1 N HCl with 5% Alcohol

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 5% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	06/29/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		18	22	22	23	25	27	30	33	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		10.2	8.5	8.7	8.7	9.6	10.9	11.3	11.1	
	04/29/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		24	25	25	25	27	28	30	32	
					Range	Min	(b) (4)								
						Max									
					% RSD		4.7	4.8	4.7	4.6	4.5	4.4	4.1	3.8	
	08/03/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		19	23	24	25	27	30	33	36	
					Range	Min	(b) (4)								
						Max									
					% RSD		5.6	2.9	2.9	4.0	6.0	7.0	7.1	7.0	
	05/5/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		22	23	24	24	25	26	28	30	
					Range	Min	(b) (4)								
						Max									
					% RSD		4.6	4.6	4.4	4.4	4.1	3.8	3.8	3.7	

4.3.1.12 Test vs RLD products, 36 mg and 54 mg in 0.1 N HCl with 5% Alcohol

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 5% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	08/05/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		16	19	20	21	24	27	30	34	
					Range	Min	(b) (4)								
						Max									
					% RSD		5.3	2.7	2.7	4.5	6.0	6.2	5.7	5.2	
	05/12/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		20	22	22	23	24	26	28	30	
					Range	Min	(b) (4)								
						Max									
					% RSD		8.0	7.7	7.8	7.6	7.3	7.1	6.5	6.2	Module 2.7
	04/06/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		20	20	21	22	24	26	29	32	
					Range	Min	(b) (4)								
						Max									
					% RSD		3.7	4.2	3.9	4.2	4.8	5.2	5.3	5.3	
	03/26/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		8	23	24	24	25	26	28	30	
					Range	Min	(b) (4)								
						Max									
					% RSD		15.2	4.8	3.9	3.6	3.4	3.6	4.0	4.3	

4.3.1.13 Test vs RLD products, 18 mg and 27 mg in 0.1 N HCl with 20% Alcohol

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 20% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	07/06/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		16	22	23	23	23	23	23	23	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		10.6	6.7	6.5	6.5	6.4	6.4	6.3	6.2	
	04/24/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		8	22	24	25	27	29	32	35	
					Range	Min	(b) (4)								
						Max									
					% RSD		15.2	6.5	6.7	6.4	5.8	5.4	5.3	5.2	
	08/04/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		17	23	24	24	24	24	24	24	
					Range	Min	(b) (4)								
						Max									
					% RSD		12.4	5.7	5.4	5.4	5.3	5.3	5.3	5.2	
	05/19/15	Concerta Lot: 15CG060 Exp date: 01/2017	27 mg ER Tablet	12	Mean		16	23	24	25	26	29	31	34	
					Range	Min	(b) (4)								
						Max									
					% RSD		13.2	6.2	5.3	5.0	4.6	4.4	4.2	4.3	

4.3.1.14 Test vs RLD products, 36 mg and 54 mg in 0.1 N HCl with 20% Alcohol

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 20% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	08/05/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean	14	19	20	20	20	20	20	21	Module 2.7
					Range Min	(b) (4)								
					Range Max									
					% RSD	7.5	4.3	4.7	4.8	4.9	4.8	4.9	4.9	
	05/08/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean	18	23	24	25	27	29	32	36	
					Range Min	(b) (4)								
					Range Max									
					% RSD	8.5	8.5	8.0	7.6	7.3	7.4	7.1	6.8	
	04/03/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean	21	21	21	21	21	21	21	22	
					Range Min	(b) (4)								
					Range Max									
					% RSD	7.3	7.1	7.1	7.0	7.0	7.0	6.9	6.9	
	03/25/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean	8	22	24	25	27	29	31	34	
					Range Min	(b) (4)								
					Range Max									
					% RSD	20.0	4.1	3.4	3.0	3.2	3.1	2.9	2.8	

4.3.1.15 Test vs RLD products, 18 mg and 27 mg in 0.1 N HCl with 40% Alcohol

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 40% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	06/26/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		16	22	23	24	25	28	31	35	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		8.7	8.9	8.8	7.9	6.3	8.4	10.1	10.3	
	04/22/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		10	22	26	28	32	36	41	47	
					Range	Min	(b) (4)								
						Max									
					% RSD		26.1	6.0	6.1	5.4	4.6	4.5	4.3	4.8	
	12/09/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		23	24	24	26	29	33	37	41	
					Range	Min	(b) (4)								
						Max									
					% RSD		3.2	2.9	3.0	5.8	8.0	9.4	9.9	10.0	
	04/30/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		21	24	25	28	32	36	42	47	
					Range	Min	(b) (4)								
						Max									
					% RSD		3.9	5.7	5.3	4.8	4.6	4.8	4.6	4.2	

4.3.1.16 Test vs RLD products, 36 mg and 54 mg in 0.1 N HCl with 40% Alcohol

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 40% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	08/06/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		6	18	20	23	26	30	34	37	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		14.2	3.4	2.4	5.9	8.7	9.9	11.4	12.4	
	05/07/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		14	22	24	27	30	33	38	42	
					Range	Min	(b) (4)								
						Max									
					% RSD		11.1	7.7	7.4	7.3	6.5	6.0	5.5	4.6	
	04/02/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		20	21	21	22	24	27	30	33	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.9	6.8	6.7	6.5	7.4	7.9	8.5	10.3	
	03/24/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		6	21	25	27	30	33	37	41	
					Range	Min	(b) (4)								
						Max									
					% RSD		34.3	5.7	4.5	4.3	4.3	4.0	3.9	3.9	

4.3.2 Dissolution Profiles

Please refer to Section 4.3.1 Dissolution Data of this review.

4.3.3 F2 Metric

F2 metric calculated?	☒ Yes ☐ No
If no, reason why F2 not calculated	N/A

F2 metric, biostudy strengths compared to other strengths of test product

Biostudy Strength	Other Strength	QC media	pH 1.2	pH 4.5	pH 6.8
54 mg	18 mg	68.2	53.0	71.0	60.0
54 mg	27 mg	72.0	64.0	55.0	55.0
54 mg	36 mg	89.0	79.4	95.0	85.4

F2 Metric Test vs Reference (all strengths), if necessary

Strength(s)	QC media	pH 1.2	pH 4.5	pH 6.8
18 mg vs 18 mg	51.4	59.0	56.1	49.0
27 mg vs 27 mg	48.2	58.0	43.0	42.0
36 mg vs 36 mg	56.1	58.0	59.0	58.0
54 mg vs 54 mg	55.0	65.1	55.0	57.0

Reviewer's comments on F2 Metric Test vs Reference: It is noted that several f2 values are less than 50 when test product is compared with the reference product (18 mg vs 18 mg in pH 6.8, f2=49.0; 27 mg vs 27 mg in QC media, pH 4.5 and 6.8 media, f2=48.2, 43.0 and 42.0, respectively). The reviewer considers it is due to different drug release mechanism between the test and reference products.

Alcohol Dose Dumping

% Drug Release of Methylphenidate Hydrochloride Extended Release Capsules **(18 mg)** in 0.1 N HCl with various concentrations of alcohol at **120 minutes**								
	Test Product (18 mg)				Reference Product (18 mg)			
Alcohol (%v/v)	Mean (%)	Range	%CV	Mean % difference between with and without alcohol	Mean (%)	Range	%CV	Mean difference between with and without alcohol
0%	36	(b) (4)	5.5	(b) (4)	30	(b) (4)	4.5	(b) (4)
5%	33		11.1		32		3.8	
20%	23		6.2		35		5.2	
40%	35		10.3		47		4.8	

% Drug Release of Methylphenidate Hydrochloride Extended Release Capsules **(27 mg)** in 0.1 N HCl with various concentrations of alcohol at **120 minutes**								
Alcohol (%v/v)	Test Product (27 mg)				Reference Product (27 mg)			
	Mean (%)	Range	%CV	Mean % difference between with and without alcohol	Mean (%)	Range	%CV	Mean difference between with and without alcohol
0%	38	(b) (4)	2.7	(b) (4)	29	(b) (4)	5.2	(b) (4)
5%	36		7.0		30		3.7	
20%	24		5.2		34		4.3	
40%	41		10.0		47		4.2	

% Drug Release of Methylphenidate Hydrochloride Extended Release Capsules **(36 mg)** in 0.1 N HCl with various concentrations of alcohol at **120 minutes**								
Alcohol (%v/v)	Test Product (36 mg)				Reference Product (36 mg)			
	Mean (%)	Range	%CV	Mean % difference between with and without alcohol	Mean (%)	Range	%CV	Mean difference between with and without alcohol
0%	36	(b) (4)	3.1	(b) (4)	29	(b) (4)	4.7	(b) (4)
5%	34		5.2		30		6.2	
20%	21		4.9		36		6.8	
40%	37		12.4		42		4.6	

% Drug Release of Methylphenidate Hydrochloride Extended Release Capsules **(54 mg)** in 0.1 N HCl with various concentrations of alcohol at **120 minutes**								
Alcohol (%v/v)	Test Product (54 mg)				Reference Product (54 mg)			
	Mean (%)	Range	%CV	Mean % difference between with and without alcohol	Mean (%)	Range	%CV	Mean difference between with and without alcohol
0%	33	(b) (4)	10.3	(b) (4)	28	(b) (4)	5.4	(b) (4)
5%	32		5.3		30		4.3	
20%	22		6.9		34		2.8	
40%	33		10.3		41		3.9	

Reviewer's Comments on Dissolution Testing:

- The dissolution testing is pending review. The dissolution testing will be reviewed separately by the biopharmaceutics quality reviewer in the Office of New Drug Products (ONDP) for establishing the quality control method and specifications for batch release. (b) (4)

(b) (4)

- The following comments concern evaluating the dissolution data for the purpose of granting the waiver request, and not for determining a regulatory (quality control) dissolution method and specification.

- Based on the above f2 value calculated by the reviewer, the dissolution profiles of the 18 mg, 27 mg and 36 mg strengths of the test product are comparable to the bio-strength (54 mg) of the test product in water, pH 1.2, 4.5 and 6.8 buffer. The dissolution profile of the test bio-batch (54 mg) is also comparable to the 54 mg strength of the reference product in water, pH 1.2, 4.5 and 6.8 buffer.

- As per the drug product BE recommendations, the firm conducted dissolution testing in three additional pH media (pH 1.2, 4.5 and 6.8 buffers). The firm's dissolution data of the test product in the above additional media showed no evidence of dose dumping. Therefore, the firm's dissolution testing in multi pH media is acceptable.

- The firm also submitted data for in vitro alcohol dose-dumping testing using various concentrations of ethanol in the dissolution medium. Dissolution testing was conducted in 0.1 N HCl in the absence and presence of various concentrations of alcohol (5, 20 and 40%).

- It is noted that in 20% alcohol, the mean % difference between with and without alcohol for all strengths of the test product is higher than that of the corresponding reference product. However, the reviewer considers it acceptable for the following reasons:

  - The mean % difference between with 20% alcohol and without alcohol between test and reference products is less than 10%.
  - The mean % difference for all strengths of test product in 20% alcohol is less than 18% of the maximum mean % difference observed for all strengths of the reference product in 40% alcohol.

- The alcohol dose-dumping testing indicated that the mean difference in the % drug dissolved in between 0% and 40% alcohol at 120 minutes for all strengths of the test product is less compared to the corresponding reference product. Therefore, the risk of alcohol dose dumping from the test product is less than for the reference product.

- The dissolution data are **adequate** with respect to supporting waiver requests for in vivo BE study requirements for the lower strengths, 18 mg, 27 mg and 36 mg of the test product.

4.4 Attachments

4.4.1 Additional Studies

- The firm submitted two pilot studies and two extra studies in the current application:
  - Pilot studies: Study No. ARL/13/061 (fasting) and ARL/13/062 (fed)
  - Extra studies: Study No. ARL/13/547 (fasting) and ARL/13/548 (fed)

- These pilot and extra BE studies were conducted before the current BE guidance for Methylphenidate HCl ER Tablets was revised on November 2014.

Pilot studies: Study No. ARL/13/061 (fasting) and ARL/13/062 (fed)

Are there any additional studies? (e.g. pilot, failed) **If yes, please provide the location of report (complete/summary).**	☒ Yes ☐ No Two pilot studies (fasting and fed) submitted. ANDA 208607, EDR 2, 05/31/2016, M.2.7. Clinical Summary, Clinical Summary 13-061-13-062 – Pilot –Word.
Number of Subjects	Three test lots (A, B, and C) were used for each pilot study: Fasting study: Test A vs RLD: N=23 Test B vs RLD: N=24 Test C vs RLD: N=24 Fed study: Test A vs RLD: N=21 Test B vs RLD: N=20 Test C vs RLD: N=20
Are the test formulations in the pilot studies and pivotal studies similar?	☐ Yes ☒ No Please see comments in Section 4.2.1 Formulation data for pilot studies of this review for details.
What was the objective of pilot study?	To examine the feasibility of an approach that is intended to ultimately be used in a pivotal study.
Please comment on reason(s) of failure.	All BE studies conducted with Test A, B and C lot did not meet the BE requirement listed in the current BE guidance possibly due to difference in formulation in ER portion based on rate controlling excipients. Please see comments in Section 4.2.1 Formulation data for extra studies of this review for details.
Any serious adverse events or deaths reported?	☐ Yes ☒ No

Pilot study-Fasting (Study No. ARL/13/061)

Methylphenidate (No of subjects completed= 24) Dose (1 x 54 mg Tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study Code: ARL/13/061)						
Parameter	**Test (A)**	**N**	**RLD (D)**	**N**	**Ratio**	**90% C.I.**
AUC_{0-3} (ng.hr/mL)	21.70	23	21.67	24	100.1809	88.5559 - 113.3319
AUC_{3-t} (ng hr/mL)	215.99	23	217.81	24	99.1615	85.3164 - 115.2534
AUC_{0-inf} (ng.hr/mL)	254.59	23	252.15	24	100.9661	87.2213 - 116.8769
C_{max} (ng/mL)	20.79	23	23.10	24	89.9984	78.8588 - 102.7116

Methylphenidate (No of subjects completed= 24) Dose (1 x 54 mg Tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study Code: ARL/13/061)						
Parameter	**Test (B)**	**N**	**RLD (D)**	**N**	**Ratio**	**90% C.I.**
AUC_{0-3} (ng.hr/mL)	16.51	24	21.67	24	76.1918	67.4718 - 86.0388
AUC_{3-t} (ng hr/mL)	179.96	24	217.81	24	82.6212	71.2406 - 95.8199
AUC_{0-inf} (ng.hr/mL)	214.73	24	252.15	24	85.1578	73.7215 - 98.3681
C_{max} (ng/mL)	16.58	24	23.10	24	71.7544	62.9937 - 81.7334

Methylphenidate (No of subjects completed= 24) Dose (1 x 54 mg Tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fasting Bioequivalence Study (Study Code: ARL/13/061)						
Parameter	**Test (C)**	**N**	**RLD (D)**	**N**	**Ratio**	**90% C.I.**
AUC_{0-3} (ng.hr/mL)	18.92	24	21.67	24	87.3312	77.3363 - 98.6179
AUC_{3-t} (ng hr/mL)	186.12	24	217.81	24	85.4491	73.6790 - 99.0995
AUC_{0-inf} (ng.hr/mL)	231.56	24	252.15	24	91.8336	79.5008 - 106.0796
C_{max} (ng/mL)	15.84	24	23.10	24	68.5836	60.2101 - 78.1217

Pilot study-Fed (Study No. ARL/13/062)

Methylphenidate (No of subjects completed= 21) Dose (1 x 54 mg Tablets) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (Study Code: ARL/13/062)						
Parameter	**Test (A)**	**N**	**RLD (D)**	**N**	**Ratio**	**90% C.I.**
AUC_{0-4} (ng.hr/mL)	30.50	21	34.81	21	87.6445	78.6167 - 97.7089
AUC_{4-t} (ng hr/mL)	203.09	21	198.69	21	102.2162	92.3030- 113.1940
AUC_{0-inf} (ng.hr/mL)	244.40	21	244.16	21	100.1000	88.5204- 113.1944
C_{max} (ng/mL)	20.07	21	21.51	21	93.2860	84.2715- 103.2648

Methylphenidate (No of subjects completed= 21) Dose (1 x 54 mg Tablets) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (Study Code: ARL/13/062)						
Parameter	**Test (B)**	**N**	**RLD (D)**	**N**	**Ratio**	**90% C.I.**

AUC_{0-t} (ng.hr/mL)	29.86	20	34.81	21	85.7925	76.8532 - 95.7717
AUC_{4-t} (ng hr/mL)	190.17	20	198.69	21	95.7134	86.3202 - 106.1289
AUC_{0-inf} (ng.hr/mL)	254.99	20	244.16	21	104.4365	92.2145 - 118.2783
C_{max} (ng/mL)	16.61	20	21.51	21	77.2075	69.6581 - 85.5750

Methylphenidate (No of subjects completed= 21) Dose (1 x 54 mg Tablets) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals						
Fed Bioequivalence Study (Study Code: ARL/13/062)						
Parameter	**Test (C)**	**N**	**RLD (D)**	**N**	**Ratio**	**90% C.I.**
AUC_{0-t} (ng.hr/mL)	27.54	20	34.81	21	79.1366	70.8547 - 88.3865
AUC_{4-t} (ng hr/mL)	162.49	20	198.69	21	81.7788	73.7168 - 90.7224
AUC_{0-inf} (ng.hr/mL)	245.26	20	244.16	21	100.4514	88.3802 - 114.1714
C_{max} (ng/mL)	13.91	20	21.51	21	64.6710	58.3191 - 71.7148

Extra studies: Study No. ARL/13/547 (fasting) and ARL/13/548 (fed)

Are there any additional studies? (e.g. pilot, failed) **If yes, please provide the location of report (complete/summary).**	☒ Yes ☐ No Two extra studies (fasting and fed) submitted. ANDA 208607, EDR 2, 05/31/2016, M.2.7. Clinical Summary, Clinical Summary ARL/13/547 and 548 Old Guidance –Word.
Number of Subjects	Two test lots (A and B) were used for each extra study Fasting study: Test A vs RLD: N=54 Test B vs RLD: N=56 Fed study: Test A vs RLD: N=56 Test B vs RLD: N=57
Are the test formulations in the extra studies and pivotal studies similar?	☐ Yes ☐ No (see comments below) Test A lot is not similar but Test B lot is the same as the bio-lot used in the pivotal studies. Please see comments in Section 4.2.2 Formulation data for extra studies of this review for details.
What was the objective of extra study?	To determine in vivo bioequivalence of two test lots
Please comment on reason(s) of failure.	The BE studies conducted with Test A lot did not meet the BE requirement listed in the current BE guidance possibly due to difference in formulation in ER portion based on rate controlling excipients. Please see comments in Section 4.2.2 Formulation data for extra studies of this review for details.
Any serious adverse events or deaths reported?	☐ Yes ☒ No

Extra study-Fasting (Study No. ARL/13/547)

Methylphenidate (No of subjects completed= 54) Dose (1 x 54 mg Tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study (Study Code: ARL/13/547)							
Parameter	**Test (A)**	**N**	**RLD (C)**	**N**	**Ratio**	**90% C.I.**	
C_{max}	19.8164	54	17.2898	54	114.61	109.42	120.05
AUC_{0-3}	20.4710	54	17.0891	54	119.79	113.06	126.92
AUC_{3-t}	150.5804	54	165.3700	54	91.06	88.12	94.09
AUC_{inf}	178.5704	54	191.3904	54	93.30	90.64	96.05

Methylphenidate (No of subjects completed= 56) Dose (1 x 54 mg Tablet) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Bioequivalence Study (Study Code: ARL/13/547)							
Parameter	**Test (B)**	**N**	**RLD (C)**	**N**	**Ratio**	**90% C.I.**	
C_{max}	17.5471	56	17.2487	56	101.73	97.20	106.47
AUC_{0-3}	17.0773	56	17.1871	56	99.36	95.35	103.54
AUC_{3-t}	151.2259	56	165.4662	56	91.39	87.96	94.96
AUC_{inf}	178.6779	55	193.0778	55	92.54	89.56	95.62

Extra study-Fed (Study No. ARL/13/548)

Methylphenidate (No of subjects completed= 56) Dose (1 x 54 mg Tablets) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (Study Code: ARL/13/548)							
Parameter	**Test (A)**	**N**	**RLD (C)**	**N**	**Ratio**	**90% C.I.**	
C_{max}	28.3649	55	19.4324	55	145.97	138.11	154.27
AUC_{0-4}	36.5329	55	30.8893	55	118.27	110.95	126.07
AUC_{4-t}	179.1121	55	181.6995	55	98.58	95.74	101.50
AUC_{inf}	223.6902	54	221.0478	54	101.20	98.96	103.48

Methylphenidate (No of subjects completed= 57) Dose (1 x 54 mg Tablets) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (Study Code: ARL/13/548)							
Parameter	**Test (B)**	**N**	**RLD (C)**	**N**	**Ratio**	**90% C.I.**	
C_{max}	22.1845	57	19.1772	57	115.68	109.32	122.42
AUC_{0-4}	29.6248	57	30.4063	57	97.43	92.50	102.62
AUC_{4-t}	170.0419	57	178.8713	57	95.06	92.44	97.76
AUC_{inf}	207.6629	56	218.0250	56	95.25	93.01	97.54

4.4.2 SAS Output/Phoenix Output

SAS output for Subject-by-formulation interaction variance

Study	SAS Data	SAS Code	SAS Stat	SAS Output/Table
Fasting (ARL/14/694)	Conc_Fasting.csv	Fasting_SBF code.sas	N/A	Fastingres.csv
Fed (ARL/14/695)	Conc_Fed.csv	Fed_SBF code.sas	N/A	Fedres.csv

Study	Phoenix Project
Fasting (ARL/14/694)	208607_Fasting 54 mg.phxproj
Fed (ARL/14/695)	208607_Fed 54 mg.phxproj

NOTE TO REGULATORY PROJECT MANAGER (RPM): The review is pending consult response from Office of Research and Standards (ORS).

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA: 208607

APPLICANT: CorePharma, LLC

DRUG PRODUCT: Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg

No letter is prepared at this time pending the outcome of the consult with ORS.

Sincerely yours,

{See appended electronic signature page}

Nilufer M. Tampal, Ph.D.
Director, Division of Bioequivalence III
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

4.5 Outcome Page

Completed Assignment for 208607 ID: 29296

Reviewer: Hwang, Sung-Yong **Date Completed:**

Verifier: , **Date Verified:**

Division: Division of Bioequivalence

Description: Methylphenidate HCl ER Tablets USP,18 mg, 27 mg, 36 mg and 54 mg (Original full review)

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
29296	4/18/2016	BIO	ANDA Original [1]	1	1
29296	4/18/2016	Complexity	pAUC Statistical Analysis [0.5]	0.5	0.5
29296	4/18/2016	Parallel	Dissolution-Based Waiver (MR) (For all waiver strengths) [0.5]	0.5	0.5
29296	4/18/2016	Parallel	In-Vitro Dose-Dumping in Alcohol (For all strengths) [0.5]	0.5	0.5
29296	4/18/2016	Parallel	Fasting Study (Full template) [1]	1	1
29296	4/18/2016	Parallel	Fed Study (Full Template) [1]	1	1
29296	10/12/2016	BIOQUALITY	Quality Assessment [1-5]	5	5
				Total:	9.5

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208607Orig1s000

OTHER REVIEW(S)

PROCESS

Product Background:

ANDA: 208607

Drug Product Name / Strength: Methylphenidate Hydrochloride Extended Release (b) (4) Tablets, 18 mg, 27 mg, 36 mg, 54 mg

Route of Administration: Oral

Applicant Name: Core Pharma

Review Summary: The drug product Methylphenidate Hydrochloride Extended Release tablets, 18 mg, 27 mg, 36 mg, 54 mg will be manufactured at (b) (4) (b) (4) (b) (4) (b) (4)

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
0000 (1) ORIG-1: Original ANDA submission	*04/18/2016*	*All*
0001 (2) ORIG-1: Original ANDA submission	05/31/2016	*All*
0010 (11): ORIG-1: Original ANDA submission	03/20/2017	*All*
0012 (13): ORIG-1: Quality response	06/12/2017	*All*

Highlight Key Outstanding Issues from Last Cycle: NA.

Concise Description Outstanding Issues Remaining: NA
ANDA is recommended for approval from Process perspective

P.3 Manufacture
Batch Formula
Information provided: All four strengths of Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg are **proportionally similar** and contain the same inactive ingredients except variation in the color overcoat (b) (4) (b) (4)

54 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Reviewer's Assessment: Adequate. The firm provided microbial testing results (USP <61> and <62>) for two selected batches.

Comparability Protocols:

Reviewer's Assessment: The applicant did not provide Comparability Protocols. No deficiencies were identified based upon the information provided.

Post-Approval Commitments

Reviewer's Assessment: NA
First Cycle Deficiency (Review #1):
Lifecycle Management Considerations

NA

List of Deficiencies: ANDA is recommended for approval from Process perspective

Primary Process Reviewer Name and Date: ***Iwona Weidlich, PhD, 06 /13/2017***

Secondary Reviewer Name and Date: I concur with primary reviewer's assessment

Arwa El Hagrasy, PhD, 06/13/2017

Iwona
Weidlich

Digitally signed by Iwona Weidlich
Date: 6/13/2017 04:34:14PM
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Arwa
El Hagrasy

Digitally signed by Arwa El Hagrasy
Date: 6/13/2017 04:45:57PM
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Office of Generic Drugs
DQMM/ORS/OGD CONSULT REVIEW

To:	Sung-Yong Hwang, Ph.D Through Nilufer M. Tampal, Ph.D Director, Division of Bioequivalence III Office of Generic Drugs Center for Drug Evaluation and Research
Re:	DBIII Request for Consultation: ANDA 208607
Consult No:	NA
Drug Product:	Methylphenidate HCl ER Tablets 18 mg, 27 mg, 36 mg, and 54 mg
Sponsor:	CorePharma, LLC
Original Submission:	04/18/2016
Date of Consult Request:	11/20/2016
Date of Review:	**0**1/05/2017
Consultant:	Lili Pan, Ph.D., DQMM/ORS/OGD
Through:	Andrew Babiskin, Ph.D., DQMM/ORS/OGD Liang Zhao, Ph.D., Director, DQMM/ORS/OGD

Reason for Consultation

CorePharma, LLC submitted ANDA 208607 seeking the approval for 18mg, 36mg, 54mg, and 72mg Methylphenidate (MPH) Hydrochloride (HCl) Extended Release (ER) Tablets, referencing Janssen Pharmaceuticals, Inc.'s Concerta (MPH HCl) ER Tablets (NDA 021121). In the submission dated April 18, 2016, the firm submitted bioequivalence (BE) studies with results of fasting and fed comparing the test product MPH HCl ER Tablets, 54mg, to the corresponding reference product, Janssen Pharmaceuticals, Inc's Concerta ER Tablets, 54mg. The BE studies were completed following the current revised draft guidance (revised November 2014) on MPH HCl ER Tablets.

The 90% confidence intervals (CI) for all the five pharmacokinetic (PK) parameters - three partial AUC ($AUC_{0\text{-}T1}$, $AUC_{T1\text{-}T2}$, $AUC_{T2\text{-}T3}$) metrics in addition to the traditional ($AUC_{0\text{-}\infty}$ and C_{max}) metrics - are within the acceptable BE limits of 80%-125% for both fasting and fed BE studies. In addition, the fasting BE studies also met the additional assessment for subject-by-formulation (SbF) interaction variance component ($\sigma_D{}^2$), for all the five PK metrics. Hence, the fasting BE study is acceptable.

However the fed BE study (No. ARL-14695) is questionable since the upper 95% confidence bound for the SbF interaction variance component $\sigma_D{}^2$, $H_{\sigma_D{}^2}$, exceeds 0.03 for the PK metrics of C_{max} and $AUC_{4\text{-}8}$, from both the reviewer and the firm's calculations.

Based on the above information, the DBIII seeks ORS's inputs on the acceptability of the fed BE study due to the failure to meet the BE requirement for the SbF interaction variance.

Executive Summary

In the submitted fasting and fed BE studies from CorePharma comparing their proposed generic product to Concerta, the studies passed all the currently recommended five BE metrics in the average BE (ABE) evaluation, all of which were associated with tight 90% CIs. However, in the SbF evaluation, the fed state failed in C_{max} and $AUC_{4\text{-}8}$ metrics with values right above the value 0.03 (the recommended allowance) for $H_{\sigma_D{}^2}$, while most of the remaining metrics of both fed and fasting states were far below this allowance. In the working group to revise the BE guidance, these two metrics were not indicated as a source of concern for the complaints about generic Concerta that triggered the Concerta BE guidance revision. In fact, later fully replicate studies conducted with these problematic products did not show evidence of a SbF issue with C_{max} and the middle pAUC. As a final point, Watson/Actavis (ANDA 76772/76655) submitted fully replicate studies against Concerta, where the $H_{\sigma_D{}^2}$ values for C_{max} and $AUC_{3\text{-}7}$ in the fasting state were above 0.03 and far higher than the value observed from CorePharma for C_{max} and $AUC_{4\text{-}8}$ in the fed state. The Watson studies were found to be adequate based upon similar rationale as above. With all these considerations, DQMM recommends that the results of CorePharma fully-replicated studies be found acceptable.

Summary of BE Guidance for MPH ER Tablets and SbF Criteria

In November 2014, FDA released a revised BE guidance on Methylphenidate HCl ER Tablet.[1] The revision was done to solve the Tracked Safety Issue (TSI) in response to the lack of efficacy found in post-market reporting for the approved Concerta generics by Kudco (ANDA 091695) and Mallinckrodt (ANDA 202608). In the new BE guidance, the *in vivo* BE studies are recommended with evaluation of the test-to-reference (T/R) ratio and subject-by-formulation (SbF) interaction variance ($\sigma_D{}^2$) of: (1) $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}3}$, $AUC_{3\text{-}7}$, $AUC_{7\text{-}12}$, and C_{max} for fasting conditions; and (2) $AUC_{0\text{-}\infty}$, $AUC_{0\text{-}4}$, $AUC_{4\text{-}8}$, $AUC_{8\text{-}12}$, and C_{max} for fed conditions.

For the BE studies under both fasting and fed conditions, the acceptability criteria for T/R ratio is that the 90% CI falls within the standard BE limits of 80-125%. For the SbF evaluation, the 95% upper confidence bound of $\sigma_D{}^2$ ($H_{\sigma_D{}^2}$) is calculated and "as per APPENDIX A in the FDA 2001 bioequivalence guidance, the recommended allowance for $\sigma_D{}^2$ is 0.03". It does not clearly state that whether the test allowance is for point estimate or the upper bound of $\sigma_D{}^2$.

In fact, $\sigma_D{}^2$ is a component from the test of IBE in the 2001 BE guidance.[2] The recommended allowance 0.03 is "associated with the percentage of individuals whose average T

[1] Draft Guidance on Methylphenidate Hydrochloride (RLD: Concerta, N21121) http://www fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm320007.pdf
[2] Guidance for Industry: Statistical Approaches to Establishing Bioequivalence, January 2001, http://www fda.gov/downloads/Drugs/.../Guidances/ucm070244.pdf

to R ratios lie outside 80%-125%." When σ_D=0.1741, ~20% of the individuals would have their average ratios outside80-125%.[3] A thorough comparison of σ_D measures *vs.* proportion of individuals outside 80-125% was provided by Hauck, *et.al.* in 2000. [4]In the full aggregate IBE test, ${\sigma_D}^2$ is one of the three major components. The determination of IBE limit is based on the consideration of average BE criterion and the addition of variance terms to the individual BE criterion:

$$\theta_I = \frac{(ln1.25)^2 + \varepsilon_I}{{\sigma_{W_0}}^2}$$

Here ε_I considers both ${\sigma_D}^2$ and the difference of within-subject variabilities (${\sigma_{WT}}^2 - {\sigma_{WR}}^2$). The recommended allowance of ε_I is 0.05, with 0.03 for ${\sigma_D}^2$ and 0.02 for (${\sigma_{WT}}^2 - {\sigma_{WR}}^2$). The 0.03 allowance for ${\sigma_D}^2$ is equivalent to 20% of individuals outside BE limits. Therefore, a test product could still pass the IBE test even though the corresponding BE metrics fail in SbF test (${\sigma_D}^2$>0.03), if they have small T/R ratios (tight 90% CI windows), or if their within-test and within-reference variability differences are small ((${\sigma_{WT}}^2 - {\sigma_{WR}}^2$) < 0.02). That is to say, for the IBE criteria it allows >20% of individuals outside the BE limits (${\sigma_D}^2$>0.03), while in the Concerta BE guidance it strictly requires <20% of the individuals outside the BE limits (${\sigma_D}^2$<0.03).

Summary of DBIII Review of ANDA 208607

CorePharma, LLC submitted in their application ANDA 208607 the results of BE studies comparing their generic version of MPH HCl ER Tablets, 54 mg, to the corresponding reference product, Janssen Pharmaceutical Inc.'s Concerta ER Tablets, 54 mg. The application includes waiver requests for the lower strengths, 18 mg, 27 mg, and 36 mg of the test product.

(b) (4)

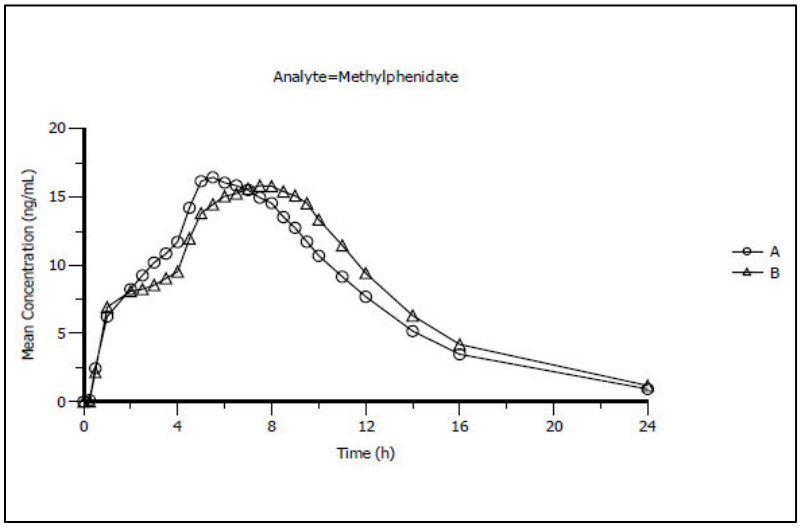
(b) (4) The *in vivo* BE studies were done under both ubjects, conducted as a single-dose, four-period, two-sequence, replicated crossover study, as per the current revised draft guidance on MPH HCl ER Tablets referencing Concerta. Table 1 provides the results of the ABE studies for both fasting and fed states and Figure 1 provides the mean PK curves under both study conditions. Since the within-reference standard deviation (s_{WR}) are all within a range of

[3] Chen, Mei-Ling, and Lawrence J. Lesko. "Individual Bioequivalence Revisited." Clinical pharmacokinetics 40.10 (2001): 701-706.
[4] Hauck, Walter W. *et.al.* "Subject-by-Formulation Interaction in Bioequivalence: Conceptual and Statistical Issues." Pharmaceutical research 17.4 (2000): 375-380.

0.14~0.19 and well below the 0.294 regulatory limit for the highly-variable drugs (HVD), reference-scaled ABE (RSABE) for HVDs does not apply and the 90% CI must be between 80-125% for the PK metric evaluation.

Table 1. ABE results for studies ARL/14/694 (fasting) and ARL/14/695 (fed). The results are reviewer-calculated and provided by DBIII. The BE calculations were performed in Phoenix. *PE* represents the point estimate, *LL* and *UL* represent the lower and upper limits of the 90% CI of the metrics respectively.

Metric	***PE***	***LL***	***UL***
Fasting			
$AUC_{0-\infty}$	94.36	91.72	97.08
AUC_{0-3}	104.48	100.75	108.35
AUC_{3-7}	112.73	108.92	116.68
AUC_{7-12}	86.75	83.94	89.65
C_{max}	101.68	97.73	105.78
Fed			
$AUC_{0-\infty}$	97.22	94.34	100.20
AUC_{0-4}	98.30	94.49	102.26
AUC_{4-8}	107.26	102.56	112.18
AUC_{8-12}	91.02	87.71	94.46
C_{max}	116.90	111.32	122.76



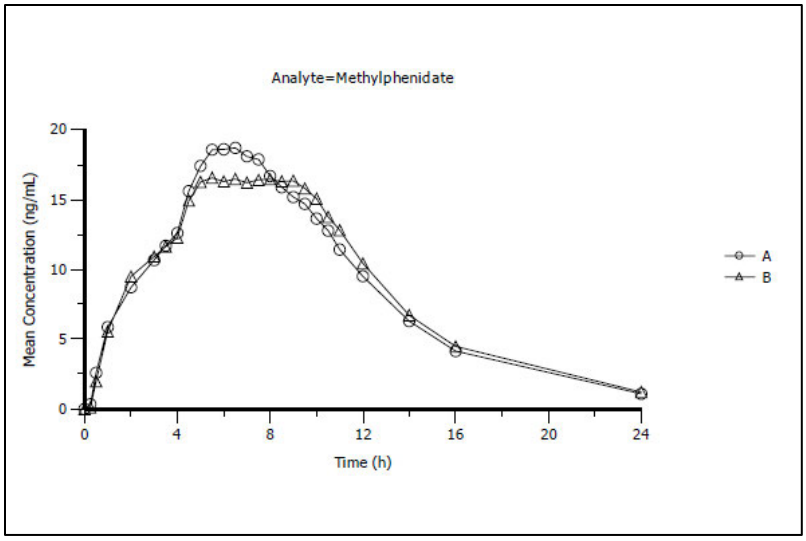


Figure 1. Mean MPH concentrations versus time for CorePharma/test formulation (A) and Concerta/reference formulation (B) in the fasting (upper panel) and fed (lower panel) states.

The SbF results are given in Table 2 for both fasting and fed studies. The within-reference standard deviation s_{WR}, within-test standard deviation s_{WT}, *SbF* interaction variance component ${\sigma_D}^2$, and its 95% upper confidence bound $H_{{\sigma_D}^2}$ are provided.

Table 2. *SbF* results for fasting (ARL/14/694) and fed (ARL/14/695) studies. The results are reviewer calculated and provided by DBIII. The SbF calculations are performed in SAS. DBIII results were confirmed by DQMM's independent analysis.

Metric	s_{WR}	s_{WT}	${\sigma_D}^2$	$H_{{\sigma_D}^2}$
Fasting				
$AUC_{0-\infty}$	0.168373	0.099611	-0.00595	0.000867117
AUC_{0-3}	0.164283	0.143203	0.003565	0.016008448
AUC_{3-7}	0.152035	0.164159	-0.00167	0.009294078
AUC_{7-12}	0.187577	0.11179	-0.00284	0.007315087
C_{max}	0.16211	0.193185	-0.00083	0.013626058
Fed				
$AUC_{0-\infty}$	0.150267	0.151495	-0.00254	0.005990668
AUC_{0-4}	0.15843	0.18801	0.009424	0.025238303
AUC_{4-8}	0.142807	0.24123	0.010484	0.030631957
AUC_{8-12}	0.162272	0.202141	-0.00061	0.013096282
C_{max}	0.154211	0.272251	0.010253	0.034414719

In the fasting studies, $H_{{\sigma_D}^2}$ for all five metrics are below the recommended 0.03 allowance. However in the fed studies, AUC_{4-8} and C_{max} are borderline above 0.03; however, the point estimates of ${\sigma_D}^2$ for all metrics fall below 0.03. According to current BE guidance for MPH HCl ER Tablets, the ${\sigma_D}^2$ evaluation is recommended for ensuring the switchability

between test and reference products. Therefore, the SbF failures initiated the consultation request from DBIII to DQMM. In the consultation, it is noted that the firm provided different values for each parameter, although the results also show failures on AUC_{4-8} (0.0305) and C_{max} (0.0347) based on the point estimate of $\sigma_D{}^2$ per firm's statistical reports.

ORS Response

Question: Based on the above information, the DBIII seeks ORS confirmation from DQMM for whether the fed BE study (No. ARL/14/695) should be considered unacceptable, due to the failure to meet the BE requirement for SbF interaction variance.

Based on an extensive analysis of the fed, fully-replicated CorePharma BE study, we concluded that the BE results acceptable. After receiving post-market complaints for two Concerta generics (by Mallinckrodt and Kudco) and initiating a TSI, OGD convened a working group that resulted in the revising of the BE guidance for generic products referencing Concerta. Since a number of complaints centered on the lack of duration of efficacy, particularly after 7 hours, additional pAUC metrics were included in the guidance to assess MPH concentrations in the associated time periods. There were also complaints related to early onset from the generics and the SbF was included in the guidance primarily as a way of controlling the variance for the early pAUCs. The detailed history and summaries of the revision could be found in the Concerta BE guidance revision memo[5] and the review of (b) (4)

The ANDA 76772/76655 submitted by Watson/Actavis, is a case similar to the CorePharma case, where the BE studies had SbF failure on its fasting AUC_{3-7} and C_{max}. Additionally, the 95% upper confidence bonds of the SbF interaction variance, are higher than that for CorePharma – 0.05098 for AUC_{3-7} and 0.05539 for C_{max}. In Watson's case, the two problematic metrics would be able to pass full IBE and NTI criteria and it was never the intention of the Concerta guidance to place criteria more stringent than that for NTI. In addition, the review concluded that C_{max} and AUC_{3-7} were not metrics of primary concern during the TSI and were not identified as needing additional level of control. As a result, the BE studies for Watson were found to be adequate, regardless of the SbF result.

In BE revision discussions, C_{max} andAUC_{4-8} (and its associated fasting metric of AUC_{3-7}) were not included as metrics needing additional control (i.e., variance control and/or point estimate restriction). In fact, the original Mallinckrodt study of two-way crossover fasting state

[5] Concerta guidance internal, "Memo: Revision of the Draft Bioequivalence Guidance for Methylphenidate Hydrochloride Extended-Release Tablets", http://panorama.fda.gov/project/view?ID=53ff812b000871179208c9f0461b1dc7

[6] Babiskin, Andrew. *et.al.* "OGD Science Staff Consult Review: Response to DBIII Request ANDA 076772 ORS Consult Request from DBIII", http://panorama.fda.gov/issue/view?ID=55ce50bc00103d3c5ce4943a05b43ce8

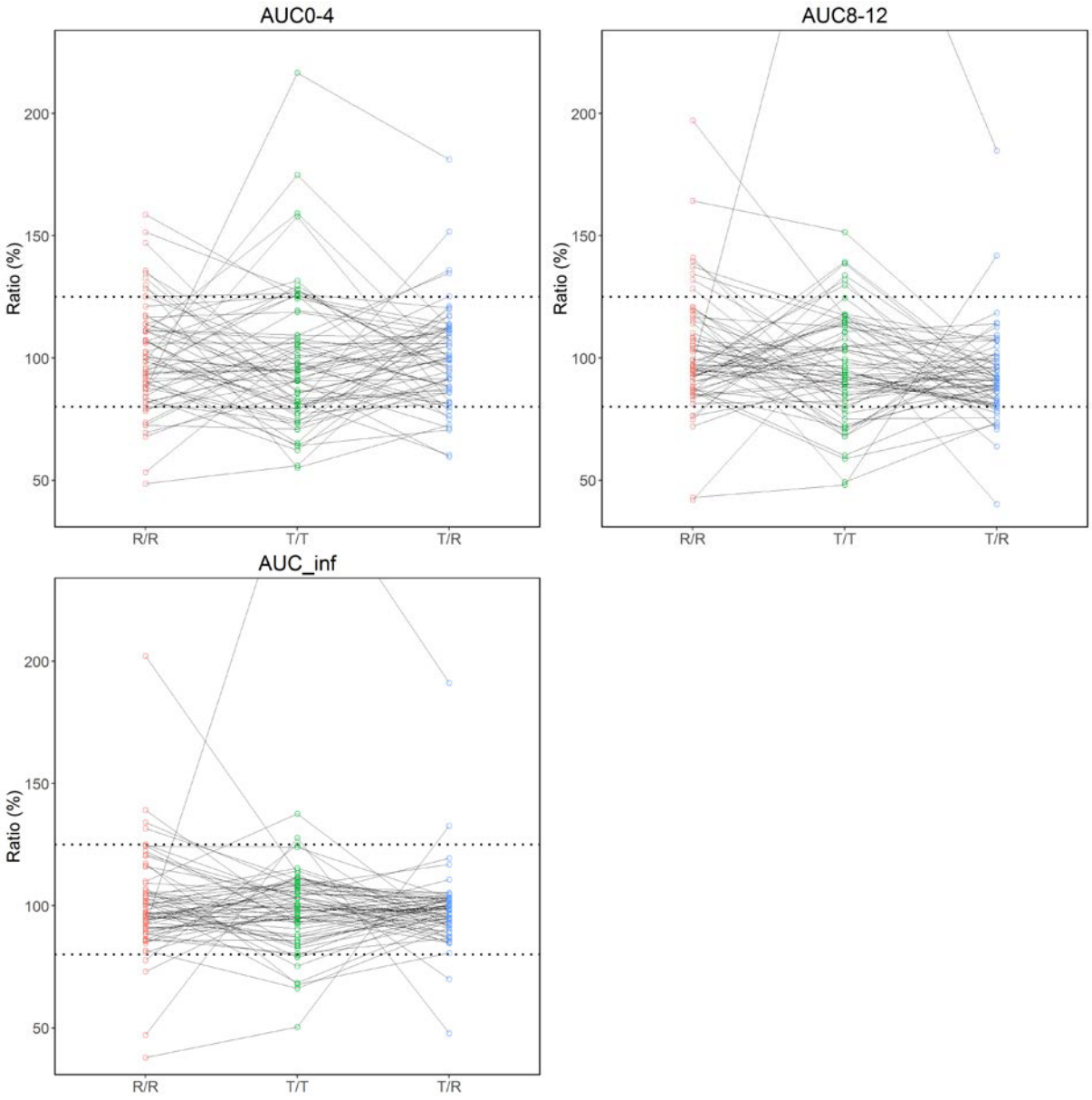
had a similar case with lower bound close to the threshold, and a significant amount of individuals are observed to be outside 80-125% for C_{max}.[7] Furthermore, in the other submission of the Concerta generics by Actavis (ANDA 76772/76655) as mentioned above, its C_{max} for fasting state actually had higher SbF upper confidence ($H_{\sigma_D^2}$=0.05539), yet still got approved. This means that for C_{max}, as long as these metrics pass the BE limit 80-125% requirement, it does not raise additional concerns if the upper bound goes beyond the SbF threshold. It should be noted that since the Concerta guidance revision, Kudco conducted new fully-replicate BE studies under fasting and fed conditions and ORS sponsored its own fasting fully-replicate BE study comparing the Mallinckrodt product to Concerta. For the Kudco studies, all metrics had $H_{\sigma_D^2}$ values below 0.03. For the Mallinckrodt study, only AUC_{7-12} had an upper bound value above 0.03 ($H_{\sigma_D^2}$=0.04782). These results demonstrates that for the complaints associated with the Mallinckrodt and Kudco products, they are not probably due to SbF issues with C_{max} and the middle pAUCs.

Recommendation: **DQMM recommends that the CorePharma fed study ARL/14/695 be found acceptable.** While the estimated 95% upper confidence bound for the subject-by-formulation interaction variance for AUC_{4-8} and C_{max} in the fed state is greater than the recommended allowance of 0.03, we find the fed study still be acceptable for the following reasons:

1. The fed study passes full NTI criteria for AUC_{4-8}, and only the variance comparison test for C_{max}. Even though C_{max} does not pass the tighter BE limit due to its high T/R point estimate, results still indicate that C_{max} has very tight 90% CI interval.
2. The $H_{\sigma_D^2}$ values above 0.03 for C_{max} and AUC_{4-8} are significant less than the $H_{\sigma_D^2}$ values that were ultimately found acceptable for the same associated metrics in the Watson product (ANDA 76772/76655).
3. The metrics of AUC_{4-8} and C_{max} are “low-risk” metrics since they were neither associated with the complaints for Mallinckrodt and Kudco generics triggering the TSI, nor were they identified as directly needing additional control in the TSI.

[7] See the previously mentioned ANDA 76772/76655 review

Appendix A. R/R, T/T, and T/R scatterplots for AUC_{0-4}, AUC_{8-12}, and $AUC_{0-\infty}$ (AUC_inf) in fed, fully-replicated CorePharma BE study (ARL/14/695). Lines connect the ratios withi the same individual.



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208607Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

Approval Type: ☒ **FULL APPROVAL** ☐ **TENTATIVE APPROVAL** ☐ **SUPPLEMENTAL APPROVAL (NEW STRENGTH)**

RPM: Megan Tychinski Team Leader: Joe Shin

☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV (***eligible for 180 day exclusivity* ☐ **Yes** ☒ **No)** ☐ **MOU** ☒ **RX or** ☐ **OTC**

ANDA #: 208607 Applicant: Impax Laboratories, Inc.
Established Product Name: Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg, and 54 mg

Basis of Submission (RLD): NDA 21121 / Concerta Extended-Release Tablets, 18 mg, 27 mg, 36 mg, and 54 mg Janssen Pharmaceuticals, Inc.

Basis Of Submission Discontinued? Yes ☐ No ☒

If yes, has FR published indicating the Agency determined the product was not withdrawn for reasons of safety or effectiveness?

Yes ☐ FR Notice dated _____; Vol. _____; No. _____

No ☐ Consult completed but not yet published in FR

(Is ANDA based on an approved Suitability Petition? ☐ Yes ☒ No, if yes, use SP language in template)

Does the ANDA contain REMS? ☐ Yes ☒ No *(If YES, initiate approval action 6 weeks prior to target action date)*

Regulatory Project Manager Evaluation: **Date: 6/27/2017**

☒ Date (Received) Acceptable for Filing -- Date 4/18/2016

☐ Date last Complete Response (CR) letter was issued -- Date N/A

☐ Previously reviewed and tentatively approved (if applicable) --- Date N/A

YES	NO		
☒	☐	All submissions have been reviewed and relevant disciplines are adequate and finalized in the platform (Date or N/A)	
		Date of Acceptable Bioequivalence 1/23/2017 • Date of BE Guidance (if any) 11/1/2014 Date of Acceptable Labeling 5/15/2017 • Date of last RLD labeling update 1/4/2017 Date of Acceptable Quality 7/3/2017 • DMF No(s) (b) (4) Date(s) Acceptable 3/20/2017 • No outstanding DMF review amendments ☒ • Date of Acceptable Overall Manufacturing Inspection 5/31/2017	If applicable: Date of Acceptable Microbiology N/A Date of Acceptable Clinical Review N/A Date of Acceptable Dissolution 6/30/2017 Date of Acceptable REMS N/A
☒	☐	**MMA:** All amendments submitted to the Agency on or after December 5, 2016 contain (1) a patent certification or section viii statement, (2) a recertification, or (3) a verification statement per 21 CFR 314.96(d).	
☐	☒	Are consults pending for any discipline?	
☒	☐	OSIS Clinical Endpoint and Bioequivalence Site Inspections are acceptable - Decline to inspect, 5/19/2016	
☒	☐	Is there a pending legal or regulatory issue (refer to Policy Alert Tracker)? If YES → OGD Policy Lead confirmed ANDA may proceed ☒; Memo uploaded (if applicable) ☐	
☐	☒	Has there been an amendment providing for a major change in formulation or new strength since filing? If YES→Verify a second filing review was completed (if applicable) and that all disciplines completed new reviews ☐	
☐	☒	Is ANDA a Priority Approval (First generic, drug shortage, PEPFAR, other OGD Communications priorities)? If YES → Email OGD Communications Staff or Division liaison 30 to 60 days prior to approval, Date emailed _____	
Review Discipline/Division and RPM TL Endorsements			
☒	☐	Applicable review discipline/division endorsements completed	
☒	☐	RPM Team Leader endorsement completed	

Evidence of review and approval can be located on the corresponding signature sheet on file with QMS.

2 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Food and Drug Administration CDER / Office of Generic Drugs	Document No.: 4000-LPS-066	Version: 02
Document Status: DRAFT		
Title: Approval Routing Summary Form	**Author:** Heather Strandberg	

ANDA APPROVAL ROUTING SUMMARY ENDORSEMENTS AND FINAL DECISION

1. Division of Legal and Regulatory Support Endorsement

Date: 7/3/2017
Name: IM for MHS

Patent/Exclusivity Certification:
☐ **PI** ☐ **PII** ☐ **PIII** ☒ **PIV** ☐ **section viii**
If Paragraph IV Certification- did applicant:
Notify patent holder/NDA holder: Yes ☒ No ☐
Was applicant sued w/in 45 days: Yes ☐ No ☒
Has case been settled: Yes ☐ No ☐
Applicant addressed all listed exclusivities Yes ☒ No ☐

Do the patent and exclusivity certifications align? Yes ☒ No ☐
Have there been any revisions to the use code since the original submission? Yes ☐ No ☒

RLD = Concerta NDA# 21121 ☒ **RX or** ☐ **OTC**
Date Checked in Orange Book#**:** 7/3/2017

Type of Letter:
☒ APPROVAL
☐ TENTATIVE APPROVAL
☐ SUPPLEMENTAL APPROVAL (NEW STRENGTH)

LETTER RECOMMENDED FOR DRUGS@FDA Yes ☐ No ☐

Forfeiture Information
Is a forfeiture memo needed for the first applicant: Yes ☐ No ☒
If yes, the date forfeiture memo was completed
Date_____ ANDA number _____

180 Day Exclusivity Information
Is applicant eligible for 180 day exclusivity Yes ☐ No ☒
☐ Sole
☐ Shared
ANDA Exclusivity for each strength: Yes ☐ No ☐
Which strength(s) eligible _____

Comments: Bos = Concerta (NDA 21121) Application submission 4/18/2016 with PIV certifications to the '373, '129, '798, '179, '038, '416 and '549 patents. Acknowledgment letter signed 6/3/2016.
Amendment 6/17/2016 CorePharma provided copies of (b) (4) PIV notice tracking sent 6/15/2016 to Janssen Pharmaceuticals, Inc. (NJ) x2, Alza Corporation (CA), Alza Corporation Intellectual Property Dept (CA) and Johnson & Johnson (NJ) and received 6/16/2016.
Amendment 8/11/2016 Corepharma states no legal action was taken on the PIV certifications within the statutory 45-day time period.

This drug product is governed by pre-MMA regulations, meaning the determination of 180-day exclusivity is on a patent-by-patent basis, rather than by drug product. 180-day with respect to the '129 and '798 patents has been previously granted, and the exclusivities have been triggered and expired. The exclusivity to the '373 patent was triggered by a CAFC decision with a mandate being issued 6/4/2010. 180-day with respect to the '179, '038, '416 and '549 patents has not been granted as these patents were listed after the previous round of 180-day on the three original patents. Applicants that have a valid PIV (b) (4) fication on the date the Agency received the '179, '038, '416 and '549 patents for listing would be eligible for 180-day exclusivity (b) (4) Osmotica (b) (4) are the first to submit a valid PIV certification to the '179 patent on 1/31/2014 and have shared exclusivity to this patent (b) (4) Osmotica (b) (4) nd Mylan submitted PIV certifications on the date the Agency received the '038, '416 and '549 patents for listing and all share exclusivity to these patents. Breaking down certification by strength based on the patent certifications is as follows:

(b) (4)

In their 2/25/2016 amendment, Mylan provided a copy of Final Judgment issued 10/16/2015 by the USC for the Eastern District of Pennsylvania, CA# 2:15-cv-02990-MAK, in which Mylan had brought declaratory judgment on the '179 patent asking the court to find their ANDA 206726 did not infringe upon the '179 patent. In the judgment, the court grants judgment that Mylan's manufacture, use, offer for sale, sale, marketing and/or importation of their product under ANDA 206726 will not infringe any claims of the '179 patent. Mylan states Janssen did not appeal the decision. In the amendment, Mylan claims that the 10/16/2015 judgment triggers 180-day exclusivity associated with the '179 patent under pre-MMA regulations. Indeed, under pre-MMA regulations, a court decision of non-

Justification for Full/Tentative Approval: pre-MMA exclusivity on the listed patents triggered and expired
180 Day Exclusivity Status/Landscape: 180-day triggered by Watson marketing an AG
Citizen Petitions Impact: Does not affect this ANDA
First Legally Approvable Date: upon the completion of the full technical review
If Tentative Approval, anticipated full approval date: N/A

2. Final Decision

Date: 7/14/2017
Name/Title: PCS

ANDA received on 4/18/2016 for the 18 mg, 27 mg, 36 mg and 54 mg strengths
RTR'd? Yes ☐ **No ☒** If yes, RTR'd on _____ and subsequently resubmitted on _____
Priority Status? **Yes ☒** No ☐ If yes, prioritization factor is drug shortage
Basis of Submission

Drug Name	Concerta Tablets
NDA#	021121
Applicant Name	Janssen Pharmaceuticals, Inc.

Patent/Exclusivity Certifications:
As of 7/14/2017, there are no applicable changes in patents/exclusivities for the RLD listed in the Orange Book since Division of Legal and Regulatory Support Endorsement dated 7/3/2017.

On Policy Alert List?
Yes ☐ Pending POLICY ALERT BASIS for CLASS/DRUG/ETC (DOCKET NUMBER).
☐ Memo dated _____ from OGDP, SIGNATURE AUTHORITY, states OGD determined LIST DETERMINATION
☐ Memo not needed
No ☒ There are no issues noted on the OGD Policy Alert List as of 7/7/2017. Per DLRS endorsement and email from Policy, policy alert list TSI issue regarding Mulitple: Methylphenidate ER is unrelated to this ANDA.

☒ All relevant disciplines are adequate and endorsements and checklists have been completed.
Additional Comments: _____

Are there visible facility alerts in the platform?
☐ Yes, comment on why alert does not affect OMIR _____
☒ No
The overall manufacturing inspection recommendation is approve (see screen shot below). This ANDA is ready for FULL APPROVAL.

(b) (4)

[redacted]

REFERENCES / ASSOCIATED DOCUMENTS

4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA

REVISION HISTORY

Version	Effective date	Name	Role	Summary of changes
01	10/1/2014	Heather Strandberg	Author	New Form
02		Kevin Denny	Reviser	• Update form to reflect revisions to SOP 4000-LPS-041 Processing Approval and Tentative Approval of an Original ANDA, Version 04 • Remove content adequately captured in the platform • Update information captured in the Division of Legal and Regulatory Support Endorsement section • Other minor administrative corrections to format and content

CHECKLIST FOR THE CHEMISTRY REVIEW:

Camille Smith, RBPM

ANDA 208607

Methylphenidate Hydrochloride Extended Release Tablets USP

18 mg, 27 mg, 36 mg and 54 mg

Function	**Performed By (Initial and Date)**	**Check appropriate box**
Is this package for new strength PAS?	RBPM	☐ Yes ☒ No
DMF adequate?	RBPM	☒ Yes ☐ No *(see comments)
Any outstanding consults?	RBPM	☐ Yes *(see comments) ☒ No
Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee	☒Yes ☐ No ☐ N/A
Are all facility inspections acceptable?	RBPM	☒ Yes ☐ No
Is microbiology recommendation adequate for sterile products?	RBPM	☐ Yes ☐ No ☒ N/A
Are there comparability protocols provided? If yes, how many?	DD, BC, or designee	☐ Yes How many:_____ ☒No
If USP monograph exists, do the specifications conform to the current USP?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A
Is the final review uploaded into the current IT platform?	RBPM	☒ Yes ☐ No

Division	Name	Date
DMRP	Helen Teng	7/7/2017


(b) (4)

Camille Smith

Digitally signed by Camille Smith
Date: 7/07/2017 10:32:28AM
GUID: 56268f11002393c2a965ba586399e57f

Yue Teng

Digitally signed by Yue Teng
Date: 7/07/2017 11:23:13AM
GUID: 508da70d0002904e3640b9b2f6ee27d8

ANDA FILING CHECKLIST

(Post June 20, 2014)

ANDA: **208607**
APPLICANT: **CorePharma**
RELATED APPLICATION(S): Related Applications

DRUG NAME: **Methylphenidate Hydrochloride**
DOSAGE FORM: **Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg**

LETTER DATE: **April 18, 2016**
RECEIVED DATE: **April 18, 2016**
GDUFA GOAL DATE: July 17, 2017

Type II DMF #: (b) (4)
Archival Copy: GATEWAY
EDR Email: YES

BASIS OF SUBMISSION:

NDA/ANDA: **NDA# 021121**
FIRM: **Janssen Pharmaceuticals Inc.**
RLD: **Concerta®**
APPROVED: **August 1, 2000**
On Cards: ☒ Yes ☐ No

Review Start Date: May 10, 2016	Recommendation: ☒ **FILE** ☐ **REFUSE to RECEIVE**

Signature of Completion

Expired certificate

X Edward Nguyen

Filing Reviewer

Signed by: Edward Nguyen -S

1. ☒ Confirm that appropriate **Application Specific Inspection Criteria** have been checked
2. ☒ Profile Codes Task Completed
3. ☒ QC Application Information Task Completed (Update Project Owner, Patent and Policy, Prioritization Factor and Product Information)
4. ☒ GDUFA Obligations Met (Filing Fee, Type II DMF Fee, and Facility Fee)- (internal notation-if not met contact: cder-gdufa-applications@fda.hhs.gov)
5. ☒ DMF Complete Assessment
6. ☒ FRS Review Completed
7. ☒ Review Recommendation in Platform

8. ☒ All documents submitted in eCTD Format (see next page)

a. ☐ No security settings
b. ☐ Fonts embedded or standard fonts used
c. ☐ Font sizes ranging from 9 to 12 point (including scanned images)
d. ☐ Correct page orientation
e. ☐ Scanned documents are text searchable
f. ☐ Easily legible
g. ☐ Adequate bookmarks (if > 5 pages)
h. ☐ Descriptive bookmarks
i. ☐ Bookmarks set to inherit zoom
j. ☐ Hyperlinks (especially if there's a Table of Contents; > 5 pages)
k. ☐ Hyperlinks set to inherit zoom
l. ☐ Hyperlinks open in a new window
m. ☐ Navigation tab open to Bookmarks Panel and Page (unless there are no bookmarks)
n. ☐ Page Layout and Magnification set to Default
o. ☐ Font > 9 point font
p. ☐ Descriptive Leaf Titles

DEVIATIONS FROM THE NORM:

Note any deviations within the ANDA submission affecting BE/OPQ review:

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

4 DISSOLUTION CONDITIONS

	USP Dissolution Test 2	USP Dissolution Test 4	CorePharma Method
Apparatus:	USP 7, USP<724>	USP 2 (Paddle), USP<711>	(b) (4)
Medium:	Acidified Water, adjusted with phosphoric acid to a pH of 3.0	0.001 N Hydrochloric acid	
Medium Volume:	50 mL	500 mL	
Temperature:	37 ± 0.5 °C	37 ± 0.5 °C	
Cycles/minutes	30	N/A	
RPM:	N/A	50	
Time Point:	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 12 hours	0.5, 1, 2, 3, 4, 5, 6, 7, 8, 9, 10 and 12 hours	
# of Tablets per test	12	12	
Sinker:	N/A	N/A	
Withdraw volume:	N/A	(b) (4)	
Filter:	N/A		

ADDITIONAL COMMENTS: **All deficiencies were resolved.**

Applicant and US Agent contact information

APPLICANT INFORMATION

2. Name of Applicant: CorePharma, LLC

3. Telephone Number *(Include country code if applicable and area code)*: 732-667-6009

4. Facsi… code i…

5. Applicant Address

Address 1 *(Street address, P.O. box, company name c/o)*: 215 Wood Avenue

Address 2 *(Apartment, suite, unit, building, floor, etc.)*: N/A

City: Middlesex

State/Province/Region: New Jersey

Country: United States of America

ZIP or Postal Code: 08846

32. Typed Name and Title of Applicant's Responsible Official: Kimberly D. Ernst, Senior Director, Regulatory Affairs

3…

34. Telephone Number *(Include country code if applicable and area code)*: (b) (6)

35. FAX Number *(Include country code if applicable and area code)*: 732-805-5643

36. Email Address: kimberly.ernst@impaxlabs.com

37. Address of Applicant's Responsible Official

Address 1 *(Street address, P.O. box, company name c/o)*: 100 Somerset Corporate Blvd.

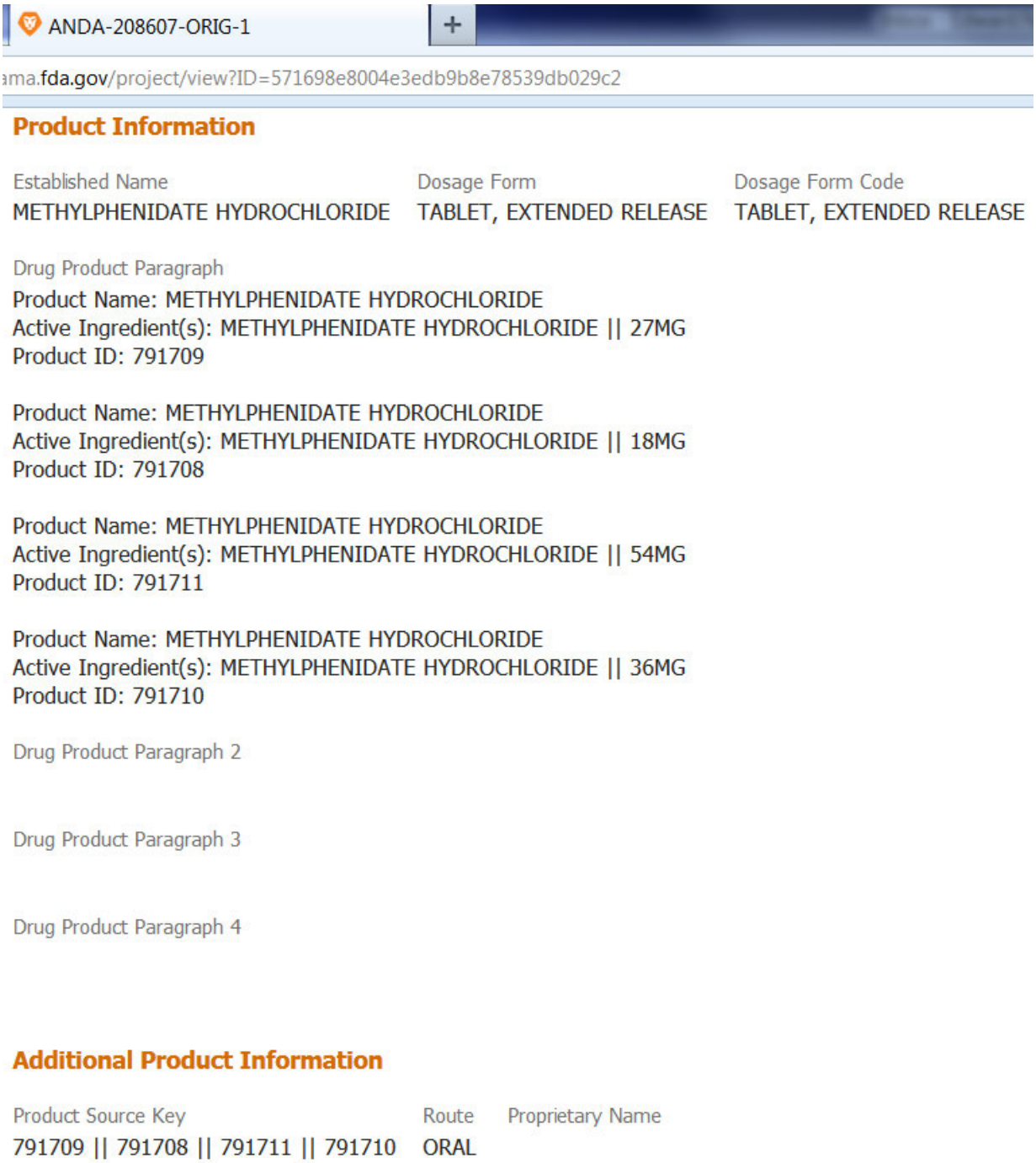
Address 2 *(Apartment, suite, unit, building, floor, etc.)*: Suite 3000

City: Bridgewater

State/Province/Region: New Jersey

Country: United States of America

ZIP or Postal Code: 08807



No deficiencies from Primary Review.

Minor deficiencies from FRS Review:

1. Address the following in section 2.7:
    a. Per the Division of Bioequivalence Model Summary Tables, located at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf
        i. Revise Table 10 (Study Information) to include the exact location of the LTSS study reports and data, including module, section, subsection and pages. Provide a working hyperlink(s) to the locations as appropriate.
        ii. Revise Table 3B (Statistical Summary of the Compartive Bioavailability Data for Reference-

Scaled Average BE Studies) to include all recommended paramaters.

2. In section 5.2, list all studies, including pilot and failed studies, under "Tabular Listing of all Clinical Studies" following the example for "Table 5.1 Listing of Clinical Studies" provided in the guidance for industry entitled, *M4E The CTD-Efficac*y, located at, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073290.pdf.

3. In section 5.3.1.2,
    a. "Fed Bioequivalence Study-Concentration-Time-Data," the file contains a duplicate of the data provided for the fasted study. Provide the data for fed study # ARL/14/695.
    b. "Fasting Bioequivalence Study Data-Listing SAS Transport Files" and "Fed Bioequivalence Study Data Listing SAS Transport File," revise the SAS files (.xpt) so that the data for each concentration is displayed in individual columns with headers across the files (C1, C2, C3, C4, etc) for each concentration.

eCTD Deficiencies

1. **There are issues with the initial view settings.** The initial view of the PDF files should be set as *Bookmarks* and *Page*. If there are no bookmarks, the initial view as *Page* only should be set. The *Magnification* and *Page* Layout should be set as default. Review all PDF files to assure the initial view settings are set appropriately. See the technical specification document, *M2 eCTD: Electronic Common Technical Document Specification* (at pg. 7-3-7-4) located at: http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **Examples of such issues are:**
    a. Section 2.7, all files
    b. Module 5, all files

2. **There are issues where documents were placed in the wrong locations.** Section 5.3.1.2 should contain Comparative BA and Bioequivalence (BE) Study Reports, section 5.3.1.3 should contain In vitro-In vivo Correlation Study Reports, and section 5.3.1.4 should contain Reports of Bioanalytical and Analytical Methods for Human Studies. See the technical specification document, *ICH M2 EWG Electronic Common Technical Document Specification* (at pg. 3-10 and 4-49 to 4-50) located at: http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **Examples of such issues are:**
    a. **The following files should be in section 5.2,**
        i. "Tabular Listing of Clinical Study-Fed"
        ii. "Tabular Listing of Clinical Study-Fasting"
    b. **The following files should be in section 5.3.1.3,**
        i. "In-Vitro-In-Vivo-Correlation Study Reports"
    c. **The following files should be in section 5.3.1.4,**
        i. "Fed Bioanalytical Study Report"
        ii. "Fed Bioanalytical Study Certificate-of-Analysis"
        iii. "Fed Bioanalytical Study-Curve-Plots"
        iv. "Fed Bioanalytical Study-Method-Validation-Report"
        v. "Fed Bioanalytical Study-Raw-Data
        vi. "Fed Bioanalytical Study-Representative-Chromatograms"
        vii. "Fed Bioanalytical Study-Standard-Operating-Procedures"
        viii. "Fasting Bioanalytical Study Report"

ix. "Fasting Bioanalytical Study-Certificate-of-Analysis"
x. "Fasting Bioanalytical Study-Curve-Plots"
xi. "Fasting Bioanalytical Study-Method-Validation-Report"
xii. "Fasting Bioanalytical Study-Raw-Data
xiii. "Fasting Bioanalytical Study-Representative-Chromatograms"
xiv. "Fasting Bioanalytical Study-Standard-Operating-Procedures"

3. **There are issues with Study Tagging Files (STF).** An STF should be provided with the submission of any file, or group of files, belonging to a study in Modules 4 and 5, and a separate STF should be provided for each study in a sequence. For every submission to FDA that includes one or more files pertaining to a specific study, provide an STF. Place the STF for the specific study in the module folder with the corresponding study files. Place a leaf element for the STF in the appropriate Module 4 or 5 eCTD Table of Contents element in the index.xml file for that sequence. **Within the STF file for Study #** ARL/14/694 and ARL/14/695**, you have documents that do not contain the proper *file-tag* element.** The *study-document* element contains information on the subject matter of each file that is cited as part of the documentation for a study. The *study-document* element includes the *doc-content* element. The *doc-content* element contains the *property* and *file-tag* elements. The *property* element is appropriate when files might need to be grouped by an applicant provided value. Currently, this element should only be used for site identification within a study. The *file-tag* element contains the attributes *name* and *info-type*. The text value of the *file-tag* element's *name* attribute indicates the subject matter of the document. See the technical specification document, *ICH M2 EWG, The eCTD Backbone File Specification for Study Tagging Files* (at pg. 4 and 7-10), located at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **An example of such an issue is:**
    a. Section 5.3.1.4, Unassigned folder, there should not be "unassigned" folders in module 5. This indicates that documents were not correctly labelled or not correctly placed per *The Comprehensive Table of Contents of Heading and Hierarchy* for XML. The folder should be labelled correctly and contain the documents highlighted above in eCTD Deficiency Comment 2.

Additional Comments

1. In section 2.7,
    a. "Summary of Results of Individual Studies," clarify the discrepancy in dosage and lot numbers in Figure 2: Graph of Multimedia Dissolution Study of 27 mg in 0.1 NHCl
    b. (b) (4) Common Adverse Events," clarify the discrepancy in study numbers in Table 8.2 Incidence of Adverse Events in Individual Studies-ARL/14/695 (Fed)
    c. "RPT 15-03-ir-001-01," clarify the discrepancy in the lot numbers for the Results for CorePharma Mehtylphenidate HCL ER 27 mg Tables and Concerta® 27 mg Tablets under CorePharma Dissoution Method.
    d. In addition to the 54 mg strength, provide the Certificates of Analysis (CoAs) for all other Reference Listed Drug (RLD) strengths used in your dissolution studies (18 mg, 27 mg and 36 mg)

CORRESPONDENCE(S)

ANDA 208607 Filing Review Comments

Gaines, Tangela

Sent: Mon 5/23/2016 6:38 AM
To: kimberly.ernst@impaxlabs.com
Cc: ANDAFiling

Dear Kimberly Ernst:

This electronic mail is in reference to ANDA 208607 submitted on April 18, 2016 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

SPECIAL INSTRUCTIONS:

- We request that you acknowledge the receipt of this email correspondence.
- Provide a complete response to all of the items identified below **within 7 calendar days** from the date of this communication. **– Response due by 5/31/16 – Responded on 5/27/16**
- If a complete response is not submitted to the ANDA and received within 7 calendar days, the application will be deemed incomplete and will be refused for receipt.
- Your response should contain a point-by-point reply to each of the identified comment(s) with corresponding hyperlink(s), where applicable, to the body of data within the ANDA.
- You should notify me via email or telephone when you have submitted your response.
- Your cover letter should clearly indicate Quality - Response to Information Request.
- Should you have any questions or need for clarification with respect to any of the following deficiencies, you must clearly identify your questions and request a teleconference within 1 business day from the date of this email. (**Note: The teleconference will be limited to only the questions provided in your teleconference request. Also, your query does not place a hold on the timeframe in which the response must be submitted, as per bullet 2.**)

REVISE AND PROVIDE THE FOLLOWING DEFICIENCIES:

1. Address the following in Module 2.7:
    a. Per the Division of Bioequivalence Model Summary Tables, located at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf
        i. Revise Table 10 (Study Information) to include the exact location of the LTSS study reports and data, including module, section, subsection and pages. Provide a working hyperlink(s) to the locations as appropriate. **Resolved on 5/27/16 from Sequence 0001.**
        ii. Revise Table 3B (Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE Studies) to include all recommended parameters. **Resolved on 5/27/16 from Sequence 0001.**

2. In Module 5.2, list all studies, including pilot and failed studies, under "Tabular Listing of all Clinical Studies" following the example for "Table 5.1 Listing of Clinical Studies" provided in the guidance for industry entitled, *M4E The CTD-Efficacy*, located at, http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073290.pdf. **Resolved on 5/27/16 from Sequence 0001.**

3. In Module 5.3.1.2,
    a. "Fed Bioequivalence Study-Concentration-Time-Data," the file contains a duplicate of the data provided for the fasted study. Provide the data for fed study # ARL/14/695. **Resolved on 5/27/16 from Sequence 0001.**
    b. "Fasting Bioequivalence Study Data-Listing SAS Transport Files" and "Fed Bioequivalence Study Data Listing SAS Transport File," revise the SAS files (.xpt) so that the data for each concentration is displayed in individual columns with headers across the files (C1, C2, C3, C4, etc) for each concentration. **Resolved on 5/27/16 from Sequence 0001.**

eCTD DEFICIENCIES:

With regards to the eCTD deficiencies identified below, we note that FDA previously refused to receive

ANDAs on the basis that the ANDA was not submitted in accordance with current eCTD format. However, FDA has determined that the GDUFA Commitment Letter contemplates addressing eCTD deficiencies differently for ANDAs eligible for metric goal dates beginning in Year 3 of GDUFA, specifically, by providing that metric goal dates will not apply to such ANDAs. See Generic Drug User Fee Act Program Performance Goals and Procedures (GDUFA Commitment Letter), at 7, available at http://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf; see also guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*, at 4 (May 2015, Rev. 1) (identical in relevant part to initial version finalized in September 2014).

An adequate response to the eCTD deficiencies identified below must be received within **7 calendar days** from the date of this communication in order for the GDUFA metric goal for this ANDA to be assigned. If a complete response to the eCTD deficiencies is not received within **7 calendar days**, we will determine that your entire application does not follow the eCTD format in effect at the date of submission. Accordingly, FDA will receive the ANDA for review (assuming all other receipt requirements have been met), but will not assign a review metric goal date. **Any questions regarding the technical component of the electronic submission and preparing your corrective submission should be directed to CDER ESUB at esub@fda.hhs.gov.**

Documents submitted electronically should follow all published eCTD specifications and FDA guidances including those on the CDER eCTD web page, which is located at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm. There are documents within your submission that do not conform to the standards outlined in the specifications or guidance recommendations that affect the display and/or reviewability of the ANDA.

The following issues regarding eCTD specifications and guidances were found:

1. **There are issues with the initial view settings.** The initial view of the PDF files should be set as *Bookmarks* and *Page*. If there are no bookmarks, the initial view as *Page* only should be set. The *Magnification* and *Page* Layout should be set as default. Review all PDF files to assure the initial view settings are set appropriately. See the technical specification document, *M2 eCTD: Electronic Common Technical Document Specification* (at pg. 7-3-7-4) located at: http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **Examples of this issue are throughout your entire application.** The *Magnification* and *Page* Layout should be set as **default** in all files. **Resolved on 5/27/16 from Sequence 0001.**

2. **There are issues where documents were placed in the wrong locations.** Module 5.3.1.2 should contain Comparative BA and Bioequivalence (BE) Study Reports, Module 5.3.1.3 should contain In vitro-In vivo Correlation Study Reports, and Module 5.3.1.4 should contain Reports of Bioanalytical and Analytical Methods for Human Studies. See the technical specification document, *ICH M2 EWG Electronic Common Technical Document Specification* (at pg. 3-10 and 4-49 to 4-50) located at: http://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **Examples of such issues are:** **Resolved on 5/27/16 from Sequence 0001.**
    a. **The following files should be in Module 5.2,**
        i. "Tabular Listing of Clinical Study-Fed"
        ii. "Tabular Listing of Clinical Study-Fasting"
    b. **The following files should be in Module 5.3.1.3,**
        i. "In-Vitro-In-Vivo-Correlation Study Reports"
    c. **The following files should be in Module 5.3.1.4,**
        i. "Fed Bioanalytical Study Report"
        ii. "Fed Bioanalytical Study Certificate-of-Analysis"
        iii. "Fed Bioanalytical Study-Curve-Plots"

iv. "Fed Bioanalytical Study-Method-Validation-Report"
v. "Fed Bioanalytical Study-Raw-Data
vi. "Fed Bioanalytical Study-Representative-Chromatograms"
vii. "Fed Bioanalytical Study-Standard-Operating-Procedures"
viii. "Fasting Bioanalytical Study Report"
ix. "Fasting Bioanalytical Study-Certificate-of-Analysis"
x. "Fasting Bioanalytical Study-Curve-Plots"
xi. "Fasting Bioanalytical Study-Method-Validation-Report"
xii. "Fasting Bioanalytical Study-Raw-Data
xiii. "Fasting Bioanalytical Study-Representative-Chromatograms"
xiv. "Fasting Bioanalytical Study-Standard-Operating-Procedures"

3. **There are issues with Study Tagging Files (STF).** An STF should be provided with the submission of any file, or group of files, belonging to a study in Modules 4 and 5, and a separate STF should be provided for each study in a sequence. For every submission to FDA that includes one or more files pertaining to a specific study, provide an STF. Place the STF for the specific study in the module folder with the corresponding study files. Place a leaf element for the STF in the appropriate Module 4 or 5 eCTD Table of Contents element in the index.xml file for that sequence. **Within the STF file for Study #** ARL/14/694 and ARL/14/695**, you have documents that do not contain the proper *file-tag* element.** The *study-document* element contains information on the subject matter of each file that is cited as part of the documentation for a study. The *study-document* element includes the *doc-content* element. The *doc-content* element contains the *property* and *file-tag* elements. The *property* element is appropriate when files might need to be grouped by an applicant provided value. Currently, this element should only be used for site identification within a study. The *file-tag* element contains the attributes *name* and *info-type*. The text value of the *file-tag* element's *name* attribute indicates the subject matter of the document. See the technical specification document, *ICH M2 EWG, The eCTD Backbone File Specification for Study Tagging Files* (at pg. 4 and 7-10), located at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **An example of such an issue is:**
    a. Module 5.3.1.4, Unassigned folder, there should not be "unassigned" folders in module 5. This indicates that documents were not correctly labelled or not correctly placed per *The Comprehensive Table of Contents of Heading and Hierarchy* for XML. The folder should be labelled correctly and contain the documents highlighted above in eCTD Deficiency Comment 2. **Resolved on 5/27/16 from Sequence 0001.**

The highlighted examples do not comprise an exhaustive list. It is incumbent upon the applicant to ensure that all documents conform to the listed standards, which includes utilizing the appropriate **operation attribute** in managing each individual file in a submission. **Any questions regarding the technical component of the electronic submission and preparing your corrective submission should be directed to CDER ESUB at esub@fda.hhs.gov.**

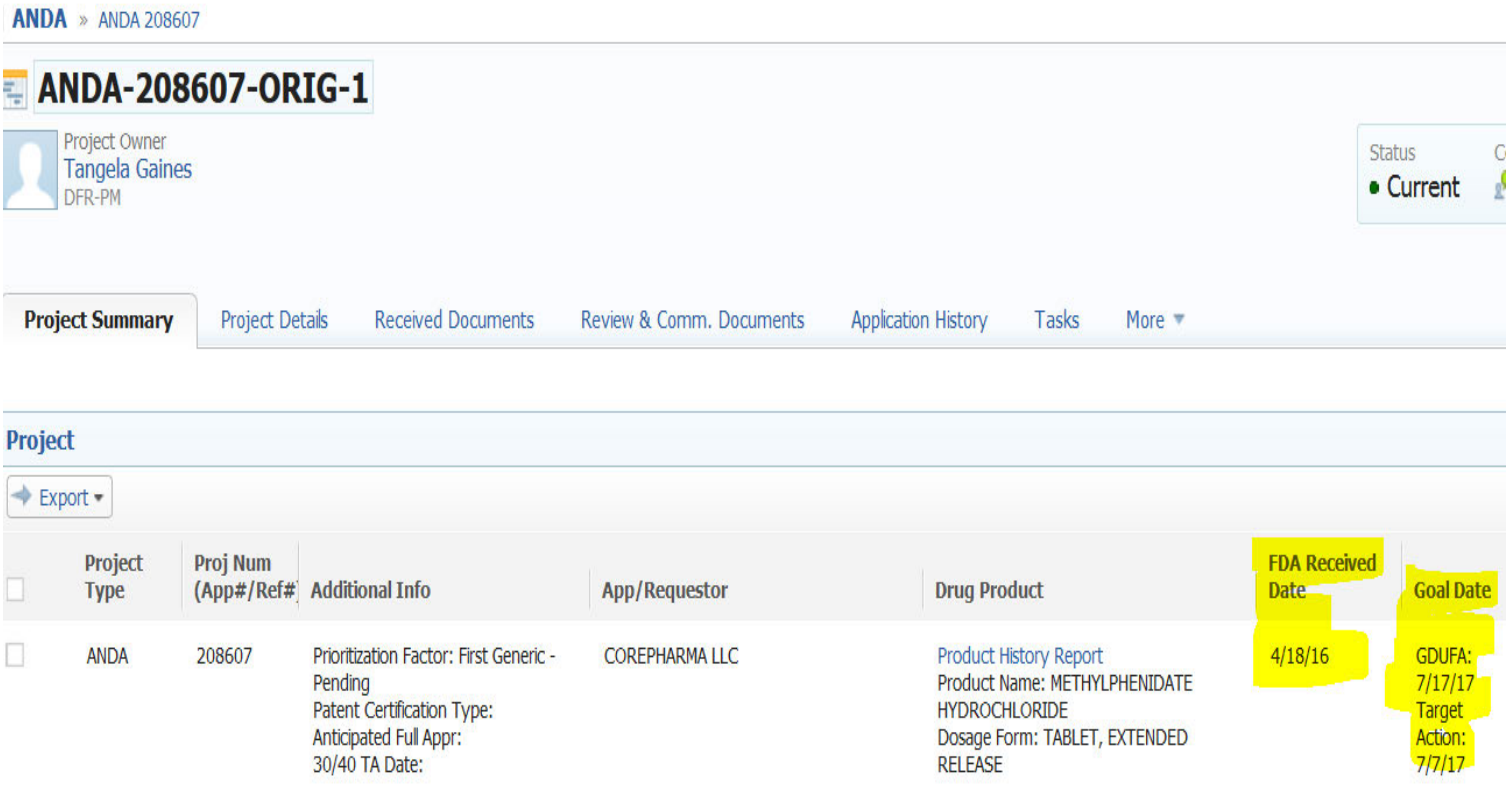
ADDITIONAL COMMENTS:

1. In Module 2.7, **Resolved on 5/27/16 from Sequence 0001.**
    a. "Summary of Results of Individual Studies," clarify the discrepancy in dosage and lot numbers in Figure 2: Graph of Multimedia Dissolution Study of 27 mg in 0.1 NHCl.
    b. "(b) (4) Common Adverse Events," clarify the discrepancy in study numbers in Table 8.2 Incidence of Adverse Events in Individual Studies-ARL/14/695 (Fed).
    c. "RPT 15-03-ir-001-01," clarify the discrepancy in the lot numbers for the Results for CorePharma Mehtylphenidate HCL ER 27 mg Tables and Concerta® 27 mg Tablets under CorePharma Dissoution Method.
    d. In addition to the 54 mg strength, provide the Certificates of Analysis (CoAs) for all other

Reference Listed Drug (RLD) strengths used in your dissolution studies (18 mg, 27 mg and 36 mg).

Note: Provide a fillable PDF copy of the 356h in all your submissions if you are submitting a scanned signed copy of the 356h, otherwise the omission of the fillable PDF copy of the 356h will be counted as a deficiency.

Best Regards,
Tangela



(b) (4)

Drug Substance USP, Drug Product USP

3 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

Bioequivalence Guidance –*6 pages*

Contains Nonbinding Recommendations

Draft Guidance on Methylphenidate Hydrochloride

This draft guidance, when finalized, will represent the current thinking of the Food and Drug Administration (FDA, or the Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the Office of Generic Drugs.

Active Ingredient: Methylphenidate Hydrochloride

Dosage Form; Route: Extended Release Tablet; Oral

Recommended Studies: Two studies

1. Type of study: Fasting
   Design: Single-dose, two-treatment, four-period, two-sequence, fully replicated crossover in-vivo
   Strength: 54 mg
   Subjects: Healthy males and nonpregnant females, general population.

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2. Type of study: Fed
   Design: Single-dose, two-treatment, four-period, two-sequence, fully replicated crossover in-vivo
   Strength: 54 mg
   Subjects: Healthy males and nonpregnant females, general population.
   Additional Comments: Please refer to the Amantadine Hydrochloride Tablet Draft Guidance for additional information regarding fed studies.

Analytes to measure (in appropriate biological fluid): Methylphenidate in plasma

Bioequivalence based on (90% CI): Methylphenidate
Please refer to Additional Comments below for more guidance regarding bioequivalence.

Waiver request of in-vivo testing: 18 mg, 27 mg, and 36 mg based on (i) acceptable bioequivalence studies on the 54 mg strength, (ii) acceptable in-vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths. Please refer to the Mirtazapine Tablet Draft Guidance for additional information regarding waivers of in-vivo testing.

Dissolution test method and sampling times:
Please note that a **Dissolution Methods Database** is available to the public at the OGD website at http://www.accessdata.fda.gov/scripts/cder/dissolution/. Please find the dissolution information for this product at this website. Please conduct comparative dissolution testing on 12

dosage units each of all strengths of the test and reference products. Specifications will be determined upon review of the application.

In addition to the method above, for modified release products, dissolution profiles on 12 dosage units each of test and reference products generated using USP Apparatus I at 100 rpm and/or Apparatus II at 50 rpm in at least three dissolution media (pH 1.2, 4.5 and 6.8 buffer) should be submitted in the application. Agitation speeds may have to be increased if appropriate. It is acceptable to add a small amount of surfactant, if necessary. Please include early sampling times of 1, 2, and 4 hours and continue every 2 hours until at least 80% of the drug is released, to provide assurance against premature release of drug (dose dumping) from the formulation. Specifications will be determined upon review of the data submitted in the application.

Due to a concern of dose dumping of drug from this drug product when taken with alcohol, the Agency currently requests that additional dissolution testing be conducted using various concentrations of ethanol in the dissolution medium, as follows:

Testing Conditions: 900 mL, 0.1 N HCl, USP apparatus 2 (paddle) @50 rpm, with or without alcohol;

Test 1: 12 units tested according to the proposed method (with 0.1N HCl), with data collected every 15 minutes for a total of 2 hours

Test 2: 12 units analyzed by substituting 5% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 3: 12 units analyzed by substituting 20% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Test 4: 12 units analyzed by substituting 40% (v/v) of test medium with Alcohol USP and data collection every 15 minutes for a total of 2 hours

Both test and RLD products must be tested accordingly and data must be provided on individual unit, means, range and %CV on all strengths.

Additional comments regarding the bioequivalence study:

1. Additional Bioequivalence Metrics – Partial AUCs

The Concerta® Tablet labeling indicates that Concerta® (methylphenidate hydrochloride) extended-release tablet is an extended-release formulation of methylphenidate with a bi-modal release profile. Each Concerta® tablet is comprised of an immediate-release component and an extended-release component, thus providing an immediate release of methylphenidate and a second extended release of methylphenidate.

Thus, Concerta® is a multiphasic modified-release formulation designed to release a bolus of methylphenidate followed by slower delivery later in the day. According to the FDA-approved

First page of the COMPLETED FRS checklist

ANDA FILING CHECKLIST

BE

ANDA:	208607
APPLICANT:	**Core Pharma, LLC**
DRUG NAME:	**Methylphenidate Hydrochloride**
DOSAGE FORM:	**Extended Release Tablets; 18 mg, 27 mg, 36 mg and 54 mg**
RECEIPT DATE:	**April 18, 2016**
GDUFA GOAL DATE:	**June 17, 2017**
NDA/ANDA:	N021121
RLD:	**Concerta**
RLD DOSAGE FORM:	**Tablet**
RLD FIRM:	Janssen Pharms
APPROVAL DATE:	August 1, 2000; December 8, 2000; April 1, 2002
PRIMARY REVIEWER:	Sun Hee Min, Pharm.D.
SECONDARY REVIEWER:	Laurie Buonaccorsi, PharmD

Primary Reviewer's Signature of Completion	**Summary:**
6/2/2016 X Sun Hee Min FRS Signed by: Sun Hee Min -A	☒ COMPLETE ☐ INCOMPLETE

☒ PK Endpoints
☐ Clinical Endpoints
☐ In Vitro BE Studies (e.g., in vitro binding assays, in vivo release tests)
☐ Nasally Administered Drug Products
  ☐ Solutions (in-vitro)
  ☐ Suspension (in-vitro and in-vivo)
☐ In Vivo BE Study(ies) with PD Endpoints (e.g., topical corticosteroid pilot and pivotal vasoconstrictor assay studies)
☐ Transdermal Delivery System
☐ BCS Class I Waivers
☐ Miscellaneous
☐ Formulation: Q1/Q2 (if applicable) Select

1. ☒ GDUFA Waiver Report

MODULE 1: ADMINISTRATIVE

1.1	1.1.2	**Rx** **Signed and Completed Application Form (356h)** (Rx / OTC Status) (original signature) **YES** **Electronic, Fillable Copy** (if a signed, scanned copy is provided) Refer to the links provided for the newly revised form 356h and updated instructions. http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM321897.pdf http://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/ucm082348.pdf **PLACE ESTABLISHMENT CONTACT INFORMATION IN SECTION 29: MANUFACTURING STEPS AND/OR TYPE OF TESTING***
		Comments
		YES *Form FDA 3794 (PDF)* GDUFA
		Comments
1.2	*	**YES** **Cover Letter** **NO** **Is the drug product subject to REMS requirements?** http://www.accessdata.fda.gov/scripts/cder/rems/index.cfm
		Comments
	1.2.1	**B** **Form FDA 3674 (PDF)** 42 U.S.C. 282(j)(5)(B) **YES** **Electronic, Fillable Copy** (if a signed, scanned copy is provided)
		Comments
*	*	**N/A** **Table of Contents** (paper submission only)
1.3	1.3.1	**Contact/Sponsor/Applicant Information** **N/A** **1.3.1.2 U.S. Agent Appointment Letter** 21 CFR §314.50(a)(5) If the applicant identifies a U.S. Agent on the 356h, a U.S. Agent Appointment letter should be provided.
		Comments
	1.3.2	**YES** **Field Copy Certification** 21CFR §314.94(d)(5) (Original Signature)
		Comments
	1.3.3	**Debarment Certification** from **Applicant** Generic Drug Enforcement Act (GDEA)/ Other: FD&C Act §306(k), §306(a) and (b) (21 U.S.C. 335a(k), 335(a) and (b)) (no qualifying statement) **YES** 1. Debarment Certification (original signature) **YES** 2. List of Convictions statement (original signature)
		Comments
	1.3.4	**Financial Certifications** 21 CFR §54 | 21 CFR §54.2(e) | 21 CFR §314.94(a)(13) **YES** Bioavailability/Bioequivalence Financial Certification (Form FDA 3454) **N/A** Disclosure Statement (Form FDA 3455)
		Comments
	1.3.5	**Patent and exclusivity** **1.3.5.1 Patent Information** 21 CFR §314.94(a)(12) | FD&C Act 505(j)(2)(A)(vii) Patents listed for the RLD in the Electronic Orange Book Approved Drug Products with Therapeutic Equivalence Evaluations **1.3.5.2 Patent Certification** 21 CFR §314.94(a)(12)(i)(A)(1) through (4) or §314.94(a)(12)(iii) 1. Patent number(s) **see below** 2. Paragraph: (Check all certifications that apply) No Relevant Patents ☐ MOU ☐ PI ☐ PII ☐ PIII ☐ PIV ☒ Statement of Notification (21 CFR §314.95 | 505(j)(2)(B)) ☐ 3. Expiration of Patent(s): **YES** a. Pediatric Extension? b. Expiration of Pediatric Extension? **See below** **1.3.5.3 Exclusivity Claim** **YES** Exclusivity Statement: State marketing intentions? **N/A** Pediatric Exclusivity (NPP, PED)
		Comments

Active Ingredient:	METHYLPHENIDATE HYDROCHLORIDE
Dosage Form;Route:	TABLET, EXTENDED RELEASE;ORAL
Proprietary Name:	CONCERTA
Applicant:	JANSSEN PHARMS
Strength:	18MG
Application Number:	N021121
Product Number:	001
Approval Date:	Aug 1, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	METHYLPHENIDATE HYDROCHLORIDE
Dosage Form;Route:	TABLET, EXTENDED RELEASE;ORAL
Proprietary Name:	CONCERTA
Applicant:	JANSSEN PHARMS
Strength:	36MG
Application Number:	N021121
Product Number:	002
Approval Date:	Aug 1, 2000
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	METHYLPHENIDATE HYDROCHLORIDE
Dosage Form;Route:	TABLET, EXTENDED RELEASE;ORAL
Proprietary Name:	CONCERTA
Applicant:	JANSSEN PHARMS
Strength:	54MG
Application Number:	N021121
Product Number:	003
Approval Date:	Dec 8, 2000
Reference Listed Drug	Yes
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Active Ingredient:	METHYLPHENIDATE HYDROCHLORIDE
Dosage Form;Route:	TABLET, EXTENDED RELEASE;ORAL
Proprietary Name:	CONCERTA
Applicant:	JANSSEN PHARMS
Strength:	27MG
Application Number:	N021121
Product Number:	004
Approval Date:	Apr 1, 2002
Reference Listed Drug	No
RX/OTC/DISCN:	RX
TE Code:	
Patent and Exclusivity Info for this product:	View

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code	Delist Requested
N021121	003	6919373	Jul 31, 2017			U - 666	
N021121	003	6919373*PED	Jan 31, 2018				
N021121	003	6930129	Jul 31, 2017			U - 666	
N021121	003	6930129*PED	Jan 31, 2018				
N021121	003	8163798	Jul 31, 2017		Y		
N021121	003	8163798*PED	Jan 31, 2018				
N021121	003	8629179	Jul 31, 2017		Y		
N021121	003	8629179*PED	Jan 31, 2018				
N021121	003	9000038	Jul 31, 2017			U - 1693	
N021121	003	9000038	Jul 31, 2017			U - 666	
N021121	003	9000038*PED	Jan 31, 2018				
N021121	003	9029416	Jul 31, 2017		Y	U - 666	
N021121	003	9144549	Jul 31, 2017			U - 1747	
N021121	003	9144549	Jul 31, 2017			U - 1748	

Exclusivity Data

There is no unexpired exclusivity for this product.

Additional information:

1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(d)(5).
2. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:

Orange Book Data - **Monthly**
Generic Drug Product Information & Patent Information - **Daily**
Orange Book Data Updated Through April 2016
Patent and Generic Drug Product Data Last Updated May 16, 2016

1.4	1.4.2	**Statement of right of references** 21 CFR §314.50(g)(1) DMF Written Statement of authorization for reference (copy of LoA received from DMF holders) YES 1. Type II DMF authorization letter(s) or synthesis for Active Pharmaceutical Ingredient 2. Type II DMF# (b) (4) YES 3. Type III DMF authorization letter(s) for container closure N/A 4. Type III or V DMF authorization letter(s) for sterile product sterilization process Comments
1.12	1.12.4	N/A **Request for Comments and Advice** – Proprietary name requested If Yes, did the firm provide the request as a separate electronic amendment labeled "Proprietary Name Request" at initial time of filing N/A 1. Yes 2. No – contact the firm to submit the request as a separate electronic amendment Comments
	1.12.11	**Basis for Submission** 21 CFR §314.94(a)(3) Applicant identifies the following: YES 1. NDA/ANDA: **NDA # 021121** YES 2. Ref Listed Drug: **Concerta®** YES 3. Firm: **Janssen Pharmaceuticals** N/A **ANDA suitability petition required?** 21 CFR §10.20 | 21 CFR §10.30 | 21 CFR §314.93 If Yes, Petition number Petition Number N/A Copy of FDA's correspondence approving the petition (21 CFR §314.94(a)(3)(iii)) N/A **ANDA Citizen's Petition required?** 21 CFR §10.25(a) | 21 CFR §10.30 | 21 CFR §314.122 If Yes, Petition number Petition Number N/A Copy of petition
		Module 1.12.11 Basis for Submission This application is being submitted to obtain approval for Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg as the therapeutic equivalents of Concerta® ER Tablets, 18 mg, 27 mg, 36 mg and 54 mg. **NDA#:** 021121 **Reference Listed Drug**: Concerta ER® Tablets, 54 mg **Firm**: JANSSEN PHARMS The RLD listing information from the online Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations is provided in Table 1.12.11-1. **ANDA Suitability Petition / ANDA Citizen's Petition**: CorePharma has no citizen petition or suitability petition associated with this ANDA.
	1.12.12	**Comparison between Generic Drug and RLD** 505(j)(2)(A) | 21 CFR §314.94(a)(4) to (6) SAME AS RLD 1. Conditions of Use SAME AS RLD 2. Active Ingredients JUSTIFIED 3. Inactive Ingredients (21 CFR §314.94(a)(9)(ii)) SAME AS RLD 4. Route of Administration SAME AS RLD 5. Dosage Form SAME AS RLD 6. Strength

Table 1.12.12-1 Comparison between Reference Listed Drug and Proposed Generic Drug

	Concerta® ER Tablets (Janssen Pharms)	Methylphenidate Hydrochloride Extended-Release Tablets, USP (CorePharma, LLC)
Conditions of use	CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65.	CNS stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in children 6 years of age and older, adolescents, and adults up to the age of 65.
Active ingredients	Methylphenidate Hydrochloride, USP	Methylphenidate Hydrochloride, USP
Inactive ingredients[1]	butylated hydroxytoluene carnauba wax cellulose acetate hypromellose lactose phosphoric acid poloxamer polyethylene glycol polyethylene oxides povidone propylene glycol sodium chloride stearic acid succinic acid synthetic iron oxides titanium dioxide triacetin	lactose monohydrate hypromellose magnesium stearate polyethylene glycol ethylcellulose (b) (4) triethyl citrate povidone titanium dioxide propylene glycol shellac ferrosoferric oxide n-butyl alcohol 18 mg tablet also contains iron oxide yellow 54 mg tablet also contains iron oxide red and iron oxide yellow
Route of administration	Oral	Oral
Dosage Form	Extended Release Tablets	Extended Release Tablets
Strengths	18 mg, 27 mg, 36 mg and 54 mg	18 mg, 27 mg, 36 mg and 54 mg
Strength used in in-vivo BE studies	54 mg (RLD)	54 mg

[1] The amounts of each inactive ingredient used in the formulation are considered acceptable for use. Please refer to Module 3.2.P.1 for details.

1.12.14 **Environmental Analysis from Applicant** 21 CFR §25.31 and §25.15(d), if applicable

N/A Environmental Assessment (EA) (21 CFR §25.20)

N/A If applicable, Environmental Impact Statement (EIS) (21 CFR 25.22)

YES Claim of Categorical Exclusion (21 CFR §25.30 or 21 CFR §25.31)

YES **Statement:** "to the applicant's best of knowledge no extraordinary circumstances exist"

Comments

1.12.15 **Request for Waiver** 21 CFR 320.22 | 320.24(b)(6)

YES Request for Waiver of In-Vivo BA/BE Study(ies)

Module 1.12.15: Request for waiver of *In-Vivo* BA/BE Studies

Pursuant to 21 CFR§ 320.22(d)(2) of the regulations, CorePharma, LLC (CorePharma) requests a waiver of the requirement for the submission of evidence, demonstrating the *in vivo* bioequivalence for the 18 mg, 27 mg and 36 mg strengths of CorePharma's Methylphenidate Hydrochloride Extended-Release Tablets, USP on the following basis:

1. The bioequivalence of CorePharma's Methylphenidate Hydrochloride Extended-Release Tablets USP, 54 mg and the Reference Listed Drug (RLD) Concerta® ER Tablets, 54 mg has been established by the following ***in-vivo*** bioequivalence studies:
   a. Fasting Study
   b. Fed Study

2. Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg are an extended-release dosage form where all strengths are proportionally similar (please refer to the Manufacturing Instructions submitted in Module 3.2.P.3.3). The composition of all strengths is provided within Module 3.2.P.1.

3. The ***in-vitro*** dissolution profiles of the 18 mg, 27 mg, and 36 mg strengths compared favorably with that of the 54 mg strength. Relevant dissolution profiles and graphs are provided in Module 2.7.1.2.

1.14

1.14.1

Draft Labeling (Multi Copies N/A for E-Submissions) 21 CFR 314.94(a)(8)(ii)

1.14.1.1 Draft carton and container labels

YES Electronic copy (each strength and container) -OR-

N/A 4 copies of draft for paper submission only (each strength and container)

1.14.1.2 Annotated draft labeling text 21 CFR §314.94(a)(8)(iv)

YES Side by side labeling comparison of container(s) and carton(s) for each strength with all differences visually highlighted and annotated

1.14.1.3 Draft labeling text

YES 1 package insert (content of labeling) in PDF and WORD format, and SPL submitted electronically

1.14.1.4 Labeling Comprehension Studies

N/A Refer to Pharmacy Bulk Package Sterility Assurance Table (for PBP's only)
See link below for table:
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM352612.pdf

Comments

1.14.3

Listed Drug Labeling

1.14.3.1 Annotated comparison with listed drug 21 CFR §314.94(a)(8)(iv)

YES Side by side labeling (package and patient insert) comparison with all differences visually highlighted and annotated

a. Container Closure system (if different from what's approved for the RLD)

N/A i. Vial or ampule vs. prefilled syringe

N/A ii. Vial vs. ampule

N/A iii. Delivery device that's different from the RLD, e.g. inhalers

N/A iv. Bottles vs blisters ("calendarized" packaging)

N/A v. Unit of use (dispensable bottle) vs. multiple use bottles (pharmacy bottle)

1.14.3.3 Labeling text for reference listed drug 21 CFR §314.94(a)(8)(iv)

YES RLD package insert, 1 RLD container label, and if applicable, 1 RLD outer container label

Comments

How Supplied for Generic

16 HOW SUPPLIED/STORAGE AND HANDLING

Methylphenidate hydrochloride extended-release tablets, USP are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow printed with **CP 342** on one side and blank on the other side. The 27 mg tablets are gray printed with **CP 340** on one side and blank on the other side. The 36 mg tablets are white printed with **CP 339** on one side and blank on the other side. The 54 mg tablets are brownish-red printed with **CP 341** on one side and blank on the other side. All four dosage strengths are supplied in bottles containing 100 tablets.

18 mg	100-count bottle	NDC 0115-1566-01
27 mg	100-count bottle	NDC 0115-1567-01
36 mg	100-count bottle	NDC 0115-1568-01
54 mg	100-count bottle	NDC 0115-1569-01

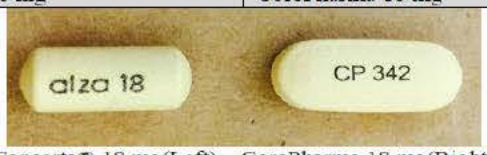
Storage and Handling

Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from humidity.

SBS Comparison of How Supplied between RLD and Generic

Referenced Listed Drug Package Labeling CONCERTA®		Proposed Generic Drug Package Labeling Methylphenidate Hydrochloride Extended-Release Tablets, USP
CONCERTA® (methylphenidate HCl) Extended-release Tablets are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow and imprinted with "alza 18". The 27 mg tablets are gray and imprinted with "alza 27". The 36 mg tablets are white and imprinted with "alza 36". The 54 mg tablets are brownish-red and imprinted with "alza 54". All four dosage strengths are supplied in bottles containing 100 tablets. 18 mg 100-count bottle NDC 50458-585-01 27 mg 100-count bottle NDC 50458-588-01 36 mg 100-count bottle NDC 50458-586-01 54 mg 100-count bottle NDC 50458-587-01	18	Methylphenidate hydrochloride extended-release tablets, USP are available in 18 mg, 27 mg, 36 mg, and 54 mg dosage strengths. The 18 mg tablets are yellow printed with **CP 342** on one side and blank on the other side. The 27 mg tablets are gray printed with **CP 340** on one side and blank on the other side. The 36 mg tablets are white printed with **CP 339** on one side and blank on the other side. The 54 mg tablets are brownish-red printed with **CP 341** on one side and blank on the other side. All four dosage strengths are supplied in bottles containing 100 tablets. 18 mg 100-count bottle NDC 0115-1566-01 27 mg 100-count bottle NDC 0115-1567-01 36 mg 100-count bottle NDC 0115-1568-01 54 mg 100-count bottle NDC 0115-1569-01
Storage and Handling Store at 25°C (77°F); excursions permitted to 15-30°C (59-86°F) [see USP Controlled Room Temperature]. Protect from humidity.		**Storage and Handling** Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Protect from humidity.

Table 3.2.P.1-11: Comparison between the RLD and Proposed Drug Product for 18 mg

Description	Reference Listed Drug Concerta® 18 mg	Test Product CorePharma 18 mg
Picture	 Concerta® 18 mg(Left) CorePharma 18 mg(Right)	
Lot No.	15BG992	SB51300301
Shape/Size*	Cylindrical Tablet Length: 11.85 mm Diameter: 5.26 mm	Modified Capsule Shape Tablet Length: 14.20 mm Width: 6.31 mm Thickness: 4.69 mm

(b) (4)

Table 3.2.P.1-12: Comparison between the RLD and Proposed Drug Product for 27 mg

Description	Reference Listed Drug Concerta® 27 mg	Test Product CorePharma 27 mg
Picture	 Concerta® 27 mg (Left) CorePharma 27 mg(Right)	
Lot No.	15CG060	SB51400301
Color	Gray	Gray
Shape/Size*	Cylindrical Tablet Length: 12.11 mm Diameter: 5.27 mm	Modified Capsule Shape Tablet Length: 14.25 mm Width: 6.32 mm Thickness: 4.76 mm

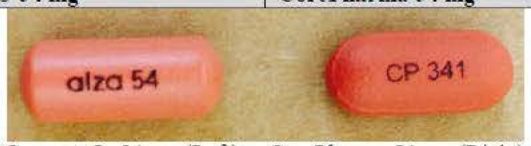
(b) (4)

Table 3.2.P.1-13: Comparison between the RLD and Proposed Drug Product for 36 mg

Description	**Reference Listed Drug Concerta® 36 mg**	**Test Product CorePharma 36 mg**
Picture	 Concerta® 36 mg (Left) CorePharma 36 mg (Right)	
Lot No.	15DG138	SB51500301
Color	White	White
Shape/Size*	Cylindrical Tablet Length: 14.93 mm Diameter: 6.48 mm	Modified Capsule Shape Tablet Length: 14.78 mm Width: 6.86 mm Thickness: 5.18 mm

(b) (4)

Table 3.2.P.1-14: Comparison between the RLD and Proposed Drug Product for 54 mg

Description	**Reference Listed Drug Concerta® 54 mg**	**Test Product CorePharma 54 mg**
Picture	 Concerta® 54 mg (Left) CorePharma 54 mg (Right)	
Lot No.	13KG402	SB69900301
Shape/Size*	Cylindrical Tablet Length: 15.12 mm Diameter: 6.46 mm	Modified Capsule Shape Tablet Length: 14.78 mm Width: 6.89 mm Thickness: 5.22 mm

(b) (4)

MODULE 2: CTD SUMMARIES

2.3	**Quality Overall Summary (QOS)** **YES** **E-Submission: PDF** **YES** **MS Word** Additional information regarding QbR may be found at the following link: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/ucm120971.htm **YES** **Question based Review (QbR)**
	Comments
	YES **2.3.S Drug Substance (Active Pharmaceutical Ingredient)** 2.3.S.1 General Information 2.3.S.2 Manufacture 2.3.S.3 Characterization 2.3.S.4 Control of Drug Substance 2.3.S.5 Reference Standards 2.3.S.6 Container Closure System 2.3.S.7 Stability
	Comments
	YES **2.3.P Drug Product** 2.3.P.1 Description and Composition of the Drug Product 2.3.P.2 Pharmaceutical Development 2.3.P.2.1 Components of the Drug Product 2.3.P.2.1.1 Drug Substance 2.3.P.2.1.2 Excipients 2.3.P.2.2 Drug Product **Oral Solids**: Immediate Release or Modified Release (Matrix Technology or Compressed Film Coated Components) tablet scoring data per Draft *Guidance for Industry, Tablet Scoring: Nomenclature, Labeling and Data for Evaluation* (if applicable) 2.3.P.2.3 Manufacturing Process Development 2.3.P.2.4 Container Closure System 2.3.P.3 Manufacture 2.3.P.4 Control of Excipients 2.3.P.5 Control of Drug Product 2.3.P.6 Reference Standards and Materials 2.3.P.7 Container Closure System 2.3.P.8 Stability
	Comments

2.7

Clinical Summary (Bioequivalence) Model BE Data Summary Tables
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf

In-vitro Binding Study Tables
http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM364105.pdf

YES E-Submission: PDF
YES MS Word

2.7.1 Summary of Biopharmaceutic Studies and Associated Analytical Methods

2.7.1.1 Background and Overview

YES Table 1. Submission Summary
YES Table 4. Bioanalytical Method Validation
YES Table 6. Formulation Data
YES Table 10. Study Information
YES ▪ LTSS data location and hyperlink
YES Table 11. Product Information
N/A Table 17. Comparative Physiochemical Data of Ophthalmic Solution Products

Missing exact location of hyperlinks in Table 10. However hyperlinks are functional
Resolved on 5/27/16 from Sequence 0001.

2.7.1.2 Summary of Results of Individual Studies

YES Table 5. Summary of In Vitro Dissolution
YES ▪ Comparative In Vitro Dissolution Data (individual)
YES ▪ Alcohol Dose Dumping Dissolution (if applicable)
N/A ▪ ½ Tablet Dissolution (if applicable)
YES ▪ COA for Test and Reference Products of the BE Strength
(should include potency, assay, content uniformity, date of manufacture and lot number)
YES Table 9. Reanalysis of Study Samples
YES Table 12. Dropout Information
YES Table 13. Protocol Deviation
YES Table 14. Summary of Standard Curve and QC Data for BE Sample Analysis

Only provided COA for RLD 54mg (BE) strength **Resolved on 5/27/16 from Sequence 0001.**

2.7.1.3 Comparison and Analyses of Results Across Studies

YES Table 2. Summary of Bioavailability (BA) Studies
Table 3. Statistical Summary of the Comparative BA Data:
YES 1. Unscaled Average – Table A
YES 2. Reference-scaled Average BE Studies – Tables A **and** B BE Studies
YES Table 16. Composition of Meal Used in Fed Bioequivalence Study

Comments

2.7.1.4 Appendix

YES Table 15. SOPs Dealing with Bioanalytical Repeats of Study Samples

Comments

2.7.4 Summary of Clinical Safety

2.7.4.1.3 Demographic and Other Characteristics of Study Population

YES Table 7. Demographic Profile of Subjects Completing the Bioequivalence Study

Comments

2.7.4.2.1.1 Common Adverse Events

	YES Table 8. Incidence of Adverse Events in Individual Studies Comments

Dissolution Guidance from USP/FDA webpage

Drug Name	Dosage Form	USP Apparatus	Speed (RPMs)	Medium	Volume (mL)	Recommended Sampling Times (minutes)	Date Updated
Dexmethylphenidate HCl	Tablet	I (Basket)	100	Water	900	10, 15, 30, and 45	06/18/2007
Dexmethylphenidate HCl	Capsule (Extended Release)	I (Basket)	100	First 2 hours: 0.01 N HCl, Hours 2-10: Phosphate Buffer, pH 6.8	Acid: 500, Buffer: 500	0.5, 1, 2, 4, 6, and 10 hours	01/14/2008
Methylphenidate	Transdermal Patch	VI (Cylinder)	50	0.01 N HCl at 32ºC	900	0.5, 1.5, 3, 4 hours and until at least 80% released	04/15/2008
Methylphenidate	Capsule (Extended Release)	II (Paddle)	50	Water	500	1, 2, 4, 6, 8, 12 hours and until at least 80% released	04/15/2008
Methylphenidate	Tablet (Extended Release)			Refer to USP			02/14/2014

USP Monographs: Methylphenidate Hydrochloride Extended-Release Tablets

o Document Section... Go

Test 2 (for products labeled for dosing every 24 h): If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 2*.

Medium: Acidified water, adjusted with phosphoric acid to a pH of 3; 50 mL, at 37 ± 0.5°

Apparatus 7 (see Drug Release ⟨724⟩): 30 cycles/min; 2–3 cm amplitude. Use *Sample Preparation A* using a metal spring sample holder (*Figure 5d*). (ERR 1-Jun-2015)

1 Tablet in the holder with the Tablet orifice facing down, and cover the top of the holder with Parafilm™. At the end of each specified test interval, the systems are transferred to the next row of new test tubes containing 50 mL of fresh *Medium*.

Times: 1-h intervals for a duration of 10 h

Test 4: If the product complies with this test, the labeling indicates that it meets USP *Dissolution Test 4*.

Medium: 0.001 N hydrochloric acid; 500 mL

Apparatus 2: 50 rpm

Times: 1, 2, 6, and 10 h

Mobile phase: Acetonitrile and water (20:80). For every L of *Mobile phase* add 1.0 mL of formic acid and 0.2 mL of trifluoroacetic acid.

Standard solution: 0.02 mg/mL of USP Methylphenidate Hydrochloride RS in *Mobile phase*

Sample solution: Pass a portion of the solution under test through a suitable PTFE filter of 0.45-µm pore size. Do not use glass fiber filters.

Chromatographic system

(See *Chromatography ⟨621⟩, System Suitability*.)

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MODULE 3: QUALITY

3.2.S DRUG SUBSTANCE (Active Pharmaceutical Ingredient)

3.2.S.1

YES **General Information** (May not refer to DMF)

3.2.S.1.1 Nomenclature

3.2.S.1.2 Structure

3.2.S.1.3 General Properties

Comments

3.2.S.2

Manufacturer

Drug Substance (Active Pharmaceutical Ingredient)

Must correlate to the establishment information submitted in annex to Form FDA 356h

YES 1. Name and Full Address(es) of the Facility(ies)
YES 2. Contact name, phone and fax numbers, email address
N/A 3. U.S. Agent's Name (if applicable)
YES 4. Specify function or responsibility
YES 5. Type II DMF number(s) for API(s)
YES 6. CFN, FEI, or DUNS number (if available)
N/A 7. Additional sources of API and information (1 through 6, if applicable)

Manufacturing, Packaging, Testing, and Labeling Facility:

(b) (4)

[redacted]

3.2.S.3

YES **Characterization**

All potential impurities should be listed in tabular format as follows:

IUPAC Chemical Name	Code #	Chemical Structure	Process/ Degradation Impurity	Source/ Mechanism

http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf

Comments

Control of Drug Substance (Active Pharmaceutical Ingredient)

3.2.S.4

3.2.S.4.1

YES **Specification**

Testing specifications and data from drug substance manufacturer(s)

Comments

3.2.S.4.2

YES **Analytical Procedures**

Comments

3.2.S.4.3

YES **Validation of Analytical Procedures**

(API that is USP or reference made to DMF, **MUST** provide verification of USP or DMF procedures)

YES 1. Spectra and chromatograms for **reference standards** and **test samples**
2. Samples-Statement of Availability and Identification (21 CFR §314.50(e)(1))
YES a. Drug Substance

(b) (4)

[redacted]

IR Spectra and chromatograms are in section 3.2.S.4.4

(b) (4)

(b) (4)

	3.2.S.4.4	**Batch Analysis** YES 1. COAs specifications and test results from DS manufacturer(s) YES 2. Drug Product manufacturer's Certificates of analysis **DS manufacturer's COAs are in section 3.2.S.4.1**
	3.2.S.4.5	YES **Justification of Specification** Provide data in tabular format: Chemical Name | Code # | MDD | IT | QT | TDI of Impurity | Proposed AC for Unspecified Impurities | Proposed AC for Specified Impurities | Justification if AC>QT for Specified Impurities http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf Comments
3.2.S.5		YES **Reference Standards or Materials** (Do NOT refer to DMF) Comments
3.2.S.6		YES **Container Closure Systems** Comments
3.2.S.7		**Stability** YES 1. Retest date or expiration date of API(s)


(b) (4)

MODULE 3: QUALITY (cont.)

3.2.P DRUG PRODUCT

3.2.P.1	**Description and Composition of the Drug Product** YES 1. Unit composition with indication of the function of the inactive ingredient(s) YES 2. Inactive ingredients and amounts are appropriate per IIG (per/dose justification) (provide justification in a tabular format) 3. Formulation YES Oral Tablet and Oral Capsules: % to mg/dosage unit N/A Oral suspensions and oral solutions: % to mg/dose N/A Parenterals: same unit of measure as RLD YES 4. Elemental iron: provide daily elemental iron calculation pursuant to 21 CFR 73.1200 (calculation of elemental iron intake based on **maximum daily dose (MDD)** of the drug product is preferred if this section is applicable) N/A 5. Injections: If the reference listed drug is packaged with a drug specific diluent, then the diluent must be Q1/Q2 and must be provided in the package configuration Comments

Composition of Generic

Concerta® is an extended release (ER) once-a-day formulation composed of both (IR) (b) (4) and extended release (ER) (b) (4) components. CorePharma's proposed generic drug product formulation consists of a core tablet composed of the drug substance and various excipients. (b) (4)

(b) (4)

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3.2.P.2		YES **Pharmaceutical Development** 1. Pharmaceutical Development Report 2. Microbial Attributes a. Container/Closure Integrity Testing Report for Sterile Products b. Antimicrobial Effectiveness Testing for Multi-dose Sterile Products Comments
3.2.P.3		**Manufacture**
	3.2.P.3.1	**Drug Product Manufacturer(s)** Must correlate to the establishment information submitted in annex to Form 356h for the finished dosage manufacturer and all outside contract testing laboratories. YES 1. Name and Full Address(es) of the Facility(ies) YES 2. Contact name, phone and fax numbers, email address N/A 3. U.S. Agent's name (if applicable) YES 4. Specify function or responsibility YES 5. cGMP Certification from **Applicant** YES 6. CFN, FEI, or DUNS numbers (if available) (b) (4) [redacted]
	3.2.P.3.2	YES **Batch Formula** Largest Intended Commercial Batch Size Comments

Scale up of Batch Formula

Table 3.2.P.3-2-1b Theoretical Batch Size for Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg

Strength	Theoretical Final Coated Tablets Batch Size / Tablet No.
18 mg	(b) (4) [redacted]

(b) (4) [redacted]

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	3.2.P.3.3	**Description of Manufacturing Process and Process Controls** YES 1. Description of the Manufacturing Process and (for aseptic fill products) Facility YES 2. Master Production Batch Record(s) for largest intended production runs (no more than 10x pilot batch) with equipment specified YES 3. Master Packaging Records for intended marketing container(s) 4. If sterile product N/A YES 5. Reprocessing Statement (cite 21 CFR 211.115) from **Applicant** Comments
	3.2.P.3.4	YES **Controls of Critical Steps and Intermediates** Comments
	3.2.P.3.5	**Process Validation and/or Evaluation** 1. Terminally Sterilized Product N/A • Is this pharmacy bulk? (Go to 1.14.1.4) 2. Aseptically Filled Product N/A • Validation (bacterial retention studies) of sterilizing grade filter(s) N/A • Is this pharmacy bulk? (Go to 1.14.1.4) Comments

Copy and Paste Bacterial Retention Filter Validation table – **not applicable**

		Controls of Excipients (Inactive Ingredients)
3.2.P.4	*	YES Source of Inactive Ingredients Identified Comments
	3.2.P.4.1	**Specifications** YES 1. Testing specifications (including identification and characterization) YES 2. Supplier's COA (specifications and test results) Comments
	3.2.P.4.2	YES **Analytical Procedures** Comments
	3.2.P.4.3	YES **Validation of Analytical Procedures** Comments
	3.2.P.4.4	**Justification of Specifications** (as applicable) YES 1. Applicant COA YES 2. Residual Solvents Statement(s) from manufacturer(s) YES 3. Bovine spongiform encephalopathy (BSE) (as applicable) YES 4. Transmissible spongiform encephalopathy (TS) (as applicable) YES 5. Melamine Certifications (as applicable) Comments
		Controls of Drug Product
3.2.P.5	3.2.P.5.1	YES **Specification(s)** Comments
	3.2.P.5.2	YES **Analytical Procedures** Comments
	3.2.P.5.3	YES **Validation of Analytical Procedures** (if using USP procedure, must provide verification of USP procedure) Samples - Statement of Availability and Identification (21 CFR §314.50(e)(1)) YES 1. Finished Dosage Form 2. Lot numbers and strength of Drug Products **See below** Comments

(b) (4)

(b) (4)

	3.2.P.5.4	**YES** **Batch Analysis** Certificates of Analysis for Finished Dosage Form Comments
	3.2.P.5.5	**YES** **Characterization of Impurities** Provide in tabular format as below: IUPAC Chemical Name | Code # | Chemical Structure | Degradation Impurity | Source/ Mechanism http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf Comments
	3.2.P.5.6	**YES** **Justification of Specifications** Provide data in tabular format: Chemical Name | Code # | MDD | IT | QT | TDI of Degradation Product | Proposed AC for Unspecified Degradation Product | Proposed AC for Specified Degradation Product | Justification if AC>QT for Degradation Product http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM380338.pdf Comments
	3.2.P.7	**Container Closure System** **YES** 1. Summary of Container/Closure System (if new resin, provide data) **YES** 2. Components Specification and Test Data **YES** 3. Packaging Configurations and Sizes 4. Container/Closure Testing (recommended additional testing for all plastic) **YES** a. Solid Orals: water permeation, light transmission **N/A** b. Liquids: leachables, extractables, light transmission **YES** 5. Source of supply and suppliers address Comments

Summary of Container Closure System

Summary

Methylphenidate Hydrochloride Extended-Release Tablets, USP are packaged in high-density polyethylene (HDPE) bottles and polypropylene CRC closures with (b) (4) liner over the bottle opening.

Table 3.2.7.1-1 below summarizes the container/closure system for Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg, packaged in 100-count bottles.

Table 3.2.P.7.1-1 Container Closure Systems for Drug Product

Strength(s)	Count	Component / Manufacturer	Description	Material Used
18 mg 27 mg 36 mg 54 mg	100	(b) (4)	120 cc Wide-Mouth Square, White HDPE Bottle with (b) (4) CR Finish (b) (4)	(b) (4)

Module 3.2.P.7.3 Packaging Configurations and Sizes

The drug product exhibit batches were packaged and are proposed for commercial production to be packaged in the following configurations:

Strength	Count	Bottle	Closure	Desiccant
Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg	100 Count	HDPE 120cc, Square, (b) (4) CR Finish	(b) (4) CR (b) (4) (b) (4) Text Top Child-resistant Closure with (b) (4) (b) (4) Liner	(2) Desiccant, (b) (4)

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Stability

3.2.P.8

3.2.P.8.1

Stability Summary and Conclusion (Finished Dosage Form)

YES 1. Stability Protocol Submitted
2. Expiration Dating Period for Marketed Packaging **2 years**
3. Expiration Dating Period for Bulk packaging (if applicable) **N/A**

3. Expiration Dating Period for Marketed Packaging

Available stability data (provided in Module 3.2.P.8.3) meets all specifications. CorePharma requests a tentative 2-year shelf-life for the drug product to be confirmed by real time long-term stability data from the ongoing stability program. (b) (4)

(b) (4)

4. Expiration Dating Period for Bulk Packaging (if applicable)

(b) (4)

3.2.P.8.2

Post-Approval Stability Protocol and Stability Commitment

YES 1. Post-Approval Protocol and Commitment from **Applicant**

Comments

3.2.P.8.3

Stability Data (Refer to the Final Guidance for Industry *ANDAs: Stability Testing Drug Substances and Products*, dated June 2013)

YES 1. 3 batches?
YES a. Two API lots used? (provide the page number in the EBR that identifies the API lot in the **comment** box below)
YES b. All presentations of container closure systems amongst the 3 batches?
N/A 2. Additional stability data to support additional API sources (if applicable)
3. Data- At minimum, 6 months **and** 3 time points
YES a. Accelerated
NO 1. Significant change occurred
YES 2. If yes, 6 months intermediate stability data
YES b. Long term storage (Room Temperature)
YES 4. Batch numbers on stability records the same as the test batch
YES 5. Date accelerated stability study initiated
YES 6. Date accelerated stability sample removed from stability chamber for each testing time point
N/A 7. For liquid and semi-solid products, upright and inverted/horizontal storage orientation

See below for the location of API lots used.

MODULE 3: QUALITY (cont.)

3.2.R REGIONAL INFORMATION 21 CFR §314.50(d)(1)(ii)(b)

REGIONAL INFORMATION (DRUG SUBSTANCE)		
3.2.R.S Drug Substance	3.2.R.1.S	N/A **Executed Batch Records for drug substance** (if available) **(Required for A3F)**
	3.2.R.2.S	N/A **Comparability Protocols**
	3.2.R.3.S	YES **Methods Validation Package (Required for Non-USP drugs)** Methods Validation Package (3 copies for paper and N/A for E-Submissions)
	Comments	

REGIONAL INFORMATION (DRUG PRODUCT)		
3.2.R.P Drug Product	3.2.R.1.P	**1. Executed Batch Records** YES Copies of Executed Batch Records with Equipment Specified, including Packaging Records (Packaging and Labeling Procedures) (Refer to batch size and packaging information that meet the minimum threshold amount for specified dosage forms, i.e., solid oral dosage forms, oral powders/solutions/suspensions, parenteral drug products, ophthalmic/otic drug products, transdermal patches, topicals (i.e., creams, lotions, gels, inhalation solutions, nasal sprays, etc.). Refer to the Final Guidance for Industry *ANDAs: Stability Testing Drug Substances and Products, Questions and Answers*. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM366082.pdf) a. Two (2) Pilot Scales and one (1) small scale OR b. Three (3) Pilot scales
		Comments
		YES Batch Reconciliation and Label Reconciliation a. Theoretical Yield Theoretical Yield b. Actual Yield Actual Yield c. Packaged Yield Packaged Yield
		Comments
		Bulk Package Reconciliation for all bulk packaging considered a commercial container is recommended if bulk packaging is used to achieve the minimum package requirement. Provide the following information in their respective sections: N/A a. Bulk Package Label (1.14.1) N/A b. Bulk Package Stability (3.2.P.8) N/A 1. If bulk is to be shipped, provide accelerated stability data at 0,3,6 months N/A 2. If bulk is only warehoused for repackaging, provide RT stability data at 0,3,6 months N/A c. Bulk Package Container and Closure information (3.2.P.7)
		Comments
		YES **2. Information on Components** Name(s) and Address(es) of the Active Pharmaceutical Ingredient (API), inactive ingredient(s), and containers and closures in **tabular format.**
		Comments
	3.2.R.2.P	N/A **Comparability Protocols**
	3.2.R.3.P	YES **Methods Validation Package** Methods Validation Package (3 copies for paper and N/A for E-Submissions) (Required for Non-USP drugs)
		Comments

MODULE 5: CLINICAL STUDY REPORTS

5.2		NO	**Tabular Listing of Clinical Studies**
			Missing Summary Tables of all studies
5.3	5.3.1		**Bioavailability/Bioequivalence** 1. **Formulation data same?** YES a. Comparison of all Strengths (proportionality of multiple strengths) N/A b. Parenterals, Ophthalmics, Otics and Topicals (21 CFR 314.94 (a)(9)(iii)-(v)) 2. **Lot Numbers and strength of Products used in BE Study(ies)** Lot numbers and strength(s) 3. **Study Type: IN-VIVO PK STUDY(IES)** (Continue with the appropriate study type box below)
			Comments
	*	YES	See Module 2.7 Clinical Summary for placement of BA/BE Summary for tables 9 – 16. The study data that support the BA/BE summary tables should be provided in the corresponding sections below: 5.3.1.2 Comparative BA/BE Study Reports **SAS data** 5.3.1.3 In Vitro-In Vivo Correlation Study Reports (exception: all dissolution data should be placed in 2.7) 5.3.1.4 Reports of Bioanalytical and Analytical Methods for Human Studies **Case Report Forms** should be placed under the study to which they pertain, and appropriate tagged. Refer to The eCTD Backbone File Specification for Study Tagging http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf
			Unassigned folder in section 5.3.1.4
5.4			**Literature References**
			Possible Study Types:
Study Type		YES YES YES	IN-VIVO BE STUDY(IES) with PK ENDPOINTS (i.e., fasting/fed/sprinkle) 1. Study(ies) meets BE criteria (90% CI of 80-125, Cmax , AUC) 2. In-Vitro Dissolution 3. FRS Review Completed
Study Type		N/A	IN-VIVO BE STUDY with CLINICAL ENDPOINTS FRS Review Completed
Study Type		N/A	IN-VITRO BE STUDY(IES) (i.e., in vitro binding assays) FRS Review Completed
Study Type		N/A	NASALLY ADMINISTERED DRUG PRODUCTS Refer to the attached links for Nasal Product BE Tables: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM209446.pdf AND http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM271017.pdf FRS Review Completed
Study Type		N/A	IN-VIVO BE STUDY(IES) with PD ENDPOINTS (e.g., topical corticosteroid vasoconstrictor studies) FRS Review Completed
Study Type		N/A	TRANSDERMAL DELIVERY SYSTEMS FRS Review Completed

Effective as of March 1, 2016

For More Information on Submission of an ANDA in Electronic Common Technical Document (eCTD) Format please go to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm
For a Comprehensive Table of Contents Headings and Hierarchy please go to: http://www.fda.gov/cder/regulatory/ersr/5640CTOC-v1.2.pdf
Draft Guidance for Industry ANDA Submissions – Content and Format of Abbreviated New Drug Applications:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM400630.pdf

Table 11 Product Information [ARL/14/694 (Fasting) & ARL/14/695 (Fed)]

Product	Test	Reference
Treatment ID	**A**	**B**
Product/Brand Name	Methylphenidate Hydrochloride Extended-Release Tablets, USP	CONCERTA® (Methylphenidate HCl) Extended-Release Tablets
Manufacturer	(b) (4) Manufactured for: CorePharma, LLC 215 Wood Avenue Middlesex, NJ 08846	Manufactured by: Janssen-Cilag Manufacturing, LLC, Gurabo, PR 00778 or Alza Corp. Vacaville, CA 95688 Manufactured for: Janssen Pharmaceuticals, Inc. Titusville, NJ 08560
Lot No.	SB69900301	13KG402
Manufacture Date	09/04/2014	N/A
Expiration Date	N/A	07/2015
Strength	54 mg	54 mg
Dosage Form	Tablet	Tablet
Bio-batch Size	(b) (4)	N/A
Production Batch Size		N/A
Potency	97.3%	101.5%
Content Uniformity (mean, SD)	96.3% (1.27)	N/A
Dose Administered	1 x 54 mg Tablet	1 x 54 mg Tablet
Route of Administration	Oral	Oral

Table 10.1 Study Information-ARL/14/694 (Fasting)

Study Number	**ARL/14/694**
Study Title	A Randomized, Balanced, Open Label, Two-Treatment, Four-Period, Two-Sequence, Single Dose, Crossover, Fully Replicated Bioequivalence Study of Test Formulation of Methylphenidate HCl Extended-Release Tablets USP, 54 mg, CorePharma, LLC, versus Reference Product Concerta® (Methylphenidate HCl) Extended-Release Tablets, 54 mg, in Normal, Healthy, Adult, Male and Female Human Subjects under Fasting Conditions
Study Type	☒In Vivo BE ☐In Vitro BE ☐Permeability ☐Other
Submission Location: Study Report	Module 5.3.1.2
Validation Report	Module 5.3.1.4
Bioanalytical Report	Module 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Accutest Research Laboratories (I) Pvt. Ltd. A-31, M.I.D.C, TTC Industrial Area Khairane, Navi Mumbai -400 709 Maharashtra, India Phone: 91.22.2778.0718/19/21 Fax: 91.22.2778.0720
Principal Clinical Investigator (Name, Email)	Vivekananda Murthi, MBBS Vivekanand.Murthy@accutestindia.com
Dosing Dates	Period 1: 25 December 2014 Period 2: 06 January 2015 Period 3: 14 January 2015 Period 4: 21 January 2015
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)
Analysis Dates	06 February 2015 to 28 February 2015
Principal Analytical Investigator (Name, Email)	(b) (4)
Sample Storage: (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	(a) 65 days (b) -15 °C to -35 °C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	91 days @ -20 °C
LTSS Data Location	Module 5.3.1.4 - Method Validation Report (Table 10)

Table 10.2 Study Information-ARL/14/695 (Fed)

Study Number	ARL/14/695
Study Title	A Randomized, Balanced, Open Label, Two-Treatment, Four-Period, Two-Sequence, Single Dose, Crossover, Fully Replicated Bioequivalence Study of Test Formulation of Methylphenidate HCl Extended-Release Tablets USP, 54 mg, CorePharma, LLC, versus Reference Product Concerta® (Methylphenidate HCl) Extended-Release Tablets, 54 mg, in Normal, Healthy, Adult, Male and Female Human Subjects under Fed Conditions
Study Type	☒In Vivo BE ☐In Vitro BE ☐Permeability ☐Other
Submission Location: Study Report	Module 5.3.1.2
Validation Report	Module 5.3.1.4
Bioanalytical Report	Module 5.3.1.4
Clinical Site (Name, Address, Phone #, Fax #)	Accutest Research Laboratories (I) Pvt. Ltd. A-31, M.I.D.C, TTC Industrial Area Khairane, Navi Mumbai -400 709 Maharashtra, India Phone: 91.22.2278.0718/19/21 Fax: 91.22.2778.0720
Principal Clinical Investigator (Name, Email)	Vivekananda Murthi, MBBS Vivekanand.Murthy@accutestindia.com
Dosing Dates	Period 1: 14 December 2014 Period 2: 23 December 2014 Period 3: 31 December 2014 Period 4: 08 January 2015
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4)
Analysis Dates	20 January 2015 to 04 February 2015
Principal Analytical Investigator (Name, Email)	(b) (4)
Sample Storage: (a) Duration (no. of days from the first day of sample collection to the last day of sample analysis) (b) Temperature Range (e.g., -20°C to -80°C)	(a) 52 days (b) -15 °C to -35 °C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	91 days @ -20 °C
LTSS Data Location	Module 5.3.1.4 - Method Validation Report (Table 10)

Table 3.1A Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies -ARL/14/694 (Fasting)

Reference Scaled Average Bioequivalence Approach Used	☒ Yes	☐ No
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B		
Methylphenidate HCl (No of subjects completed=58) Dose (1 x 54 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals **Fasting Bioequivalence Study (4002731, ARL/14/694)**		

Parameter	Test	N	RLD	N	Ratio	90% C.I.	
Cmax	17.1553	58	16.8722	58	101.68	97.73	105.78
AUC0-3	18.2354	58	17.4532	58	104.48	100.75	108.35
AUC3-7	54.4274	58	48.2797	58	112.73	108.92	116.68
AUC7-12	56.1426	58	64.7174	58	86.75	83.94	89.65
AUC∞	171.9476	58	182.2264	58	94.36	91.72	97.08

Table 3.1B Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE Studies-ARL/14/694 (Fasting)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	σ^2_D [a]	Method Used	Outcome
Cmax	101.68	97.73	105.78	-0.0018	ANOVA	BE
AUC0-3	104.48	100.75	108.35	0.0030	ANOVA	BE
AUC3-7	112.73	108.92	116.68	-0.0021	ANOVA	BE
AUC7-12	86.75	83.94	89.65	-0.0023	ANOVA	BE
AUC∞	94.36	91.72	97.08	-0.0056	ANOVA	BE

[a] = Subject-by-formulation interaction variance. Reference is made to the Controlled Correspondence (CC) # 49819 enclosed in this section for ease of review. In response to CC, the OGD stated that the subject-by-formulation interaction variance for each PK metric should be less than or equal to 0.03.

Test (T) = Methylphenidate HCl ER Tablets (CorePharma)

Reference (R) = Concerta® ER Tablets

Table 3.2A Statistical Summary of the Comparative Bioavailability Data for Unscaled Average BE studies -ARL/14/695 (Fed)

Reference Scaled Average Bioequivalence Approach Used	☒ Yes	☐ No
If No, then complete Table 3A only If Yes, then complete Tables 3A and 3B		
Methylphenidate HCl (No of subjects completed=70) Dose (1 x 54 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals **Fed Bioequivalence Study (4002730, ARL/14/695)**		

Parameter	Test	N	RLD	N	Ratio	90% C.I.	
Cmax	20.9932	70	17.9581	70	116.90	111.32	122.76
AUC0-4	29.2895	70	29.7970	70	98.30	94.49	102.26
AUC4-8	65.0814	70	60.6755	70	107.26	102.56	112.18
AUC8-12	49.1990	70	54.0537	70	91.02	87.71	94.46
AUC∞	193.3395	70	198.8586	70	97.22	94.34	100.20

Table 3.2B Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE Studies - ARL/14/695 (Fed)

Parameter	T/R Ratio	Lower 90% CI	Upper 90% CI	σ^2_D [a]	Method Used	Outcome
Cmax	116.90	111.32	122.76	0.0105	ANOVA	BE
AUC0-4	98.30	94.49	102.26	0.0090	ANOVA	BE
AUC4-8	107.26	102.56	112.18	0.0104	ANOVA	BE
AUC8-12	91.02	87.71	94.46	-0.0009	ANOVA	BE
AUC∞	97.22	94.34	100.20	-0.0026	ANOVA	BE

[a] = Subject-by-formulation interaction variance. Reference is made to the Controlled Correspondence (CC) # 49819 enclosed in this section for ease of review. In response to CC, the OGD stated that the subject-by-formulation interaction variance for each PK metric should be less than or equal to 0.03.

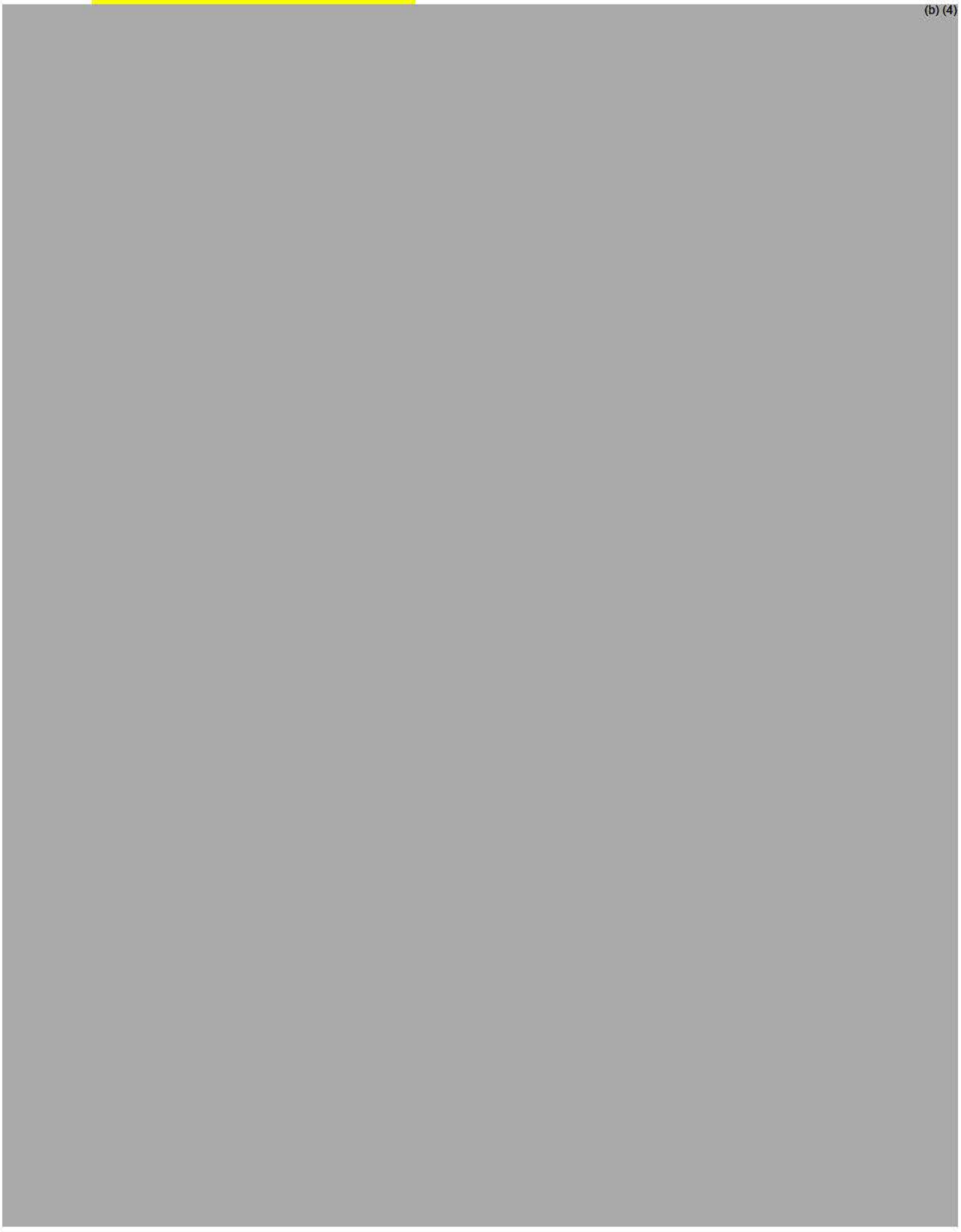
N/A = Not applicable

Test (T) = Methylphenidate HCl ER Tablets (CorePharma)

Reference (R) = Concerta® ER Tablets

Table 5.1 Comparative Dissolution Studies (18 mg and 27 mg)

(b) (4)



(b) (4)

Table 5.4 Multi-Media (pH 1.2) Dissolution Studies (36 mg and 54mg)

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid (pH 1.2)**
	Volume:	**500 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (hours) 0.5	1	2	4	6	8	10	12	Study Report Location
Report #: 15-03-IR-002-01R	07/21/15 & 07/23/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		17	22	33	58	76	89	96	98	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		3.2	3.9	5.1	4.7	4.2	3.7	2.6	1.8	
	04/20/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		22	25	30	50	78	102	107	107	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.3	5.4	5.0	4.9	5.0	2.9	2.0	1.9	
	04/02/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		18	22	31	54	73	87	96	99	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.5	6.7	7.6	5.9	4.8	3.8	3.2	2.5	
	03/25/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		21	24	28	47	70	95	104	105	
					Range	Min	(b) (4)								
						Max									
					% RSD		5.4	5.0	3.8	4.4	4.9	5.2	2.0	2.2	

Table 5.5 Multi-Media (pH 4.5) Dissolution Studies (18 mg and 27 mg)

Dissolution Conditions															
			Apparatus:	II (Paddle), USP <711>											
			Speed of Rotation:	50 rpm											
			Medium:	pH 4.5 (b) (4)											
			Volume:	500 mL											
			Temperature:	37°C ± 0.5°C											
Firm's Proposed Specifications			N/A												
Dissolution Testing Site (Name, Address)			CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846												
Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (hours)								Study Report Location
							0.5	1	2	4	6	8	10	12	
Report #: 15-03-IR-002-01R	06/29/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		21	28	40	67	86	96	101	103	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		5.2	5.6	6.5	3.9	2.8	1.8	1.4	1.3	
	04/24/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		22	26	32	54	82	105	108	109	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.4	5.7	4.7	3.2	3.3	2.8	3.1	3.2	
	07/08/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		25	30	46	72	90	100	104	105	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.1	5.4	4.9	3.7	3.1	2.8	2.7	2.6	
	04/23/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		20	23	28	50	74	98	103	103	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.7	6.0	5.0	4.5	4.3	2.7	2.8	2.8	

Table 5.6 Multi-Media (pH 4.5) Dissolution Studies (36 mg and 54mg)

Dissolution Conditions															
			Apparatus:	II (Paddle), USP <711>											
			Speed of Rotation:	50 rpm											
			Medium:	pH 4.5 (b) (4)											
			Volume:	500 mL											
			Temperature:	37°C ± 0.5°C											
Firm's Proposed Specifications			N/A												
Dissolution Testing Site (Name, Address)			CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846												
Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (hours)								Study Report Location
							0.5	1	2	4	6	8	10	12	
Report #: 15-03-IR-002-01R	07/27/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		18	24	37	62	80	92	98	100	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		4.3	4.2	4.9	3.8	3.0	2.5	2.3	2.3	
	04/22/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		20	24	30	51	78	101	105	105	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.7	6.1	6.3	6.0	5.3	2.6	1.6	1.7	
	04/08/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		19	25	37	62	81	93	100	103	
					Range	Min	(b) (4)								
						Max									
					% RSD		5.6	5.4	4.5	3.7	2.9	2.5	2.0	1.9	
	03/25/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		21	24	29	47	75	100	106	106	
					Range	Min	(b) (4)								
						Max									
					% RSD		5.8	5.6	5.8	6.4	5.9	4.5	2.3	2.2	

Table 5.7 Multi-Media (pH 6.8) Dissolution Studies (18 mg and 27 mg)

Dissolution Conditions															Study Report Location
Apparatus:	II (Paddle), USP <711>														
Speed of Rotation:	50 rpm														
Medium:	pH 6.8 (b) (4)														
Volume:	500 mL														
Temperature:	37°C ± 0.5°C														
Firm's Proposed Specifications	N/A														
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846														
Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (hours) 0.5	1	2	4	6	8	10	12	
Report #: 15-03-IR-002-01R	06/30/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		22	25	39	69	86	95	98	99	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		9.7	10.0	8.9	6.9	4.9	4.4	3.6	3.1	
	04/13/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		21	24	29	49	73	97	102	102	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.6	6.0	5.2	4.1	3.8	3.1	2.8	2.7	
	07/06/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		23	27	41	70	90	98	102	103	
					Range	Min	(b) (4)								
						Max									
					% RSD		5.3	4.9	4.7	4.6	4.7	3.9	3.2	3.0	
	04/15/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		20	23	27	46	69	93	100	101	
					Range	Min	(b) (4)								
						Max									
					% RSD		7.8	7.6	6.1	4.3	4.1	3.3	2.3	2.2	

Table 5.8 Multi-Media (pH 6.8) Dissolution Studies (36 mg and 54mg)

Dissolution Conditions															Study Report Location
Apparatus:	II (Paddle), USP <711>														
Speed of Rotation:	50 rpm														
Medium:	pH 6.8 (b) (4)														
Volume:	500 mL														
Temperature:	37°C ± 0.5°C														
Firm's Proposed Specifications	N/A														
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846														
Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (hours) 0.5	1	2	4	6	8	10	12	
Report #: 15-03-IR-002-01R	07/21/15 & 07/23/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		18	22	34	60	82	92	95	96	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		4.7	4.1	3.9	3.6	4.4	3.2	2.7	2.6	
	04/17/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		21	23	28	48	73	97	103	103	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.3	5.9	4.9	3.0	2.9	2.0	1.5	1.6	
	04/07/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		19	23	33	57	80	93	99	101	
					Range	Min	(b) (4)								
						Max									
					% RSD		9.7	9.0	7.2	5.9	4.5	4.0	3.2	2.9	
	03/30/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		21	23	28	45	68	93	105	105	
					Range	Min	(b) (4)								
						Max									
					% RSD		4.9	5.4	5.5	4.9	3.4	3.1	2.2	2.5	

Table 5.9 Dose Dumping Dissolution Studies (0.1N HCl; 18 mg and 27 mg)

Dissolution Conditions															
			Apparatus:	II (Paddle), USP <711>											
			Speed of Rotation:	50 rpm											
			Medium:	0.1N Hydrochloric acid											
			Volume:	900 mL											
			Temperature:	37°C ± 0.5°C											
Firm's Proposed Specifications			N/A												
Dissolution Testing Site (Name, Address)			CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846												
Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes)								Study Report Location
							15	30	45	60	75	90	105	120	
Report #: 15-03-IR-003-00R	06/25/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		20	22	23	24	27	30	33	36	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		6.5	5.9	5.3	3.8	4.5	5.0	5.3	5.5	
	04/28/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		24	25	25	25	26	27	29	30	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.1	6.0	5.8	5.5	5.3	5.0	4.7	4.5	
	07/28/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		20	23	24	26	28	31	34	38	
					Range	Min	(b) (4)								
						Max									
					% RSD		3.5	2.9	2.8	2.8	3.1	3.0	3.5	2.7	
	05/06/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		23	23	24	24	25	26	27	29	
					Range	Min	(b) (4)								
						Max									
					% RSD		4.9	5.2	5.1	5.2	5.1	5.2	5.2	5.2	

Table 5.10 Dose Dumping Dissolution Studies (0.1N HCl; 36 mg and 54 mg)

Dissolution Conditions															
			Apparatus:	II (Paddle), USP <711>											
			Speed of Rotation:	50 rpm											
			Medium:	0.1N Hydrochloric acid											
			Volume:	900 mL											
			Temperature:	37°C ± 0.5°C											
Firm's Proposed Specifications			N/A												
Dissolution Testing Site (Name, Address)			CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846												
Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes)								Study Report Location
							15	30	45	60	75	90	105	120	
Report #: 15-03-IR-003-00R	08/04/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		17	19	20	22	25	29	32	36	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		2.9	2.4	2.4	3.0	3.0	3.3	3.3	3.1	
	05/18/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		18	22	23	24	24	26	27	29	
					Range	Min	(b) (4)								
						Max									
					% RSD		5.4	6.5	6.1	5.9	5.5	5.2	4.9	4.7	
	04/07/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		20	21	21	22	25	27	30	33	
					Range	Min	(b) (4)								
						Max									
					% RSD		9.7	9.9	10.6	11.4	11.4	11.0	10.7	10.3	
	03/27/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		19	23	24	24	25	26	27	28	
					Range	Min	(b) (4)								
						Max									
					% RSD		7.4	7.2	7.1	6.9	6.6	6.3	5.7	5.4	

Table 5.11 Dose Dumping Dissolution Studies (0.1N HCl w/5% v/v Alcohol; 18 mg and 27 mg)

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 5% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	06/29/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		18	22	22	23	25	27	30	33	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		10.2	8.5	8.7	8.7	9.6	10.9	11.3	11.1	
	04/29/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		24	25	25	25	27	28	30	32	
					Range	Min	(b) (4)								
						Max									
					% RSD		4.7	4.8	4.7	4.6	4.5	4.4	4.1	3.8	
	08/03/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		19	23	24	25	27	30	33	36	
					Range	Min	(b) (4)								
						Max									
					% RSD		5.6	2.9	2.9	4.0	6.0	7.0	7.1	7.0	
	05/5/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		22	23	24	24	25	26	28	30	
					Range	Min	(b) (4)								
						Max									
					% RSD		4.6	4.6	4.4	4.4	4.1	3.8	3.8	3.7	

Table 5.12 Dose Dumping Dissolution Studies (0.1N HCl w/5% v/v Alcohol; 36 mg and 54mg)

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 5% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	08/05/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		16	19	20	21	24	27	30	34	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		5.3	2.7	2.7	4.5	6.0	6.2	5.7	5.2	
	05/12/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		20	22	22	23	24	26	28	30	
					Range	Min	(b) (4)								
						Max									
					% RSD		8.0	7.7	7.8	7.6	7.3	7.1	6.5	6.2	
	04/06/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		20	20	21	22	24	26	29	32	
					Range	Min	(b) (4)								
						Max									
					% RSD		3.7	4.2	3.9	4.2	4.8	5.2	5.3	5.3	
	03/26/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		8	23	24	24	25	26	28	30	
					Range	Min	(b) (4)								
						Max									
					% RSD		15.2	4.8	3.9	3.6	3.4	3.6	4.0	4.3	

Table 5.13 Dose Dumping Dissolution Studies (0.1N HCl w/20% v/v Alcohol; 18 mg and 27 mg)

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 20% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	07/06/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		16	22	23	23	23	23	23	23	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		10.6	6.7	6.5	6.5	6.4	6.4	6.3	6.2	
	04/24/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		8	22	24	25	27	29	32	35	
					Range	Min	(b) (4)								
						Max									
					% RSD		15.2	6.5	6.7	6.4	5.8	5.4	5.3	5.2	
	08/04/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		17	23	24	24	24	24	24	24	
					Range	Min	(b) (4)								
						Max									
					% RSD		12.4	5.7	5.4	5.4	5.3	5.3	5.3	5.2	
	05/19/15	Concerta Lot: 15CG060 Exp date: 01/2017	27 mg ER Tablet	12	Mean		16	23	24	25	26	29	31	34	
					Range	Min	(b) (4)								
						Max									
					% RSD		13.2	6.2	5.3	5.0	4.6	4.4	4.2	4.3	

Table 5.14 Dose Dumping Dissolution Studies (0.1N HCl w/20% v/v Alcohol; 36 mg and 54 mg)

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 20% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	08/05/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		14	19	20	20	20	20	20	21	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		7.5	4.3	4.7	4.8	4.9	4.8	4.9	4.9	
	05/08/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		18	23	24	25	27	29	32	36	
					Range	Min	(b) (4)								
						Max									
					% RSD		8.5	8.5	8.0	7.6	7.3	7.4	7.1	6.8	
	04/03/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		21	21	21	21	21	21	21	22	
					Range	Min	(b) (4)								
						Max									
					% RSD		7.3	7.1	7.1	7.0	7.0	7.0	6.9	6.9	
	03/25/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		8	22	24	25	27	29	31	34	
					Range	Min	(b) (4)								
						Max									
					% RSD		20.0	4.1	3.4	3.0	3.2	3.1	2.9	2.8	

Table 5.15 Dose Dumping Dissolution Studies (0.1N HCl w/40% v/v Alcohol; 18 mg and 27 mg)

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 40% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	06/26/15	Methylphenidate HCl Lot: SB51300301 Mfr date: 03/20/2015	18 mg ER Tablet	12	Mean		16	22	23	24	25	28	31	35	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		8.7	8.9	8.8	7.9	6.3	8.4	10.1	10.3	
	04/22/15	Concerta Lot: 14NG790 Exp date: 07/2016	18 mg ER Tablet	12	Mean		10	22	26	28	32	36	41	47	
					Range	Min	(b) (4)								
						Max									
					% RSD		26.1	6.0	6.1	5.4	4.6	4.5	4.3	4.8	
	12/09/15	Methylphenidate HCl Lot: SB51400301 Mfr date: 04/21/2015	27 mg ER Tablet	12	Mean		23	24	24	26	29	33	37	41	
					Range	Min	(b) (4)								
						Max									
					% RSD		3.2	2.9	3.0	5.8	8.0	9.4	9.9	10.0	
	04/30/15	Concerta Lot: 15AG834 Exp date: 09/2016	27 mg ER Tablet	12	Mean		21	24	25	28	32	36	42	47	
					Range	Min	(b) (4)								
						Max									
					% RSD		3.9	5.7	5.3	4.8	4.6	4.8	4.6	4.2	

Table 5.16 Dose Dumping Dissolution Studies (0.1N HCl w/40% v/v Alcohol; 36 mg and 54 mg)

Dissolution Conditions	**Apparatus:**	**II (Paddle), USP <711>**
	Speed of Rotation:	**50 rpm**
	Medium:	**0.1 N Hydrochloric acid with 40% ethanol (v/v)**
	Volume:	**900 mL**
	Temperature:	**37°C ± 0.5°C**
Firm's Proposed Specifications	**N/A**	
Dissolution Testing Site (Name, Address)	CorePharma, LLC, 215 Wood Ave, Middlesex, NJ 08846	

Study Ref No.	Testing Date	Product ID \ Lot No. (Test - Mfr Date)	Dosage Strength & Form	No. of Dosage Units			Collection Times (minutes) 15	30	45	60	75	90	105	120	Study Report Location
Report #: 15-03-IR-003-00R	08/06/15	Methylphenidate HCl Lot: SB51500301 Mfr date: 04/22/2015	36 mg ER Tablet	12	Mean		6	18	20	23	26	30	34	37	Module 2.7
					Range	Min	(b) (4)								
						Max									
					% RSD		14.2	3.4	2.4	5.9	8.7	9.9	11.4	12.4	
	05/07/15	Concerta Lot: 15AG842 Exp date: 11/2016	36 mg ER Tablet	12	Mean		14	22	24	27	30	33	38	42	
					Range	Min	(b) (4)								
						Max									
					% RSD		11.1	7.7	7.4	7.3	6.5	6.0	5.5	4.6	
	04/02/15	Methylphenidate HCl Lot: SB69900301 Mfr date: 4/09/2014	54 mg ER Tablet	12	Mean		20	21	21	22	24	27	30	33	
					Range	Min	(b) (4)								
						Max									
					% RSD		6.9	6.8	6.7	6.5	7.4	7.9	8.5	10.3	
	03/24/15	Concerta Lot: 13KG402 Exp date: 7/2015	54 mg ER Tablet	12	Mean		6	21	25	27	30	33	37	41	
					Range	Min	(b) (4)								
						Max									
					% RSD		34.3	5.7	4.5	4.3	4.3	4.0	3.9	3.9	

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

ANDA 208607

INFORMATION REQUEST

Impax Laboratories, Inc.
Attention: Kimberly D. Ernst,
Senior Director, Regulatory Affairs
30831 Huntwood Avenue
Hayward, CA 94544
RegAffairs@impaxlabs.com

Dear Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated April 18, 2016, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Methylphenidate Hydrochloride Extended-Release Tablets, USP, 18 mg, 27 mg, 36 mg and 54 mg.

We also refer to your March 17, 2017 and March 20, 2017 submissions.

We are reviewing the Quality section of your submission and have the following comments and information requests. We request a prompt written response, no later than 10 days, (Note for ANDA products: in general the requested date should not exceed 30 days per SOP 2501.01: Process for Issuing Deficiencies and Information Requests for Generic Drug Chemistry Review) in order to continue our evaluation of your ANDA.

List of the deficiencies:

(b) (4)

(b) (4)

2. Please provide updated post-approval stability commitment to reflect following suggested changes.

   i. Change of ownership

   ii. Specify the drug substance manufacturing process (b) (4) (b) (4)

   iii. Since the initial submission does not include stability data on production batches, a stability commitment should be made to place the first three production batches on long term stability studies through the proposed shelf life and on accelerated studies for 6 months as per Q1A (R2).

   iv. Also include a statement that if there are any changes to the manufacturing process, API vendors, API manufacturing process etc., then those batches will also be placed on stability.

3. Please provide the available long-term stability data from exhibit batches.

C. Biopharmaceutics Deficiencies

(b) (4)

Please note, if information or data submitted exceeds the data requested in the IR/ECD this may result in conversion to a Tier 2 Unsolicited Amendment (i.e., an amendment with information not requested by FDA).
If the submitted data is determined to be a tier 2 unsolicited amendment, this may affect the goal date.

All items listed on this Information Request shall be addressed in its entirety, any partial or incomplete response will not be reviewed and the same deficiency list will be issued to you again as part of the Complete Response Letter issued by OGD. Please note that a commitment to address an item in the future is not considered satisfying the Information Request.

Send your submission through the Electronic Submission Gateway http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway/default.htm. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

INFORMATION REQUEST
QUALITY
REFERENCE# 14762309

If you have any questions, please contact Camille Smith, Regulatory Business Process Manager, at (240) 402-6958.

Sincerely,

Camille Smith, MS, PharmD, RAC
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 5/19/2016

TO: Office of Bioequivalence
Office of Generic Drugs

FROM: Division of Generic Drug Bioequivalence Evaluation (DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Recommendation to accept data without an on-site inspection**

RE: ANDA 208607

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without an on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the sites listed below. The inspectional outcome from the inspections was classified as No Action Indicated (NAI).

Inspection Sites

Facility Type	Facility Name	Facility Address
Clinical	Accutest Research Labs	A-31, MIDC, TTC Industrial Area, Khairane, Navi Mumbai, Maharashtra, India
		(b) (4)

1 Page has been Withheld in Full as b4 (CCI/TS) immediately following this page

From: Gaines Tangela
To: kimberly.ernst@impaxlabs.com
Cc: ANDAFiling
Bcc: Nguyen Edward; Buonaccorsi Laurie
Subject: ANDA 208607 F ling Rev ew Comments
Date: Monday May 23 2016 6:38:00 AM
Attachments: image002.png

Dear Kimberly Ernst

This electronic mail is in reference to ANDA 208607 submitted on April 18, 2016 pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act.

SPECIAL INSTRUCTIONS:

- We request that you acknowledge the receipt of this email correspondence.
- Provide a complete response to all of the items identified below **within 7 calendar days** from the date of this communication.
- If a complete response is not submitted to the ANDA and received within 7 calendar days, the application will be deemed incomplete and will be refused for receipt.
- Your response should contain a point-by-point reply to each of the identified comment(s) with corresponding hyperlink(s), where applicable, to the body of data within the ANDA.
- You should notify me via email or telephone when you have submitted your response.
- Your cover letter should clearly indicate Quality - Response to Information Request.
- Should you have any questions or need for clarification with respect to any of the following deficiencies, you must clearly identify your questions and request a teleconference within 1 business day from the date of this email. (**Note: The teleconference will be limited to only the questions provided in your teleconference request. Also, your query does not place a hold on the timeframe in which the response must be submitted, as per bullet 2.**)

REVISE AND PROVIDE THE FOLLOWING DEFICIENCIES:

1. Address the following in Module 2.7
   a. Per the Division of Bioequivalence Model Summary Tables, located at http ://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/AbbreviatedNewDrugApplicationANDAGenerics/UCM120957.pdf
      i. Revise Table 10 (Study Information) to include the exact location of the LTSS study reports and data, including module, section, subsection and pages. Provide a working hyperlink(s) to the locations as appropriate.
      ii. Revise Table 3B (Statistical Summary of the Comparative Bioavailability Data for Reference-Scaled Average BE Studies) to include all recommended parameters.

2. In Module 5.2, list all studies, including pilot and failed studies, under "Tabular Listing of all Clinical Studies" following the example for "Table 5.1 Listing of Clinical Studies" provided in the guidance for industry entitled, *M4E The CTD-Efficacy*, located at, http ://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm073290.pdf.

3. In Module 5.3.1.2,
   a. "Fed Bioequivalence Study-Concentration-Time-Data," the file contains a duplicate of the data provided for the fasted study. Provide the data for fed study # ARL/14/695.
   b. "Fasting Bioequivalence Study Data-Listing SAS Transport Files" and "Fed Bioequivalence Study Data Listing SAS Transport File," revise the SAS files (.xpt) so that the data for each concentration is displayed in individual columns with headers across the files (C1, C2, C3, C4, etc) for each concentration.

eCTD DEFICIENCIES:

With regards to the eCTD deficiencies identified below, we note that FDA previously refused to receive ANDAs on the basis that the ANDA was not submitted in accordance with current eCTD format. However, FDA has determined that the GDUFA Commitment Letter contemplates addressing eCTD deficiencies differently for ANDAs eligible for metric goal dates beginning in Year 3 of GDUFA, specifically, by providing that metric goal dates will not apply to such ANDAs. See Generic Drug User Fee Act Program Performance Goals and Procedures (GDUFA Commitment Letter), at 7, available at http ://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM282505.pdf; see also guidance for industry on *ANDA Submissions – Refuse-to-Receive Standards*, at 4 (May 2015, Rev. 1) (identical in relevant part to initial version finalized in September 2014).

An adequate response to the eCTD deficiencies identified below must be received within **7 calendar days** from the date of this communication in order for the GDUFA metric goal for this ANDA to be assigned. If a complete response to the eCTD deficiencies is not received within **7 calendar days**, we will determine that your entire application does not follow the eCTD format in effect at the date of submission. Accordingly, FDA will receive the ANDA for review (assuming all other receipt requirements have been met), but will not assign a review metric goal date. **Any questions regarding the technical component of the electronic submission and preparing your corrective submission should be directed to CDER ESUB at esub@fda hhs gov.**

Documents submitted electronically should follow all published eCTD specifications and FDA guidances including those on the CDER eCTD web page, which is located at http ://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm. There are documents within your submission that do not conform to the standards outlined in the specifications or guidance recommendations that affect the display and/or reviewability of the ANDA.

The following issues regarding eCTD specifications and guidances were found

1. **There are issues with the initial view settings.** The initial view of the PDF files should be set as *Bookmarks* and *Page*. If there are no bookmarks, the initial view as *Page* only should be set. The *Magnification* and *Page* Layout should be set as default. Review all PDF files to assure the initial view settings are set appropriately. See the technical specification document, *M2 eCTD Electronic Common Technical Document Specification* (at pg. 7-3-7-4) located at http ://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **Examples of this issue are throughout your entire application.** The *Magnification* and *Page* Layout should be set as **default** in all files.

2. **There are issues where documents were placed in the wrong locations.** Module 5.3.1.2 should contain Comparative BA and Bioequivalence (BE) Study Reports, Module 5.3.1.3 should contain In vitro-In vivo Correlation Study Reports, and Module 5.3.1.4 should contain Reports of Bioanalytical and Analytical Methods for Human Studies. See the technical specification document, *ICH M2 EWG Electronic Common Technical Document Specification* (at pg. 3-10 and 4-49 to 4-50) located at http ://estri.ich.org/eCTD/eCTD_Specification_v3_2_2.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **Examples of such issues are:**
   a. **The following files should be in Module 5.2,**
      i. "Tabular Listing of Clinical Study-Fed"
      ii. "Tabular Listing of Clinical Study-Fasting"
   b. **The following files should be in Module 5.3.1.3,**
      i. "In-Vitro-In-Vivo-Correlation Study Reports"
   c. **The following files should be in Module 5.3.1.4,**
      i. "Fed Bioanalytical Study Report"
      ii. "Fed Bioanalytical Study Certificate-of-Analysis"
      iii. "Fed Bioanalytical Study-Curve-Plots"
      iv. "Fed Bioanalytical Study-Method-Validation-Report"
      v. "Fed Bioanalytical Study-Raw-Data
      vi. "Fed Bioanalytical Study-Representative-Chromatograms"
      vii. "Fed Bioanalytical Study-Standard-Operating-Procedures"
      viii. "Fasting Bioanalytical Study Report"
      ix. "Fasting Bioanalytical Study-Certificate-of-Analysis"
      x. "Fasting Bioanalytical Study-Curve-Plots"
      xi. "Fasting Bioanalytical Study-Method-Validation-Report"
      xii. "Fasting Bioanalytical Study-Raw-Data
      xiii. "Fasting Bioanalytical Study-Representative-Chromatograms"
      xiv. "Fasting Bioanalytical Study-Standard-Operating-Procedures"

3. **There are issues with Study Tagging Files (STF).** An STF should be provided with the submission of any file, or group of files, belonging to a study in Modules 4 and 5, and a separate STF should be provided for each study in a sequence. For every submission to FDA that includes one or more files pertaining to a specific study, provide an STF. Place the STF for the specific study in the module folder with the corresponding study files. Place a leaf element for the STF in the appropriate Module 4 or 5 eCTD Table of Contents element in the index.xml file for that sequence. **Within the STF file for Study #** ARL/14/694 and ARL/14/695**, you have documents that do not contain the proper *file-tag* element.** The *study-document* element contains information on the subject matter of each file that is cited as part of the documentation for a study. The *study-document* element includes the *doc-content* element. The *doc-content* element contains the *property* and *file-tag* elements. The *property* element is appropriate when files might need to be grouped by an applicant provided value. Currently, this element should only be used for site identification within a study. The *file-tag* element contains the attributes *name* and *info-type*. The text value of the *file-tag* element s *name* attribute indicates the subject matter of the document. See the technical specification document, *ICH M2 EWG The eCTD Backbone File Specification for Study Tagging Files* (at pg. 4 and 7-10), located at http ://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf incorporated by reference into the guidance for industry *Providing Regulatory Submissions in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*. **An example of such an issue is:**
   a. Module 5.3.1.4, Unassigned folder, there should not be "unassigned" folders in module 5. This indicates that documents were not correctly labelled or not correctly placed per *The Comprehensive Table of Contents of Heading and Hierarchy* for XML. The folder should be labelled correctly and contain the documents highlighted above in eCTD Deficiency Comment 2.

The highlighted examples do not comprise an exhaustive list. It is incumbent upon the applicant to ensure that all documents conform to the listed standards, which includes utilizing the appropriate **operation attribute** in managing each individual file in a submission. **Any questions regarding the technical component of the electronic submission and preparing your corrective submission should be directed to CDER ESUB at esub@fda.hhs.gov.**

ADDITIONAL COMMENTS:

1. In Module 2.7,

a. "Summary of Results of Individual Studies," clarify the discrepancy in dosage and lot numbers in Figure 2 Graph of Multimedia Dissolution Study of 27 mg in 0.1 NHCl.
b. (b) (4)Common Adverse Events," clarify the discrepancy in study numbers in Table 8.2 Incidence of Adverse Events in Individual Studies-ARL/14/695 (Fed).
c. "RPT 15-03-ir-001-01," clarify the discrepancy in the lot numbers for the Results for CorePharma Mehtylphenidate HCL ER 27 mg Tables and Concerta® 27 mg Tablets under CorePharma Dissoution Method.
d. In addition to the 54 mg strength, provide the Certificates of Analysis (CoAs) for all other Reference Listed Drug (RLD) strengths used in your dissolution studies (18 mg, 27 mg and 36 mg).

Note Provide a fillable PDF copy of the 356h in all your submissions if you are submitting a scanned signed copy of the 356h, otherwise the omission of the fillable PDF copy of the 356h will be counted as a deficiency.

Best Regards,
Tangela

Tangela Gaines PA-C
Project Manager-Division of Filing Review
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EASILY CORRECTABLE DEFICIENCY

ANDA 208607

OFFICE OF GENERIC DRUGS, CDER, FDA
Document Control Room, Metro Park North VII
7620 Standish Place
Rockville, Maryland 20855

APPLICANT: CorePharma, LLC

TEL: 732-667-6009

ATTN: Kimberly D. Ernst

EMAIL: kimberly.ernst@impaxlabs.com

FROM: Juliette Larmie-Gyamfi

FDA CONTACT EMAIL:
Juliette.Larmie-Gyamfi@fda.hhs.gov

Dear Ms. Ernst:

This communication is in reference to your abbreviated new drug application (ANDA) dated April 18, 2016, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Hydrochloride Extended-Release Tablets USP, 18 mg, 27 mg, 36 mg and 54 mg .

The deficiencies presented below represent *EASILY CORRECTABLE DEFICIENCIES* identified during the review and the current review cycle will remain open. You should provide a complete response to these deficiencies within ten (10) U.S. business days.

Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

EASILY CORRECTABLE DEFICIENCY
LABELING
REFERENCE # 13536904

If you do not submit a complete response within ten (10) U.S. business days, the review will be closed and the listed deficiencies will be incorporated in the next COMPLETE RESPONSE. Please provide your response after that complete response communication is received along with your response to any other issued comments.

If you are unable to submit a complete response within ten (10) U.S. business days, please contact the Labeling Project Manager immediately so a complete response may be issued if appropriate.

Please submit official archival copies of your response to the ANDA, facsimile or e-mail responses will not be accepted. A partial response to this communication will not be processed as an amendment and will not start a review.

We have completed our review and have the following comments:

LABELING DEFICIENCIES:

PRESCRIBING INFORMATION

a. FULL PRESCRIBING INFORMATION: We encourage you to add "USP" to the established name in the DOSAGE FORMS AND STRENGTHS, and DESCRIPTION sections of the package insert.
b. FULL PRESCRIBING INFORMATION, DESCRIPTION, last sentence: Please revise (b) (4) (b) (4) to read "USP dissolution test is pending."

Submit your revised labeling electronically. The prescribing information and any patient labeling should reflect the full content of the labeling as well as the planned ordering of the content of the labeling. The container label and any outer packaging should reflect the content as well as an accurate representation of the layout, color, text size, and style.

To facilitate review of your next submission, please provide a side-by-side comparison of your proposed labeling with your last submitted labeling with all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

However, prior to the submission of your amendment, please check labeling resources, including DRUGS@FDA, the electronic Orange Book and the NF-USP online, for recent updates and make any necessary revisions to your labels and labeling.

In order to keep ANDA labeling current, we suggest that you subscribe to the daily or weekly updates of new documents posted on the CDER web site at the following address –
http://service.govdelivery.com/service/subscribe.html?code=USFDA_17

If you have questions regarding these deficiencies or would like acknowledgement of receipt of your amendment upon submission, please contact the Labeling Project Manager, Juliette Larmie-Gyamfi, at Juliette.Larmie-Gyamfi@fda.hhs.gov.

Sincerely,

Juliette Larmie-Gyamfi, Pharm.D.
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research