CENTER FOR DRUG EVALUATION AND RESEARCH

<u>Approval Package for:</u>

APPLICATION NUMBER:

ANDA 211796

Name:	Methylphenidate Hydrochloride Capsule; 10MG, 20MG, 30MG, 40MG, 60MG
Sponsor:	Granules Pharmaceuticals Inc.
Approval Date:	May 23, 2019

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211796

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CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211796

<u>APPROVAL LETTER</u>

ANDA 211796

ANDA APPROVAL

Granules Pharmaceuticals Inc.
3701 Concorde Parkway
Chantilly, VA 20151
Attention: Vamsi Nama
Director, Regulatory Affairs

Dear Madam:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 2, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.[1]

Reference is also made to the complete response letter issued by this office on January 29, 2019, and to any amendments thereafter.

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 Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg, to be bioequivalent and, therefore, therapeutically equivalent to the reference listed drug (RLD), Ritalin LA Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg, of Novartis Pharmaceuticals Corporation (Novartis).

The RLD upon which you have based your ANDA, Novartis's Ritalin LA Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg, is subject to a period of patent protection. The following patent and expiration date is currently listed in the Agency's publication titled *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"):

U.S. Patent Number	Expiration Date
6,228,398 (the '398 patent)	November 1, 2019*

*10 mg, 20 mg, 30 mg, and 40 mg strengths only

Your ANDA contains a paragraph IV certification to the '398 patent under section 505(j)(2)(A)(vii)(IV) of the FD&C Act stating that the patent is invalid, unenforceable, or will not be infringed by your manufacture, use, or sale of Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg, under this ANDA. You have notified the Agency that Granules Pharmaceuticals Inc. (Granules) complied with the requirements of section 505(j)(2)(B) of the FD&C Act and that no action for infringement was brought against Granules 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 and at section 506I of the FD&C Act. The Agency should be advised of any change in the marketing status of this drug or if this drug will not be available for sale after approval. In particular, under section 506I(b) of the FD&C Act, you are required to notify the Agency in writing within 180 days from the date of this letter if this drug will not be available for sale within 180 days from the date of approval. As part of such written notification, you must include (1) the identity of the drug by established name and proprietary name (if any); (2) the ANDA number; (3) the strength of the drug; (4) the date on which the drug will be available for sale, if known; and (5) the reason for not marketing the drug after approval.

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[2] 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.

Sincerely yours,

{See appended electronic signature page}

For Vincent Sansone, PharmD
Deputy Director
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

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[1] We note that the RLD upon which you have based this ANDA, Novartis's Ritalin LA Extended-Release Capsules, 60 mg, is no longer being marketed in the United States and is currently listed in the discontinued section of FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the "Orange Book"). The Agency has determined that Novartis's Ritalin LA Extended-Release Capsules, 60 mg, was not withdrawn from sale for reasons of safety or effectiveness. FDA published this determination in the *Federal Register* (82 FR 42103; September 6, 2017). This determination allows the Agency to approve ANDAs for the discontinued drug product.

[2] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

Heidi
Lee

Digitally signed by Heidi Lee
Date: 5/23/2019 12:14:48PM
GUID: 52795fe90009070673e7de063d080d1f

[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 211796

<u>LABELING</u>

HIGHLIGHTS OF PRESCRIBING INFORMATION

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

METHYLPHENIDATE HYDROCHLORIDE extended-release capsules, for oral use, CII
Initial U.S. Approval: 1955

WARNING: DRUG DEPENDENCE

See full prescribing information for complete boxed warning.

- **CNS stimulants, including methylphenidate hydrochloride extended-release capsules, other methylphenidate containing products, and amphetamines, have a high potential for abuse and dependence (5.1, 9.2, 9.3).**
- **Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy (5.1, 9.2)**

---RECENT MAJOR CHANGES---

Boxed Warning	1/2019
Contraindications (4)	1/2019
Warnings and Precautions (5)	1/2019

---INDICATIONS AND USAGE---

Methylphenidate hydrochloride extended-release capsule is a central nervous system (CNS) stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD) in pediatric patients 6 to 12 years of age. (1)

---DOSAGE AND ADMINISTRATION---

- Administer orally once daily in the morning (2.2)
- Capsules may be swallowed whole, or opened and the entire contents sprinkled on applesauce (2.2)
- Should not be crushed, chewed, or divided (2.2)
- Patients new to methylphenidate: Start at 20 mg daily, titrating the dose weekly in 10 mg increments. Doses above 60 mg daily are not recommended (2.3)
- For patients currently using methylphenidate hydrochloride tablets or methylphenidate hydrochloride extended-release tablets: Dosage is based on current dose regimen (2.4)
- If switching from other methylphenidate products, discontinue treatment and titrate with methylphenidate hydrochloride extended-release capsules (2.4)

---DOSAGE FORMS AND STRENGTHS---

Extended-release capsules: 10, 20, 30, 40 and 60 mg (3)

---CONTRAINDICATIONS---

- Known hypersensitivity to methylphenidate or product components (4)
- Concurrent treatment with a monoamine oxidase inhibitor (MAOI), or use of an MAOI within the preceding 14 days (4)

---WARNINGS AND PRECAUTIONS---

- *Serious Cardiovascular Events*: Sudden death has been reported in association with CNS stimulant treatment at usual doses in pediatric patients with structural cardiac abnormalities or other serious heart problems. In adults, sudden death, stroke, and myocardial infarction have been reported. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm arrhythmias, or coronary artery disease (5.2).
- *Blood Pressure and Heart Rate Increases*: Monitor blood pressure and pulse. Consider the benefits and risk in patients for whom an increase in blood pressure or heart rate would be problematic (5.3).
- *Psychiatric Adverse Reactions*: Use of stimulants may cause psychotic or manic symptoms in patients with no prior history or exacerbation of symptoms in patients with preexisting psychiatric illness. Evaluate for preexisting psychotic or bipolar disorder prior to methylphenidate hydrochloride extended-release capsules use (5.4).
- *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 prolonged penile erections or priapism are observed (5.5).
- *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 (5.6).
- *Long-Term Suppression of Growth*: Monitor height and weight at appropriate intervals in pediatric patients (5.7).

---ADVERSE REACTIONS---

Most common adverse reactions (greater than 5% during incidence) were headache, insomnia, upper abdominal pain, appetite decreased and anorexia (6).

To report SUSPECTED ADVERSE REACTIONS, contact Granules Pharmaceuticals Inc., at 1-877-770-3183 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

---DRUG INTERACTIONS---

- Antihypertensive drugs: Monitor blood pressure and heart. Adjust dosage of antihypertensive drug as needed (7).
- Avoid use of methylphenidate hydrochloride extended-release capsules on the day of surgery if halogenated anesthetics will be used (7).

See 17 for PATIENT COUNSELING INFORMATION and Medication Guide.

Revised: 02/2019

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FULL PRESCRIBING INFORMATION

WARNING: ABUSE AND DRUG DEPENDENCE

CNS stimulants, including methylphenidate hydrochloride extended-release capsules, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Warning and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]*.

1 INDICATIONS AND USAGE

Methylphenidate hydrochloride extended-release capsules are indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD), in pediatric patients 6 to 12 years of age *[see Clinical Studies (14)]*.

2 DOSAGE AND ADMINISTRATION

2.1 Pretreatment Screening

Prior to initiating treatment with central nervous system (CNS) stimulants, including methylphenidate hydrochloride extended-release capsules, assess for the presence of cardiac disease (i.e., perform a careful history including family history of sudden death or ventricular arrhythmia, and physical examination) *[see Warnings and Precautions (5.2)]*.

Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy. Maintain careful prescription records, educate patients about abuse, monitor for signs of abuse and overdose, and periodically reevaluate the need for methylphenidate hydrochloride extended-release capsules use *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9)]*.

2.2 General Dosing Information

The recommended starting dose for methylphenidate hydrochloride extended-release capsule is 20 mg once daily. Increase dosage gradually, in increments of 10 mg weekly. Daily dosage above 60 mg is not recommended. When a lower initial dose is appropriate, patients may begin treatment with 10 mg.

Administer methylphenidate hydrochloride extended-release capsules orally once daily in the morning. Methylphenidate hydrochloride extended-release capsules may be swallowed as whole capsules or may be administered by sprinkling the capsule contents on a small amount of applesauce (see specific instructions below). Methylphenidate hydrochloride extended-release capsules and/or their contents should not be crushed, chewed, or divided.

The capsules may be carefully opened and the beads sprinkled over a spoonful of applesauce. The applesauce should not be warm because it could affect the modified release properties of this formulation. The mixture of drug and applesauce should be consumed immediately in its entirety. The drug and applesauce mixture should not be stored for future use.

Pharmacological treatment of ADHD may be needed for extended periods. Periodically re-evaluate the long-term use of methylphenidate hydrochloride tablets and methylphenidate hydrochloride extended-release tablets, and adjust dosage as needed.

2.3 Patients Currently Using Methylphenidate Hydrochloride Tablets and Methylphenidate Hydrochloride Extended-Release Tablets

The recommended dose of methylphenidate hydrochloride extended-release capsules for patients currently taking methylphenidate hydrochloride tablets twice daily or methylphenidate hydrochloride extended-release tablets is provided below.

TABLE 1: Recommended Dose Conversion from Methylphenidate Hydrochloride Tablets and Methylphenidate Hydrochloride Extended-Release Tablets

Previous Methylphenidate Hydrochloride Tablets or Methylphenidate Hydrochloride Extended-Release Tablets Dose	Recommended Methylphenidate Hydrochloride Extended-Release Capsules Dose
5 mg methylphenidate hydrochloride tablets twice daily	10 mg once daily
10 mg methylphenidate hydrochloride tablets twice daily or 20 mg methylphenidate hydrochloride extended-release tablets	20 mg once daily
15 mg methylphenidate hydrochloride tablets twice daily	30 mg once daily
20 mg methylphenidate hydrochloride tablets twice daily or 40 mg of methylphenidate hydrochloride extended-release tablets	40 mg once daily
30 mg methylphenidate hydrochloride tablets twice daily or 60 mg methylphenidate hydrochloride extended-release tablets	60 mg once daily

2.4 Switching from other Methylphenidate Products

If switching from other methylphenidate products, discontinue that treatment, and titrate with methylphenidate hydrochloride extended-release capsules using the titration schedule.

Do not substitute for other methylphenidate products on a milligram-per-milligram basis, because different methylphenidate base compositions and differing pharmacokinetic profiles *[see Description (11), Clinical Pharmacology (12.3)]*.

Clinical judgment should be used when selecting the starting dose. Daily dosage above 60 mg is not recommended.

2.5 Dose Reduction and Discontinuation

If paradoxical worsening of symptoms or other adverse reactions occur, reduce the dosage, or, if necessary, discontinue methylphenidate hydrochloride extended-release capsules. If improvement is not observed after appropriate dosage adjustment over a one-month period, the drug should be discontinued.

3 DOSAGE FORMS AND STRENGTHS

10 mg

Hard gelatin capsules, yellow opaque cap printed with "G 10mg" and white opaque body printed with "012" contains white to off-white pellets.

20 mg

Hard gelatin capsules, white opaque cap printed with "G 20mg" and white opaque body printed with "013" contains white to off-white pellets.

30 mg

Hard gelatin capsules, yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014" contains white to off-white pellets.

40 mg

Hard gelatin capsules, yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015" contains white to off-white pellets.

60 mg

Hard gelatin capsules, yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets.

4 CONTRAINDICATIONS

- Hypersensitivity to methylphenidate or other components of methylphenidate hydrochloride extended-release capsules. Hypersensitivity reactions such as angioedema and anaphylactic reactions have been reported in patients treated with methylphenidate *[see Adverse Reactions (6.1)]*.
- Concomitant treatment with monoamine oxidase inhibitors (MAOIs), or within 14 days following discontinuation of treatment with an MAOI, because of the risk of hypertensive crises *[see Drug Interactions (7.1)]*.

5 WARNINGS AND PRECAUTIONS

5.1 Potential for Abuse and Dependence

CNS stimulants, including methylphenidate hydrochloride extended-release capsules, other methylphenidate-containing products, and amphetamines, have a high potential for abuse and dependence. Assess the risk of abuse prior to prescribing, and monitor for signs of abuse and dependence while on therapy *[see Boxed Warning, Drug Abuse and Dependence (9.2, 9.3)]*.

5.2 Serious Cardiovascular Reactions

Sudden death, stroke and myocardial infarction have been reported in adults with CNS stimulant treatment at recommended doses. Sudden death has been reported in pediatric patients with structural cardiac abnormalities and other serious heart problems taking CNS stimulants at recommended doses for ADHD. Avoid use in patients with known structural cardiac abnormalities, cardiomyopathy, serious heart rhythm abnormalities, coronary artery disease, and other serious heart problems.

Further evaluate patients who develop exertional chest pain, unexplained syncope, or arrhythmias during methylphenidate hydrochloride extended-release capsules treatment.

5.3 Blood Pressure and Heart Rate Increases

CNS stimulants cause an increase in blood pressure (mean increase approximately 2 to 4 mmHg) and heart rate (mean increase approximately 3 to 6 bpm). Individuals may have larger increases. Monitor all patients for hypertension and tachycardia.

5.4 Psychiatric Adverse Reactions

Exacerbation of Preexisting Psychosis

CNS stimulants may exacerbate symptoms of behavior disturbance and thought disorder in patients with a preexisting psychotic disorder.

Induction of a Manic Episode in Patients with Bipolar Disorder

CNS stimulants may induce a manic or mixed mood episode in patients. Prior to initiating treatment, screen patients for risk factors for developing a manic episode (e.g., comorbid or history of depressive symptoms or a family history of suicide, bipolar disorder, or depression).

New Psychotic or Manic Symptoms

CNS stimulants, at recommended doses, may cause psychotic or manic symptoms (e.g., hallucinations, delusional thinking, or mania) in patients without a prior history of psychotic illness or mania. If such symptoms occur, consider discontinuing methylphenidate hydrochloride extended-release capsules. In a pooled analysis of multiple short-term, placebo-controlled studies of CNS stimulants, psychotic or manic symptoms occurred in approximately 0.1% of CNS stimulant-treated patients, compared to 0 in placebo-treated patients.

5.5 Priapism

Prolonged and painful erections, sometimes requiring surgical intervention, have been reported with methylphenidate products in both pediatric and adult patients. 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.

5.6 Peripheral Vasculopathy, Including Raynaud's Phenomenon

Stimulants, including methylphenidate hydrochloride extended-release capsules, 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 postmarketing 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.

5.7 Long-Term Suppression of Growth

CNS stimulants have been associated with weight loss and slowing of growth rate in pediatric patients.

Careful follow-up of weight and height in pediatric patients ages 7 to 10 years who were randomized to either methylphenidate or non-medication treatment groups over 14 months, as well as in naturalistic subgroups of newly methylphenidate-treated and non-medication treated patients over 36 months (to the ages of 10 to 13 years), suggests that consistently medicated pediatric patients (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.

Closely monitor growth (weight and height) in pediatric patients treated with CNS stimulants, including methylphenidate hydrochloride extended-release capsules, Patients who are not growing or gaining height or weight as expected may need to have their treatment interrupted.

5.8 Risk of Allergic Reactions Due to Tartrazine

This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity.

6 ADVERSE REACTIONS

The following are discussed in more detail in other sections of the labeling:

- Abuse and Dependence *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.2, 9.3)]*
- Known hypersensitivity to methylphenidate or other ingredients of methylphenidate hydrochloride extended-release capsules *[see Contraindications (4)]*
- Hypertensive crisis when used concomitantly with monoamine oxidase inhibitors *[see Contraindications (4), Drug Interactions (7.1)]*
- Serious cardiovascular reactions *[see Warnings and Precautions (5.2)]*
- Blood pressure and heart rate increases *[see Warnings and Precautions (5.3)]*
- Psychiatric adverse reactions *[see Warnings and Precautions (5.4)]*
- Priapism *[see Warnings and Precautions (5.5)]*
- Peripheral vasculopathy, including Raynaud's phenomenon *[see Warnings and Precautions (5.6)]*
- Long-term suppression of growth *[see Warnings and Precautions (5.7)]*

6.1 Clinical Trial Experience

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 the clinical trials of another drug and may not reflect the rates observed in practice.

The clinical program for methylphenidate hydrochloride extended-release capsules consisted of 6 studies: 2 controlled clinical studies conducted in children with ADHD aged 6 to 12 years and

4 clinical pharmacology studies conducted in healthy adult volunteers. These studies included a total of 256 subjects; 195 children with ADHD and 61 healthy adult volunteers. The subjects received methylphenidate hydrochloride extended-release capsules in doses of 10 to 40 mg per day. Safety of methylphenidate hydrochloride extended-release capsules was assessed by evaluating frequency and nature of adverse events, routine laboratory tests, vital signs, and body weight. A placebo-controlled, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of methylphenidate hydrochloride extended-release capsules in children with ADHD aged 6 to 12 years. All subjects received methylphenidate hydrochloride extended-release capsules for up to 4 weeks, and had their dose optimally adjusted, prior to entering the double-blind phase of the trial. In the 2-week double-blind treatment phase of this study, patients received either placebo or methylphenidate hydrochloride extended-release capsules at their individually-titrated dose (range 10 mg to 40 mg).

Adverse reactions with an incidence greater than 5% during the initial 4-week single-blind methylphenidate hydrochloride extended-release capsules titration period of this study were headache, insomnia, upper abdominal pain, appetite decreased, and anorexia.

Adverse reactions with an incidence greater than 2% among methylphenidate hydrochloride extended-release capsules-treated subjects, during the 2-week double blind phase of the clinical study, are shown in Table 2:

Table 2: Adverse Reactions in Greater Than 2% Methylphenidate Hydrochloride Extended-Release Capsules-Treated Subjects in the 2-Week Double-Blind Phase

Preferred Term	Methylphenidate Hydrochloride Extended-Release Capsules N = 65 N (%)	Placebo N = 71 N (%)
Anorexia	2 (3.1)	0 (0)
Insomnia	2 (3.1)	0 (0)

Adverse Events Associated with Discontinuation of Treatment

In the 2-week double-blind treatment phase of a placebo-controlled parallel-group study in children with ADHD, one methylphenidate hydrochloride extended-release capsules -treated subject (1/65, 1.5%) discontinued due to an adverse event (depressed mood).

In the single-blind titration period of this study, subjects received methylphenidate hydrochloride extended-release capsules for up to 4 weeks. During this period a total of 6 subjects (6/161, 3.7%) discontinued due to adverse events. The adverse events leading to discontinuation were anger (2 patients), hypomania, anxiety, depressed mood, fatigue, migraine and lethargy.

6.2 Postmarketing Experience

The following adverse reactions have been identified during the post approval use of methylphenidate products. Because these reactions were reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Adverse Reactions Reported with methylphenidate hydrochloride tablets, methylphenidate hydrochloride extended-release tablets, and methylphenidate hydrochloride extended-release capsules

Infections and Infestations: nasopharyngitis

Blood and the Lymphatic System Disorders: leukopenia, thrombocytopenia, anemia

Immune System Disorders: hypersensitivity reactions, including angioedema and anaphylaxis

Metabolism and Nutrition Disorders: decreased appetite, reduced weight gain, and suppression of growth during prolonged use in children

Psychiatric Disorders: insomnia, anxiety, restlessness, agitation, psychosis (sometimes with visual and tactile hallucinations), depressed mood

Nervous System Disorders: headache, dizziness, tremor, dyskinesia including choreoathetoid movements, drowsiness, convulsions, cerebrovascular disorders (including vasculitis, cerebral hemorrhages and cerebrovascular accidents), serotonin syndrome in combination with serotonergic drugs

Eye Disorders: blurred vision, difficulties in visual accommodation

Cardiac Disorders: tachycardia, palpitations, increased blood pressure, arrhythmias, angina pectoris

Respiratory, Thoracic and Mediastinal Disorders: cough

Gastrointestinal Disorders: dry mouth, nausea, vomiting, abdominal pain, dyspepsia

Hepatobiliary Disorders: abnormal liver function, ranging from transaminase elevation to severe hepatic injury

Skin and Subcutaneous Tissue Disorders: hyperhidrosis, pruritus, urticaria, exfoliative dermatitis, scalp hair loss, erythema multiforme rash, thrombocytopenic purpura

Musculoskeletal and connective tissue disorders: arthralgia, muscle cramps, rhabdomyolysis

Investigations: weight loss (adult ADHD patients)

Adverse Reactions Reported with Other Methylphenidate-Containing Products

The list below shows adverse reactions not listed with methylphenidate hydrochloride tablets, methylphenidate hydrochloride extended-release tablets, or methylphenidate hydrochloride extended-release capsules formulations that have been reported with other methylphenidate-containing products.

Blood and Lymphatic Disorders: pancytopenia

Immune System Disorders: hypersensitivity reactions such as auricular swelling, bullous conditions, eruptions, exanthemas

Psychiatric Disorders: affect lability, mania, disorientation, libido changes,

Nervous System disorders: migraine

Eye Disorders: diplopia, mydriasis

Cardiac Disorders: sudden cardiac death, myocardial infarction, bradycardia, extrasystole

Vascular Disorders: peripheral coldness, Raynaud's phenomenon

Respiratory, Thoracic and Mediastinal Disorders: pharyngolaryngeal pain, dyspnea

Gastrointestinal Disorders: diarrhea, constipation

Skin and Subcutaneous Tissue Disorders: angioneurotic edema, erythema, fixed drug eruption

Musculoskeletal, Connective Tissue and bone Disorders: myalgia, muscle twitching

Renal and Urinary Disorders: hematuria

Reproductive System and Breast Disorders: gynecomastia

General Disorders: fatigue, hyperpyrexia

Urogenital Disorders: priapism

7 DRUG INTERACTIONS

7.1 Clinically Important Interactions with methylphenidate hydrochloride extended-release capsules

Table 3 presents clinically important drug interactions with methylphenidate hydrochloride extended-release capsules

Table 3: Drugs Having Clinically Important Drug Interactions with Methylphenidate Hydrochloride Extended-Release Capsules

Monoamine Oxidase Inhibitors (MAOI)	
Clinical Impact	Concomitant use of MAOIs and CNS stimulants, including methylphenidate hydrochloride extended-release capsules, can cause hypertensive crisis. Potential outcomes include death, stroke, myocardial infarction, aortic dissection, ophthalmological complications, eclampsia, pulmonary edema, and renal failure *[see Contraindications (4)]*.
Intervention	Concomitant use of methylphenidate hydrochloride extended-release capsules with monoamine oxidase inhibitors (MAOIs) or within 14 days after discontinuing MAOI treatment is contraindicated.
Examples	selegiline, tranylcypromine, isocarboxazid, phenelzine, linezolid, methylene blue
Antihypertensive Drugs	
Clinical Impact	Methylphenidate hydrochloride extended-release capsules may decrease the effectiveness of drugs used to treat hypertension *[see Warnings and Precautions (5.3)]*.
Intervention	Monitor blood pressure and adjust the dosage of the antihypertensive drug as needed.
Examples	Potassium-sparing and thiazide diuretics, calcium channel blockers, ACE inhibitors, ARBs, beta blockers, centrally acting alpha-2 receptor agonists.
Halogenated Anesthetics	
Clinical Impact	Concomitant use of halogenated anesthetics and methylphenidate hydrochloride extended-release capsules may increase the risk of sudden blood pressure and heart rate increase during surgery.
Intervention	Avoid use of methylphenidate hydrochloride extended-release capsules in patients

	being treated with anesthetics on the day of surgery.
Examples	halothane, isoflurane, enflurane, desflurane, sevoflurane

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Pregnancy Category C:

In studies conducted in rats and rabbits, methylphenidate was administered orally at doses of up to 75 and 200 mg/kg/day, respectively, during the period of organogenesis. Teratogenic effects (increased incidence of fetal spina bifida) were observed in rabbits at the highest dose, which is approximately 40 times the maximum recommended human dose (MRHD) on a mg/m^2 basis. The no effect level for embryo-fetal development in rabbits was 60 mg/kg/day (11 times the MRHD on a mg/m^2 basis). There was no evidence of specific teratogenic activity in rats, although increased incidences of fetal skeletal variations were seen at the highest dose level (7 times the MRHD on a mg/m^2 basis), which was also maternally toxic. The no effect level for embryo-fetal development in rats was 25 mg/kg/day (2 times the MRHD on a mg/m^2 basis). When methylphenidate was administered to rats throughout pregnancy and lactation at doses of up to 45 mg/kg/day, offspring body weight gain was decreased at the highest dose (4 times the MRHD on a mg/m^2 basis), but no other effects on postnatal development were observed. The no effect level for pre and postnatal development in rats was 15 mg/kg/day (equal to the MRHD on a mg/m^2 basis).

Adequate and well-controlled studies in pregnant women have not been conducted. Methylphenidate hydrochloride extended-release capsules should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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 capsules are administered to a nursing woman.

8.4 Pediatric Use

The safety and effectiveness of methylphenidate hydrochloride extended-release capsules for the treatment of ADHD have been established in pediatric patients 6 to 12 years.

The safety and effectiveness of methylphenidate hydrochloride extended-release capsules in pediatric patients less than 6 years have not been established. The long-term efficacy of methylphenidate hydrochloride extended-release capsules in pediatric patients has not been established.

<u>Long-Term Suppression of Growth</u>

Growth should be monitored during treatment with stimulants, including methylphenidate hydrochloride extended-release capsules. Pediatric patients who are not growing or gaining weight as expected may need to have their treatment interrupted *[see Warnings and Precautions (5.7)]*.

<u>Juvenile Animal Toxicity Data</u>
In a study conducted in young rats, methylphenidate was administered orally at doses of up to 100 mg/kg/day for 9 weeks, starting early in the postnatal period (Postnatal Day 7) and continuing through sexual maturity (postnatal Week 10). When these animals were tested as adults (Postnatal Weeks 13 to 14), decreased spontaneous locomotor activity was observed in males and females

previously treated with 50 mg/kg/day (approximately 6 times the MRHD on a mg/m^2 basis) or greater, and a deficit in the acquisition of a specific learning task was seen in females exposed to the highest dose (12 times the MRHD on a mg/m^2 basis). The no effect level for juvenile neurobehavioral development in rats was 5 mg/kg/day (half the MRHD on a mg/m^2 basis). The clinical significance of the long-term behavioral effects observed in rats is unknown.

8.5 Geriatric Use

Methylphenidate hydrochloride extended-release capsules has not been studied in the geriatric population.

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

Methylphenidate hydrochloride extended-release capsules contains methylphenidate hydrochloride, a Schedule II controlled substance.

9.2 Abuse

CNS stimulants, including methylphenidate hydrochloride extended-release capsules, have a high potential for abuse. Abuse is characterized by impaired control over drug use despite harm, and craving.

Signs and symptoms of CNS stimulant abuse include increased heart rate, respiratory rate, blood pressure, and/or sweating, dilated pupils, hyperactivity, restlessness, insomnia, decreased appetite, loss of coordination, tremors, flushed skin, vomiting, and/or abdominal pain. Anxiety, psychosis, hostility, aggression, and suicidal or homicidal ideation have also been observed. Abusers of CNS stimulants may chew, snort, inject, or use other unapproved routes of administration which may result in overdose and death *[see Overdosage (10)]*.

To reduce the abuse of CNS stimulants including methylphenidate hydrochloride extended-release capsules, assess the risk of abuse prior to prescribing. After prescribing, keep careful prescription records, educate patients and their families about abuse and on proper storage and disposal of CNS stimulants *[see How Supplied/Storage and Handling (16)]*, monitor for signs of abuse while on therapy, and re-evaluate the need for methylphenidate hydrochloride tablets and methylphenidate hydrochloride extended-release tablets use.

9.3 Dependence

Tolerance

Tolerance (a state of adaptation in which exposure to a drug results in a reduction of the drug's desired and/or undesired effects over time) can occur during chronic therapy with CNS stimulants, including methylphenidate hydrochloride extended-release capsules.

Dependence

Physical dependence (which is manifested by a withdrawal syndrome produced by abrupt cessation, rapid dose reduction, or administration of an antagonist) may occur in patients treated with CNS stimulants including methylphenidate hydrochloride tablets and methylphenidate hydrochloride extended-release tablets. Withdrawal symptoms after abrupt cessation following prolonged high-dosage administration of CNS stimulants include dysphoric mood; fatigue; vivid, unpleasant dreams; insomnia or hypersomnia; increased appetite; and psychomotor retardation or agitation.

10 OVERDOSAGE

Human Experience

Signs and symptoms of acute overdosage, resulting principally from overstimulation of the central nervous system and from excessive sympathomimetic effects, may include the following: nausea, vomiting, diarrhea, restlessness, anxiety, agitation, tremors, hyperreflexia, muscle twitching, convulsions (which may be followed by coma), euphoria, confusion, hallucinations, delirium, sweating, flushing, headache, hyperpyrexia, tachycardia, palpitations, cardiac arrhythmias, hypertension, hypotension, tachypnea, mydriasis, dryness of mucous membranes, and rhabdomyolysis

Overdose Management

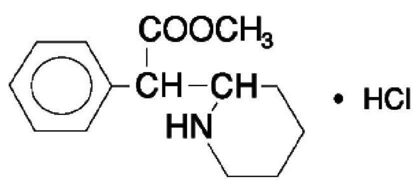
Consult with a Certified Poison Control Center (1-800-222-1222) for the latest recommendations.

11 DESCRIPTION

Methylphenidate hydrochloride extended-release capsules contains methylphenidate hydrochloride, a CNS stimulant.

Methylphenidate hydrochloride extended-release capsules is an extended-release formulation of methylphenidate for oral administration with a bi-modal release profile. Each bead-filled methylphenidate hydrochloride extended-release capsule contains half the dose as immediate-release beads and half as enteric-coated beads, thus providing an immediate release of methylphenidate and a second delayed release of methylphenidate.

The active substance in methylphenidate hydrochloride extended-release capsules is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is



Methylphenidate hydrochloride USP is a white, odorless, fine 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 g/mol.

Inactive ingredients: Acetyltributyl citrate, cellaburate, corn starch, gelatin, hypromellose acetate succinate, polyethylene glycol, sucrose, talc, and titanium dioxide. The 10 mg, 30 mg, 40 mg, and 60 mg capsules contain FD & C Yellow #6. The 10 mg, 30 mg, and 60 mg capsules also contain FD&C Yellow #5. The 40 mg and 60 mg capsules contain D&C Yellow #10. In addition, capsule printing ink contains ammonium hydroxide, black iron oxide, propylene glycol, and shellac glaze.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Methylphenidate hydrochloride is a central nervous system (CNS) stimulant. The mode of therapeutic action in ADHD is not known.

12.2 Pharmacodynamics

Methylphenidate is a racemic mixture comprised of the *d-* and *l-threo* enantiomers. The *d-threo* enantiomer is more pharmacologically active than the *l-threo* enantiomer. 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.

Cardiac Electrophysiology

A formal QT study has not been conducted in patients taking methylphenidate hydrochloride extended-release capsules.

The effect of dexmethylphenidate, the pharmacologically active d-enantiomer of methylphenidate hydrochloride, on the QT interval was evaluated in a double-blind, placebo- and open-label active (moxifloxacin)-controlled study following single doses of dexmethylphenidate XR 40mg (maximum recommended adult total daily dosage) in 75 healthy volunteers. ECGs were collected up to 12 hours postdose. Frederica's method for heart rate correction was employed to derive the corrected QT interval (QTcF). The maximum mean prolongation of QTcF intervals was less than 5 ms, and the upper limit of the 90% confidence interval (CI) was below 10 ms for all time matched comparisons versus placebo. This was below the threshold of clinical concern and there was no evident-exposure response relationship

12.3 Pharmacokinetics

Methylphenidate hydrochloride extended-release capsules produces a bi-modal plasma concentration-time profile (i.e., 2 distinct peaks approximately 4 hours apart) when administered orally to children diagnosed with ADHD and healthy adults.

No accumulation of methylphenidate is expected following multiple once daily oral dosing with methylphenidate hydrochloride extended-release capsules, however, there is a slight upward trend in the methylphenidate area under the curve (AUC) and peak plasma concentrations (C_{max1} and C_{max2}) after oral administration of methylphenidate hydrochloride extended-release capsules 20 mg and 40 mg capsules to adults.

Absorption

The absolute oral bioavailability of methylphenidate in children was 22 ± 8% for d-methylphenidate and 5 ± 3% for l-methylphenidate. The relative bioavailability of methylphenidate hydrochloride extended-release capsules given once daily is comparable to the same total dose of methylphenidate hydrochloride tablets given in 2 doses 4 hours apart in both children and adults.

The initial rate of absorption for methylphenidate hydrochloride extended-release capsules is similar to that of methylphenidate hydrochloride tablets as shown by the similar rate parameters between the 2 formulations, i.e., initial lag time (T_{lag}), first peak concentration (C_{max1}), and time to the first peak (T_{max1}), which is reached in 1 to 3 hours. The mean time to the interpeak minimum (T_{minip}), and time to the second peak (T_{max2}) are also similar for methylphenidate hydrochloride extended-release capsules given once daily and methylphenidate hydrochloride tablets given in 2 doses 4 hours apart (see Figure 1 and Table 1), although the ranges observed are greater for methylphenidate hydrochloride extended-release capsules.

Methylphenidate hydrochloride extended-release capsules given once daily exhibits a lower second peak concentration (C_{max2}), higher interpeak minimum concentrations (C_{minip}), and less peak and trough fluctuations than methylphenidate hydrochloride tablets given in 2 doses given 4 hours apart. This is due to an earlier onset and more prolonged absorption from the delayed-release beads (see Figure 1 and Table 4).

Figure 1: Mean Plasma Concentration Time-profile of Methylphenidate After a Single Dose of Methylphenidate Hydrochloride Extended-Release Capsules, 40 mg and Methylphenidate Hydrochloride Tablets, 20 mg Given in Two Doses 4 Hours Apart

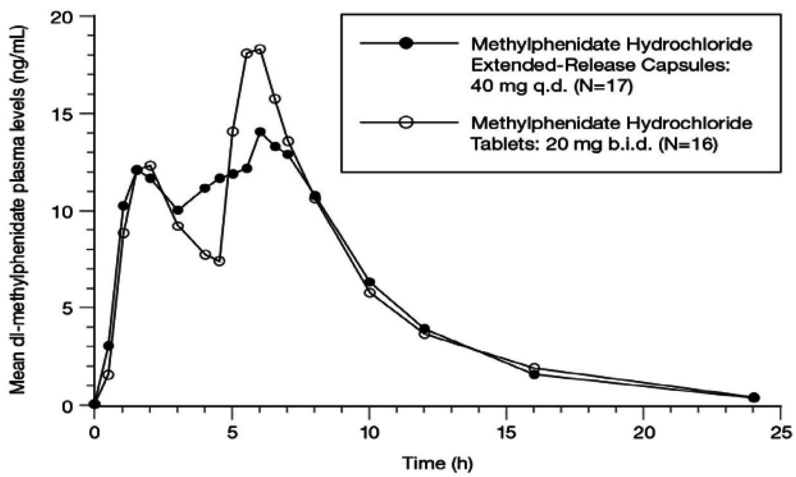


Table 4: Mean ± SD and Range of Pharmacokinetic Parameters of Methylphenidate After a Single Dose of Methylphenidate Hydrochloride Extended-Release Capsules and Methylphenidate Hydrochloride Tablets Given in Two Doses 4 Hours Apart

Population	**Children**		**Adult Males**	
Formulation	**Methylphenidate Hydrochloride Tablets**	**Methylphenidate Hydrochloride Extended-Release Capsules**	**Methylphenidate Hydrochloride Tablets**	**Methylphenidate Hydrochloride Extended-Release Capsules**
Dose	**10 mg &10 mg**	**20 mg**	**10 mg & 10 mg**	**20 mg**
N	**21**	**18**	**9**	**8**
T_{lag} (h)	0.24 ± 0.44	0.28 ± 0.46	1 ± 0.5	0.7 ± 0.2
	0 to 1	0 to 1	0.7 to 1.3	0.3 to 1
T_{max1} (h)	1.8 ± 0.6	2 ± 0.8	1.9 ± 0.4	2 ± 0.9
	1 to 3	1 to 3	1.3 to 2.7	1.3 to 4
C_{max1} (ng/mL)	10.2 ± 4.2	10.3 ± 5.1	4.3 ± 2.3	5.3 ± 0.9
	4.2 to 20.2	5.5 to 26.6	1.8 to 7.5	3.8 to 6.9
T_{minip} (h)	4 ± 0.2	4.5 ± 1.2	3.8 ± 0.4	3.6 ± 0.6
	4 to 5	2 to 6	3.3 to 4.3	2.7 to 4.3

C_{minip}	5.8 ± 2.7	6.1 ± 4.1	1.2 ± 1.4	3 ± 0.8
(ng/mL)	3.1 to 14.4	2.9 to 21	0 to 3.7	1.7 to 4
T_{max2} (h)	5.6 ± 0.7	6.6 ± 1.5	5.9 ± 0.5	5.5 ± 0.8
	5 to 8	5 to 11	5 to 6.5	4.3 to 6.5
C_{max2}	15.3 ± 7	10.2 ± 5.9	5.3 ± 1.4	6.2 ± 1.6
(ng/mL)	6.2 to 32.8	4.5 to 31.1	3.6 to 7.2	3.9 to 8.3
$AUC_{(0-\infty)}$ (ng/mL x h-1)	102.4 ± 54.6	86.6 ± 64[a]	37.8 ± 21.9	45.8 ± 10
	40.5 to 261.6	43.3 to 301.44	14.3 to 85.3	34 to 61.6
$t_{1/2}$ (h)	2.5 ± 0.8	2.4 ± 0.7[a]	3.5 ± 1.9	3.3 ± 0.4
	1.8 to 5.3	1.5 to 4	1.3 to 7.7	3 to 4.2

[a]N = 15

Effect of Food

Administration times relative to meals and meal composition may need to be individually titrated.

When methylphenidate hydrochloride extended-release capsules was administered with a high fat breakfast to adults, methylphenidate hydrochloride extended-release capsules had a longer lag time until absorption began and variable delays in the time until the first peak concentration, the time until the interpeak minimum, and the time until the second peak. The first peak concentration and the extent of absorption were unchanged after food relative to the fasting state, although the second peak was approximately 25% lower. The effect of a high fat lunch was not examined.

There were no differences in the pharmacokinetics of methylphenidate hydrochloride extended-release capsules when administered with applesauce, compared to administration in the fasting condition. There is no evidence of dose dumping in the presence or absence of food.

Effect of Alcohol

An *in vitro* study was conducted to explore the effect of alcohol on the release characteristics of methylphenidate from the methylphenidate hydrochloride extended-release capsules 40 mg capsule dosage form. At an alcohol concentration of 40% there was a 98% release of methylphenidate in the first hour. The results with the 40 mg capsule are considered to be representative of the other available capsule strengths.

Distribution

Binding to plasma proteins is low (10% to 33%). The volume of distribution was 2.65 ± 1.11 L/kg for d-methylphenidate and 1.80 ± 0.91 L/kg for l-methylphenidate.

Elimination

The systemic clearance is 0.40 ± 0.12 L/h/kg for d-methylphenidate and 0.73 ± 0.28 L/h/kg for l-methylphenidate. In studies with methylphenidate hydrochloride extended-release capsules and methylphenidate hydrochloride tablets in adults, methylphenidate from methylphenidate hydrochloride tablets is eliminated from plasma with an average half-life of about 3.5 hours, (range 1.3 to 7.7 hours). In children the average half-life is about 2.5 hours, with a range of about 1.5 to 5 hours. The rapid half-life in both children and adults may result in un-measurable concentrations between the morning and mid-day doses with methylphenidate hydrochloride tablets. No accumulation of methylphenidate is expected following multiple once a day oral dosing with methylphenidate hydrochloride extended-release capsules. The half-life of ritalinic acid is about 3 to 4 hours.

Metabolism

The absolute oral bioavailability of methylphenidate in children was 22 ± 8% for d-methylphenidate and 5 ± 3% for l-methylphenidate, suggesting pronounced presystemic metabolism. Biotransformation of methylphenidate by the carboxylesterase CES1A1 is rapid and extensive leading to the main, de-esterified metabolite α-phenyl-2-piperidine acetic acid (ritalinic acid), which has little or no pharmacologic activity. Only small amounts of hydroxylated metabolites (e.g., hydroxymethylphenidate and hydroxyritalinic acid) are detectable in plasma. Therapeutic activity is principally due to the parent compound.

Excretion

After oral administration of an immediate release formulation of methylphenidate, 78% to 97% of the dose is excreted in the urine and 1% to 3% in the feces in the form of metabolites within 48 to 96 hours. Only small quantities (less than 1%) of unchanged methylphenidate appear in the urine. Most of the dose is excreted in the urine as ritalinic acid (60% to 86%), the remainder being accounted for by minor metabolite.

Studies in Specific Populations

Male and Female Patients

There were no apparent gender differences in the pharmacokinetics of methylphenidate between healthy male and female adults when administered methylphenidate hydrochloride extended-release capsules.

Racial or Ethnic Groups

There is insufficient experience with the use of methylphenidate hydrochloride extended-release capsules to detect ethnic variations in pharmacokinetics.

Pediatric Patients

The pharmacokinetics of methylphenidate hydrochloride extended-release capsules was examined in 18 children with ADHD between 7 and 12 years of age. Fifteen of these children were between 10 and 12 years of age. The time until the between peak minimum, and the time until the second peak were delayed and more variable in children compared to adults. After a 20-mg dose of methylphenidate hydrochloride extended-release capsules, concentrations in children were approximately twice the concentrations observed in 18 to 35 year old adults. This higher exposure is almost completely due to the smaller body size and total volume of distribution in children, as apparent clearance normalized to body weight is independent of age.

Patients with Renal Impairment

Methylphenidate hydrochloride extended-release capsules has not been studied in renally-impaired patients. Renal impairment is expected to have minimal effect on the pharmacokinetics of methylphenidate since less than 1% of a radiolabeled dose is excreted in the urine as unchanged compound, and the major metabolite (ritalinic acid), has little or no pharmacologic activity.

Patients with Hepatic Impairment

Methylphenidate hydrochloride extended-release capsules has not been studied in patients with hepatic impairment. Hepatic impairment is expected to have minimal effect on the pharmacokinetics of methylphenidate since it is metabolized primarily to ritalinic acid by nonmicrosomal hydrolytic esterases that are widely distributed throughout the body.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, and 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 2 times the maximum recommended human dose (MRHD) in children on a mg/m^2 basis. 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 increase 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 4 times the MRHD in children on a mg/m^2 basis.

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, in the *in vitro* mouse lymphoma cell forward mutation assay, or in the *in vitro* chromosomal aberration assay using human lymphocytes. Sister chromatid exchanges and chromosome aberrations were increased, indicative of a weak clastogenic response, in an in vitro assay in cultured Chinese Hamster Ovary (CHO) cells. Methylphenidate was negative *in vivo* in males and females in the mouse bone marrow micronucleus assay.

Impairment of Fertility

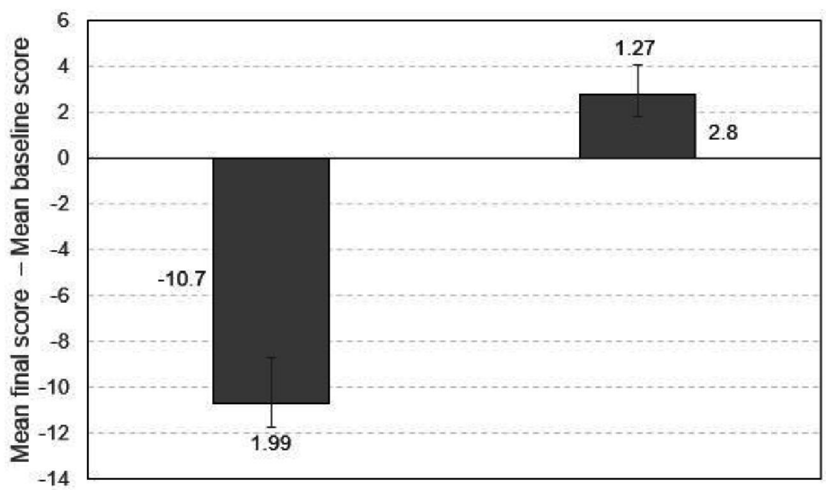
Methylphenidate did not impair fertility in male or female mice that were fed diets containing the drug in an 18-week continuous breeding study. The study was conducted at doses up to 160 mg/kg/day, approximately 10-fold the highest recommended dose in adolescents on a mg/m^2 basis.

14 CLINICAL STUDIES

14.1 Children and Adolescents

Methylphenidate hydrochloride extended-release capsules was evaluated in a randomized, double-blind, placebo-controlled, parallel group clinical study in which 134 children, ages 6 to 12, with DSM-IV diagnoses of ADHD received a single morning dose of methylphenidate hydrochloride extended-release capsules in the range of 10 to 40 mg/day, or placebo, for up to 2 weeks. The doses used were the optimal doses established in a previous individual dose titration phase. In that titration phase, 53 of 164 patients (32%) started on a daily dose of 10 mg and 111 of 164 patients (68%) started on a daily dose of 20 mg or higher. The patient's regular schoolteacher completed the Conners ADHD/DSM-IV Scale for Teachers (CADS-T) at baseline and the end of each week. The CADS-T assesses symptoms of hyperactivity and inattention. The change from baseline of the (CADS-T) scores during the last week of treatment was analyzed as the primary efficacy parameter. Patients treated with methylphenidate hydrochloride extended-release capsules showed a statistically significant improvement in symptom scores from baseline [Mean (final score - baseline)] = -10.7 points) over patients who received placebo [Mean (final score - baseline)] = +2.8 points). The lower the final score on the CADS-T scale from baseline, the less severe the disease is. This demonstrates that a single morning dose of methylphenidate hydrochloride extended-release capsules exerts a treatment effect in ADHD.

Figure 2: CADS-T Total Subscale - Mean Change From Baseline*



Methylphenidate hydrochloride extended-release capsules (n=63) | Placebo (n=71)

*Error bars represent standard error of the mean

16 HOW SUPPLIED/STORAGE AND HANDLING

Methylphenidate hydrochloride extended-release capsules are supplied as:

10 mg:

Hard gelatin capsules, yellow opaque cap printed with "G 10mg" and white opaque body printed with "012" contains white to off-white pellets.

Bottles of 100 NDC 70010-012-01

20 mg:

Hard gelatin capsules, white opaque cap printed with "G 20mg" and white opaque body printed with "013" contains white to off-white pellets.

Bottles of 100 NDC 70010-013-01

30 mg:

Hard gelatin capsules, yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014" contains white to off-white pellets.

Bottles of 100 NDC 70010-014-01

40 mg:

Hard gelatin capsules, yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015" contains white to off-white pellets.

Bottles of 100 NDC 70010-015-01

60 mg:

Hard gelatin capsules, yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets.

Bottles of 30 NDC 70010-016-03

Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature]
Dispense in a tight container as defined in the USP with a child-resistant closure.

Disposal

Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired methylphenidate hydrochloride extended-release capsules by a medicine take-back program or by an authorized collector registered with the Drug Enforcement Administration. If no take-back program or authorized collector is available, mix methylphenidate hydrochloride extended-release capsules with an undesirable, nontoxic substance to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and discard methylphenidate hydrochloride extended-release capsules in the household trash.

17 PATIENT COUNSELING INFORMATION

Advise the patient to read the FDA-approved patient labeling (Medication Guide).

Controlled Substance Status/High Potential for Abuse and Dependence

Advise patients that methylphenidate hydrochloride extended-release capsules are controlled substances, and they can be abused and lead to dependence. Instruct patients that they should not give methylphenidate hydrochloride extended-release capsules to anyone else. Advise patients to store methylphenidate hydrochloride extended-release capsules in a safe place, preferably locked, to prevent abuse. Advise patients to comply with laws and regulations on drug disposal. Advise patients to dispose of remaining, unused, or expired methylphenidate hydrochloride extended-release capsules by a medicine take-back program if available *[see Boxed Warning, Warnings and Precautions (5.1), Drug Abuse and Dependence (9.1, 9.2, 9.3), How Supplied/Storage and Handling (16)].*

Serious Cardiovascular Risks

Advise patients that there is a potential serious cardiovascular risk including sudden death, myocardial infarction, stroke, and hypertension with methylphenidate hydrochloride extended-release capsules use. Instruct patients to contact a healthcare provider immediately if they develop symptoms such as exertional chest pain, unexplained syncope, or other symptoms suggestive of cardiac disease *[see Warnings and Precautions (5.2)]*.

Blood Pressure and Heart Rate Increases

Instruct patients that methylphenidate hydrochloride extended-release capsules can cause elevations of their blood pressure and pulse rate *[see Warnings and Precautions (5.3)]*.

Psychiatric Risks

Advise patients that methylphenidate hydrochloride extended-release capsules, at recommended doses, can cause psychotic or manic symptoms, even in patients without prior history of psychotic symptoms or mania *[see Warnings and Precautions (5.4)]*.

Priapism

Advise patients of the possibility of painful or prolonged penile erections (priapism). Instruct them to seek immediate medical attention in the event of priapism *[see Warnings and Precautions (5.5)]*.

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

Instruct patients beginning treatment with methylphenidate hydrochloride extended-release capsules 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 capsules. Further clinical evaluation (e.g., rheumatology referral) may be appropriate for certain patients *[see Warnings and Precautions (5.6)]*.

Suppression of Growth

Advise patients that methylphenidate hydrochloride extended-release capsules may cause slowing of growth and weight loss *[see Warnings and Precautions (5.7)]*.

Alcohol Effect

Advise patients to avoid alcohol while taking methylphenidate hydrochloride extended-release capsules. Consumption of alcohol while taking methylphenidate hydrochloride extended-release capsules may result in a more rapid release of the dose of methylphenidate *[see Clinical Pharmacology (12.3)]*.

Manufactured by:
Granules Pharmaceuticals Inc.,
Chantilly, VA 20151

Rev. 02/2019

MEDICATION GUIDE

Methylphenidate Hydrochloride Extended-Release Capsules CII

(METH-il-FEN-i-date HYE-droe-KLOR-ide)

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

Methylphenidate hydrochloride extended-release capsules is a federal controlled substance (CII) because it can be abused or lead to dependence.

Keep methylphenidate hydrochloride extended-release capsules in a safe place to prevent misuse and abuse. Selling or giving away methylphenidate hydrochloride extended-release capsules may harm others, and is against the law. Tell your doctor if you or your child have ever abused or been dependent on alcohol, prescription medicines or street drugs.

The following have been reported with use of methylphenidate hydrochloride 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 have 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 capsules.

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

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 capsules.

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**
- **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 have any new or worsening mental symptoms or problems while taking methylphenidate hydrochloride extended-release capsules, especially seeing or hearing things that are not real, believing things that are not real, or are suspicious.

What are methylphenidate hydrochloride extended-release capsules?
Methylphenidate hydrochloride extended-release capsules are a central nervous system stimulant prescription medicine. **It is used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD).** Methylphenidate hydrochloride extended-release capsules may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD.

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

It is not known if methylphenidate hydrochloride extended-release capsules are safe and effective in children under 6 years of age.

Who should not take methylphenidate hydrochloride extended-release capsules?

Methylphenidate hydrochloride extended-release capsules should not be taken if you or your child:

- are allergic to methylphenidate hydrochloride, or any of the ingredients in in methylphenidate hydrochloride extended-release capsules. See the end of this Medication Guide for a complete list of ingredients in methylphenidate hydrochloride extended-release capsules.
- are taking or have taken within the past 14 days an anti-depression medicine called a monoamine oxidase inhibitor or MAOI.

Methylphenidate hydrochloride extended-release capsules may not be right for you or your child. Before starting methylphenidate hydrochloride extended-release capsules tell your or your child's doctor about all health conditions (or a family history of) including:

- heart problems, heart defects, high blood pressure
- mental problems including psychosis, mania, bipolar illness, or depression
- circulation problems in fingers or toes
- if you are pregnant or plan to become pregnant. It is not known if methylphenidate hydrochloride extended-release capsules will harm your unborn baby. Talk to your doctor if you are pregnant or plan to become pregnant.
- if you are breastfeeding or plan to breastfeed. Methylphenidate hydrochloride passes into your breast milk. You and your doctor should decide if you will take methylphenidate hydrochloride extended-release capsules or breastfeed.

Tell your doctor about all of the medicines that you or your child take including prescription and over-the-counter medicines, vitamins, and herbal supplements. Methylphenidate hydrochloride extended-release capsules 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 capsules.

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

Especially tell your doctor if you or your child takes:

- anti-depression medicines including MAOIs
- blood pressure medicines (anti-hypertensive)

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 capsules without talking to your doctor first.

How should methylphenidate hydrochloride extended-release capsules be taken?

- Take methylphenidate hydrochloride extended-release capsules exactly as prescribed. Your doctor may adjust the dose until it is right for you or your child.
- Take methylphenidate hydrochloride extended-release capsules once a day in the morning. methylphenidate hydrochloride extended-release capsules are an extended-release capsule.
- **Do not chew or crush methylphenidate hydrochloride extended-release capsules or the medicine inside the capsule.** Swallow methylphenidate hydrochloride extended-release capsules whole with water or other liquids.
- If you cannot swallow the capsule whole, open it and sprinkle the medicine over a spoonful of applesauce. Swallow the applesauce and medicine mixture without chewing. Follow with a drink of water or other liquid.
- You should avoid drinking alcohol during treatment with methylphenidate hydrochloride extended-release capsules. This may cause a faster release of methylphenidate hydrochloride extended-release capsules.
- From time to time, your doctor may stop methylphenidate hydrochloride extended-release capsules 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 capsules. Children should have their height and weight checked often while taking methylphenidate hydrochloride extended-release capsules. Methylphenidate hydrochloride extended-release capsules treatment may be stopped if a problem is found during these check-ups.

In case of poisoning, call your poison control center at 1-800-222-1222 right away or go to the nearest hospital emergency room.

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

- See **"What is the most important information I should know about methylphenidate hydrochloride extended-release capsules?"** for information on reported heart and mental problems.
- **painful and prolonged erections (priapism)** have occurred with methylphenidate. If you or your child develops priapism, seek medical help right away. Because of the potential for lasting damage, priapism should be evaluated by a doctor immediately.
- **circulation problems in fingers and toes** (Peripheral vasculopathy, including Raynaud's phenomenon):
  - o fingers or toes may feel numb, cool, painful
  - o fingers or toes may change color from pale, to blue, to red

Tell your doctor if you or your child have numbness, pain, skin color change, or sensitivity to temperature in the 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 capsules.**
- **slowing of growth (height and weight) in children**

Common side effects include:

- fast heart beat
- Abnormal
- headache
- trouble
- nervousness

	heartbeat (palpitations)		sleeping	
• sweating a lot	• decreased appetite	• dry mouth	• nausea	• stomach pain

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

How should I store methylphenidate hydrochloride extended-release capsules?

- Store methylphenidate hydrochloride extended-release capsules in a safe place and in a tightly closed container at room temperature, 68°F to 77°F (20°C to 25°C).
- Protect from moisture.
- Dispose of remaining, unused, or expired methylphenidate hydrochloride extended-release capsules by a medicine take-back program at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix methylphenidate hydrochloride extended-release capsules with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away (discard) methylphenidate hydrochloride extended-release capsules in the household trash.
- **Keep methylphenidate hydrochloride extended-release capsules and all medicines out of the reach of children.**

General information about the safe and effective use methylphenidate hydrochloride extended-release capsules

Medicines are sometimes prescribed for purposes other than those listed in a Medication Guide. You can ask your pharmacist or doctor for information about **methylphenidate hydrochloride extended-release capsules** that is written for healthcare professionals. Do not use methylphenidate hydrochloride extended-release capsules for a condition for which it was not prescribed. Do not give methylphenidate hydrochloride extended-release capsules to other people, even if they have the same symptoms. It may harm them and it is against the law.

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

Active Ingredient: methylphenidate hydrochloride

Inactive Ingredients: Acetyltributyl citrate, cellaburate, corn starch, gelatin, hypromellose acetate succinate, polyethylene glycol, sucrose, talc, and titanium dioxide. The 10 mg, 30 mg, 40 mg, and 60 mg capsules contain FD & C Yellow #6. The 10 mg, 30 mg, and 60 mg capsules also contain FD&C Yellow #5. The 40 mg and 60 mg capsules contain D&C Yellow #10. In addition, capsule printing ink contains ammonium hydroxide, black iron oxide, propylene glycol, and shellac glaze.

Methylphenidate Hydrochloride Extended-Release Capsules contain FD&C Yellow #5 (tartrazine).

Manufactured by:
Granules Pharmaceuticals Inc.,
Chantilly, VA 20151

Rev. 02/2019

For more information, call 1-877-770-3183.

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

Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg

NDC 70010-**012**-01

Once Daily

Methylphenidate Hydrochloride Extended-Release Capsules (LA)

CII

10 mg

Dispense the accompanying Medication Guide to each patient.

Rx only **100 Capsules**

Each Extended-Release Capsule Contains:
Methylphenidate Hydrochloride, USP....10 mg

Contains FD&C Yellow No. 5 (tartrazine) as a color additive.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP with a child-resistant closure.

Keep this and all medications out of the reach of children.

Manufactured by:
Granules Pharmaceuticals Inc.,
Chantilly, VA 20151

Rev. 07/18

3 70010-01201 1

PXXXXX

LOT:

EXP.:

<u>Methylphenidate Hydrochloride Extended-Release Capsules (LA), 20 mg</u>

NDC 70010-**013**-01

Once Daily
Methylphenidate Hydrochloride Extended-Release Capsules (LA)

CII

20 mg

Dispense the accompanying Medication Guide to each patient.

Rx only **100 Capsules**

Each Extended-Release Capsule Contains:
Methylphenidate Hydrochloride, USP....20 mg

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP with a child-resistant closure.

Keep this and all medications out of the reach of children.

Manufactured by:
Granules Pharmaceuticals Inc.,
Chantilly, VA 20151

Rev. 07/18

3 70010-01301 8

PXXXXX

LOT:

EXP.:

Methylphenidate Hydrochloride Extended-Release Capsules (LA), 30 mg

NDC 70010-**014**-01

Once Daily

Methylphenidate Hydrochloride Extended-Release Capsules (LA)

CII

30 mg

Dispense the accompanying Medication Guide to each patient.

Rx only **100 Capsules**

Each Extended-Release Capsule Contains:
Methylphenidate Hydrochloride, USP....30 mg

Contains FD&C Yellow No. 5 (tartrazine) as a color additive.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP with a child-resistant closure.

Keep this and all medications out of the reach of children.

Manufactured by:
Granules Pharmaceuticals Inc.,
Chantilly, VA 20151

Rev. 07/18

3 70010-01401 5

PXXXXX

LOT:

EXP.:

Methylphenidate Hydrochloride Extended-Release Capsules (LA), 40 mg

NDC 70010-**015**-01

Once Daily
Methylphenidate Hydrochloride Extended-Release Capsules (LA)

CII

40 mg

Dispense the accompanying Medication Guide to each patient.

Rx only **100 Capsules**

Each Extended-Release Capsule Contains:
Methylphenidate Hydrochloride, USP....40 mg

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP with a child-resistant closure.

Keep this and all medications out of the reach of children.

Manufactured by:
Granules Pharmaceuticals Inc.,
Chantilly, VA 20151

Rev. 07/18

3 70010-01501 2

PXXXXX

LOT:

EXP.:

Methylphenidate Hydrochloride Extended-Release Capsules (LA), 60 mg

NDC 70010-**016**-03

Once Daily

Methylphenidate Hydrochloride Extended-Release Capsules (LA)

CII

60 mg

Dispense the accompanying Medication Guide to each patient.

Rx only **30 Capsules**

Each Extended-Release Capsule Contains:
Methylphenidate Hydrochloride, USP.......60 mg
Contains FD&C Yellow No. 5 (tartrazine) as a color additive.

Usual Dosage: See package insert for full prescribing information.

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

Dispense in a tight container as defined in the USP with a child-resistant closure.

Keep this and all medications out of the reach of children.

Manufactured by:
Granules Pharmaceuticals Inc.,
Chantilly, VA 20151

Rev. 07/18

3 70010-01603 3

PXXXXX

LOT.:
EXP.:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211796

<u>LABELING REVIEW(s)</u>

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	April 1, 2019
ANDA Number(s)	211796
Review Number	3
Applicant Name	Granules Pharmaceuticals Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg
Proposed Proprietary Name	None
Submission Received Date	February 26, 2019 (amendment)
Primary Labeling Reviewer	Jeanne Skanchy
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments

☒ ACCEPTABLE – Include Post Approval Comments

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

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☐ Yes ☒ No

Combined Insert/Outsert ☐ Yes ☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

1. GENERAL COMMENTS
   Comment
2. CONTAINER LABEL
   a. Comment
   b. Comment
3. CARTON LABELING
4. PRESCRIBING INFORMATION
   a. Comment
   b. Subheading
      i. Comment
      ii. Comment
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

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.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

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) received date February 26, 2019.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).

(b) (4)

[redacted]

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) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments: Labeling review C2 was adequate thus no comments were conveyed to the applicant.

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:

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:

a. Please note that the RLD for this application is Ritalin LA; [redacted] (b) (4) Lastly, there is no USP monograph for this drug product.

b. STRUCTURED PRODUCT LABELING (SPL)

[redacted] (b) (4).

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO 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? NO If Yes, please explain.
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL LABELING

Table 1: Review Model 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, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)

NDA# /Supplement# (S-000 if original): 021284/S-016 & S-029

Supplement Approval Date: 1/10/2019

Proprietary Name: Ritalin SR Extended-Release Capsule

Established Name: Methylphenidate Extended-Release Capsules

Description of Supplement:

These Prior Approval supplemental new drug applications provide for:

- NDA 10187/S-071; NDA 18029/S-041; NDA 21284/S-016: Conversion of the prescribing information to the Physician's Labeling Rule (PLR) format;
- NDA 10187/S-082; NDA 18029/S-051; NDA 21284/S-029: Updates to the Carcinogenesis/Mutagenesis/Impairment of Fertility and Pregnancy sections of the prescribing information.

☐**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):** Click here to enter text.

Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) 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), or 201.66 (OTC)? **YES**

Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:

The following comments will be conveyed to the applicant as post approval communication:

(b) (4)

[redacted]

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 21284/S-029 SPL]


NDC 0078-0424-05
Rx only
Ritalin LA®
(methylphenidate HCl)
extended-release capsules
10 mg
CII
100 capsules
Dispense with Medication Guide attached or provided separately.
NOVARTIS


NDC 0078-0370-05
Rx only
Ritalin LA®
(methylphenidate HCl)
extended-release capsules
20 mg
CII
100 capsules
Dispense with Medication Guide attached or provided separately.
NOVARTIS


NDC 0078-0371-05
Rx only
Ritalin LA®
(methylphenidate HCl)
extended-release capsules
30 mg
CII
100 capsules
Dispense with Medication Guide attached or provided separately.
NOVARTIS

3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 4/1/2019.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	Click here to enter the date when the monograph becomes official.	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:
Click here to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 4/1/2019.

Table 3 provides Orange Book patents for the Model Labeling NDA 021284 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)
6228398	11/01/2019	U-472	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER USING METHYLPHENIDATE BI-MODAL RELEASE PROFILE EXTENDED-RELEASE CAPSULES	PIV	2/26/2019	None

Reviewer Assessment:

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

Reviewer Comments:

Applicant has amended the patent certification from PIII to PIV in the February 26, 2019 amendment. However, there are no carve-outs in the labeling. Lastly, please note that the 60 mg strength has been discontinued in the Orange Book and no patent is associated with the respective strength.

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)**
NA					

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

4. <u>DESCRIPTION, HOW SUPPLIED AND MANUFACTURED BY STATEMENT</u>

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)? **NO** 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**

Table 5: Comparison of DESCRIPTION Section or Inactive Ingredients Subsection (OTC)		
Inactive ingredients: Acetyltributyl citrate, cellaburate, corn starch, gelatin, hypromellose acetate succinate, polyethylene glycol, sucrose, talc, and titanium dioxide. The 10 mg, 30 mg, 40 mg, and 60 mg capsules contain FD & C Yellow #6. The 10 mg, 30 mg, and 60 mg capsules also contain FD&C Yellow #5. The 40 mg and 60 mg capsules contain D&C Yellow #10. In addition, capsule printing ink contains ammonium hydroxide, black iron oxide, propylene glycol, and shellac glaze.	Inactive ingredients: Acetyltributyl citrate, cellaburate, corn starch, gelatin, hypromellose acetate succinate, polyethylene glycol, sucrose, talc, and titanium dioxide. The 10 mg, 30 mg, 40 mg, and 60 mg capsules contain FD & C Yellow #6. The 10 mg, 30 mg, and 60 mg capsules also contain FD&C Yellow #5. The 40 mg and 60 mg capsules contain D&C Yellow #10. In addition, capsule printing ink contains ammonium hydroxide, black iron oxide, propylene glycol, and shellac glaze.	There is no change.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Methylphenidate hydrochloride extended-release capsules are supplied as: 10 mg: Hard gelatin capsules, yellow opaque cap printed with "G 10mg" and white opaque body printed with "012" contains white to off-white pellets. Bottles of 100 NDC 70010-012-01 20 mg: Hard gelatin capsules, white opaque cap printed with "G 20mg" and white opaque body printed with "013" contains white to off-white pellets. Bottles of 100 NDC 70010-013-01 30 mg: Hard gelatin capsules, yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014" contains white to off-white pellets. Bottles of 100 NDC 70010-014-01 40 mg: Hard gelatin capsules, yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015" contains white to off-white pellets. Bottles of 100 NDC 70010-015-01 60 mg: Hard gelatin capsules, yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets. Bottles of 30 NDC 70010-016-03 Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature] Dispense in a tight container as defined in the USP with a child-resistant closure.	Methylphenidate hydrochloride extended-release capsules are supplied as: 10 mg: Hard gelatin capsules, yellow opaque cap printed with "G 10mg" and white opaque body printed with "012" contains white to off-white pellets. Bottles of 100 NDC 70010-012-01 20 mg: Hard gelatin capsules, white opaque cap printed with "G 20mg" and white opaque body printed with "013" contains white to off-white pellets. Bottles of 100 NDC 70010-013-01 30 mg: Hard gelatin capsules, yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014" contains white to off-white pellets. Bottles of 100 NDC 70010-014-01 40 mg: Hard gelatin capsules, yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015" contains white to off-white pellets. Bottles of 100 NDC 70010-015-01 60 mg: Hard gelatin capsules, yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets. Bottles of 30 NDC 70010-016-03 Store at 20° to 25°C (68° to 77°F). [See USP Controlled Room Temperature] Dispense in a tight container as defined in the USP with a child-resistant closure.	There is no change.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured by: Granules Pharmaceuticals Inc., Chantilly, VA 20151	Manufactured by: Granules Pharmaceuticals Inc., Chantilly, VA 20151	There is no change.

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue). Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:
Click here to enter text.

6. 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	Final	100's (10 mg, 20 mg, 30 mg, and 40 mg) 30's (60 mg)	7/12/2018	Satisfactory
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
(Other – specify)	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
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	Draft *	2/2019	2/26/2019	Satisfactory
Medication Guide	Draft	2/2019	2/26/2019	Satisfactory
Patient Information	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements		2/2019	2/26/2019	Satisfactory

Prescribing Information (PI) and Medication Guide (MG) were submitted in draft and final printed labeling. However, the draft PI and MG were used to model with the reference listed drug labeling.

APPEARS THIS WAY ON ORIGINAL

Jeanne Skanchy

Digitally signed by Jeanne Skanchy
Date: 4/18/2019 07:46:25AM
GUID: 508da70800028bd836b811ba0ad71161

Betty Turner

Digitally signed by Betty Turner
Date: 4/18/2019 09:28:38AM
GUID: 508da70600028acef381be737f7836a9

[redacted]

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	November 29, 2018
ANDA Number(s)	211796
Review Number	2
Applicant Name	Granules Pharmaceuticals Inc.
Established Name & Strength(s) [Add "(OTC)" after strength if applicable]	Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg
Proposed Proprietary Name	None
Submission Received Date	July 12, 2018 (amendment)
Primary Labeling Reviewer	Jeanne Skanchy
Secondary Labeling Reviewer	Refer to signature page

Review Conclusion

☐ ACCEPTABLE – No Comments

☒ ACCEPTABLE – Include Post Approval Comments

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

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List	☐ Yes	☒ No
Acceptable for Filing	☒ Yes	☐ No
Combined Insert/Outsert	☐ Yes	☒ No (If yes, indicate ANDA number)

1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on (add date) based on your submission(s) received (add date):

1. GENERAL COMMENTS
   Comment

2. CONTAINER LABEL
   a. Comment
   b. Comment

3. CARTON LABELING
4. PRESCRIBING INFORMATION
   a. Comment
   b. Subheading
      i. Comment
      ii. Comment
5. MEDICATION GUIDE
6. STRUCTURED PRODUCT LABELING (SPL)

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 Choose an item. all differences annotated and explained. We also advise that you only address the deficiencies noted in this communication.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

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) received July 12, 2018.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 **POST APPROVAL REVISIONS**

These comments will be addressed post approval (in the first labeling supplement review).

(b) (4)

[redacted]

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) [e.g. "The below comments are from the labeling review C3 based on the submission dated 7/4/15"].

Reviewer Comments: The following comments are from Labeling Review#1:

Labeling Deficiencies determined on June 13, 2018, based on your submission(s) dated March 31, 2018:

1. GENERAL COMMENT
   Please provide a statement to ensure adequate number of medication guide(s) will be provided for each package size.

2. CONTAINER LABEL
   a. Please confirm that the container closure system meets 21 CFR 1302.06 for tamper evident sealing.
   b. Add "(LA)" at the end of the established name in the principal display panel (PDP) to read as follows: Methylphenidate Hydrochloride Extended-Release Capsules (LA).
   c. Increase the prominence and relocate the controlled substance sign to appear closer to the established name.
   d. Relocate the period to appear inside the bracket for "See USP Controlled Room Temperature.]" statement.
   e. Revise [redacted] to read "Usual Dosage" on the side panel.
   f. Please include one of the following statements on the side panel: Contains FD&C Yellow No. 5 (tartrazine) as a color additive" or "[redacted].
   g. [redacted].

3. PRESCRIBING INFORMATION
   a. [redacted].
   b. PRECAUTIONS: We note that your drug product contains FD&C Yellow #5, tartrazine. Please include the following statement at the end of the PRECAUTIONS section to read as follows: "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

4. MEDICATION GUIDE
   a. What are the ingredients in methylphenidate hydrochloride extended-release capsules? Include the following statement at the end of this section: Methylphenidate Hydrochloride Extended-Release Capsules contain FD&C Yellow #5 (tartrazine).
   b. [redacted]

5. STRUCTURED PRODUCT LABELING (SPL)
   We note that D&C Yellow No.10 is listed for the 10 mg, 20 mg, and 30 mg strengths; FD&C Yellow No. 5 is listed for the 20 mg and 40 mg strengths; and FD&C Yellow No. 6 is listed for 20 mg strength in the inactive ingredients section of the data elements of the SPL. [redacted]. Please comment and/or revise accordingly.

Applicant has revised the containers, prescribing information, medication guide, and SPL.

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:

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:
Please note that the RLD for this application is Ritalin LA; however, [redacted] (b) (4) Lastly, there is no USP monograph for this drug product.

3. LABELING REVIEW INFORMATION AND REVIEWER ASSESSMENT

3.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO 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? NO If Yes, please explain.
Is the drug product listed on the Susceptibility Test Interpretive Criteria web page? NO

3.2 MODEL LABELING

Table 1: Review Model 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, indicate whether the application has been withdrawn and if so enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** 021284/S-034 **Supplement Approval Date:** 1/4/2017 **Proprietary Name:** Ritalin LA Capsules **Established Name:** Methylphenidate Hydrochloride Extended-Release Capsules **Description of Supplement:** We also refer to our letter dated September 21, 2016, notifying you, under Section 505(o)(4) of the FDCA, 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, and the association between the use of methylphenidate products and severe hepatic injury.

Table 1: Review Model Labeling (Check the box used as the Model Labeling)
☐ **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):** Click here to enter text.

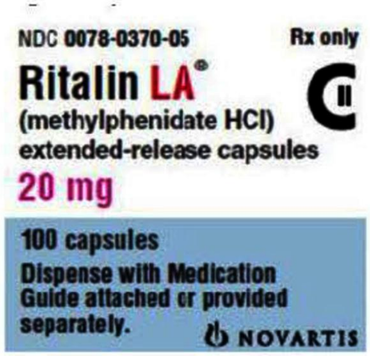
Reviewer Assessment:

Is the Prescribing Information or Drug Facts Labeling (OTC) 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), or 201.66 (OTC)? **YES**
Does the Model Labeling have combined insert labeling for multiple dosage forms? **NO**

Reviewer Comments:
Click here to enter text.

3.3 MODEL CONTAINER LABELS

Model container/carton/blister labels [Source: NDA 021284/S-034 SPL)]



3.4 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 11/30/2018.

	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)
Currently Official	NO		NA	NA
Not Yet Official	NO	Click here to enter the date when the monograph becomes official.	NA	NA

Reviewer Assessment:

Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling and labels? **NA**

Reviewer Comments:

Click here to enter text.

3.5 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 11/30/2018.

Table 3 provides Orange Book patents for the Model Labeling NDA 021284 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)**
6228398	11/01/2019	U-472	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER USING METHYLPHENIDATE BI-MODAL RELEASE PROFILE EXTENDED-RELEASE CAPSULES	PIII	4/2/2018	None

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

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)**
NA					

Reviewer Assessment:

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

Reviewer Comments:

Click here to enter text.

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**
(b) (4) [redacted]	Inactive ingredients: Acetyltributyl citrate, cellaburate, corn starch, gelatin, hypromellose acetate succinate, polyethylene glycol, sucrose, talc, and titanium dioxide. The 10 mg, 30 mg, 40 mg, and 60 mg capsules contain FD & C Yellow #6. The 10 mg, 30 mg, and 60 mg capsules also contain FD&C Yellow #5. The 40 mg and 60 mg capsules contain D&C Yellow #10. In addition, capsule printing ink contains ammonium hydroxide, black iron oxide, propylene glycol, and shellac glaze.	[redacted] (b) (4) This is acceptable.

Table 6: Comparison of HOW SUPPLIED Section or Packaging Sizes for OTC Products		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Methylphenidate hydrochloride extended-release capsules, USP are supplied as: 10 mg: Hard gelatin capsules, yellow opaque cap printed with "G 10mg" and white opaque body printed with "012" contains white to off-white pellets. Bottles of 100 NDC 70010-012-01 20 mg: Hard gelatin capsules, white opaque cap printed with "G 20mg" and white opaque body printed with "013" contains white to off-white pellets. Bottles of 100 NDC 70010-013-01 30 mg: Hard gelatin capsules, yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014" contains white to off-white pellets. Bottles of 100 NDC 70010-014-01 40 mg: Hard gelatin capsules, yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015" contains white to off-white pellets. Bottles of 100 NDC 70010-015-01 60 mg: Hard gelatin capsules, yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets. Bottles of 30 NDC 70010-016-03 Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature] Dispense in a tight container as defined in the USP with a child-resistant closure.	Methylphenidate hydrochloride extended-release capsules are supplied as: 10 mg: Hard gelatin capsules, yellow opaque cap printed with "G 10mg" and white opaque body printed with "012" contains white to off-white pellets. Bottles of 100 NDC 70010-012-01 20 mg: Hard gelatin capsules, white opaque cap printed with "G 20mg" and white opaque body printed with "013" contains white to off-white pellets. Bottles of 100 NDC 70010-013-01 30 mg: Hard gelatin capsules, yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014" contains white to off-white pellets. Bottles of 100 NDC 70010-014-01 40 mg: Hard gelatin capsules, yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015" contains white to off-white pellets. Bottles of 100 NDC 70010-015-01 60 mg: Hard gelatin capsules, yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets. Bottles of 30 NDC 70010-016-03 Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature] Dispense in a tight container as defined in the USP with a child-resistant closure.	There is no change.

Table 7: Manufacturer/Distributor/Packer Statements		
Previous Labeling Review	**Currently Proposed**	**Assessment**
Manufactured by: Granules Pharmaceuticals Inc., Chantilly, VA 20151	Manufactured by: Granules Pharmaceuticals Inc., Chantilly, VA 20151	There is no change.

5. COMMENTS FOR OTHER DISCIPLINES

Describe questions/issue(s) sent to and/or received from other discipline(s) (e.g., OPQ, OB, DCR):

(For Issues, include the following information: discipline and description of issue, issue reference number or link, and date of issue)

Reminder: Refer to chemistry review to verify labeling section (per Chemistry-Labeling MOU) is complete. Refer to DCR review for combination product to verify if labeling comments were communicated to applicant.

Reviewer Comments:
Click here to enter text.

6. 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	Final	100's (10 mg, 20 mg, 30 mg, and 40 mg) 30's (60 mg)	7/12/2018	Satisfactory
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
(Other – specify)	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
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	Draft *	7/2018	7/12/2018	Satisfactory
Medication Guide	Draft	7/2018	7/12/2018	Satisfactory
Patient Information	NA	Click here to enter text.		Click here to enter text.
SPL Data Elements		7/2018	7/12/2018	Satisfactory

*Prescribing information (PI) was submitted in draft and final printed labeling. However, draft PI was used for comparison with the reference listed drug labeling.

APPEARS THIS WAY ON ORIGINAL

Jeanne Skanchy

Digitally signed by Jeanne Skanchy
Date: 12/06/2018 09:21:32AM
GUID: 508da70800028bd836b811ba0ad71161

Betty Turner

Digitally signed by Betty Turner
Date: 12/07/2018 10:29:25AM
GUID: 508da70600028acef381be737f7836a9

[redacted]

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	June 11, 2018
ANDA Number(s)	211796
Review Number	1
Applicant Name	Granules Pharmaceuticals Inc.
Established Name & Strength(s)	Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg
Proposed Proprietary Name	None
Submission Received Date	April 2, 2018 (DARRTS submission date of March 31, 2018)
Primary Labeling Reviewer	Jeanne Skanchy
Secondary Labeling Reviewer	Angela Payne (Acting)

Review Conclusion

☐ ACCEPTABLE – No Comments

☐ ACCEPTABLE – Include Post Approval Comments

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

☐ Major Deficiency† – Refer to Labeling Deficiencies and Comments for Letter to Applicant

†Theme - Choose an item.

Justification for Major Deficiency - Choose an item.

*Please Note: The Regulatory Project Manager (RPM) may change the recommendation from Minor Deficiency to Discipline Review Letter/Information Request (DRL/IR) if all other OGD reviews are acceptable. Otherwise, the labeling minor and major deficiencies will be included in the Complete Response Letter (CRL) letter to the applicant.

On Policy Alert List ☐ Yes ☒ No

Acceptable for Filing ☒ Yes ☐ No

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1. LABELING COMMENTS

1.1 LABELING DEFICIENCIES AND COMMENTS FOR LETTER TO APPLICANT

Labeling Deficiencies determined on June 13, 2018, based on your submission(s) dated March 31, 2018:

1. GENERAL COMMENT
   Please provide a statement to ensure adequate number of medication guide(s) will be provided for each package size.

2. CONTAINER LABEL
   a. Please confirm that the container closure system meets 21 CFR 1302.06 for tamper evident sealing.
   b. Add "(LA)" at the end of the established name in the principal display panel (PDP) to read as follows: Methylphenidate Hydrochloride Extended-Release Capsules (LA).
   c. Increase the prominence and relocate the controlled substance sign to appear closer to the established name.
   d. Relocate the period to appear inside the bracket for "See USP Controlled Room Temperature.]" statement.
   e. Revise [redacted] (b) (4) to read "Usual Dosage" on the side panel.
   f. Please include one of the following statements on the side panel: Contains FD&C Yellow No. 5 (tartrazine) as a color additive" or [redacted] (b) (4)
   g. [redacted] (b) (4)

3. PRESCRIBING INFORMATION
   a. DESCRIPTION: [redacted] (b) (4).
   b. PRECAUTIONS: We note that your drug product contains FD&C Yellow #5, tartrazine. Please include the following statement at the end of the PRECAUTIONS section to read as follows: "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

4. MEDICATION GUIDE
   a. What are the ingredients in methylphenidate hydrochloride extended-release capsules? Include the following statement at the end of this section: Methylphenidate Hydrochloride Extended-Release Capsules contain FD&C Yellow #5 (tartrazine).
   b. [redacted] (b) (4)

5. STRUCTURED PRODUCT LABELING (SPL)
   We note that D&C Yellow No.10 is listed for the 10 mg, 20 mg, and 30 mg strengths; FD&C Yellow No. 5 is listed for the 20 mg and 40 mg strengths; and FD&C Yellow No. 6 is listed for 20 mg strength in the inactive ingredients section of the data elements of the SPL. [redacted] (b) (4) Please comment and/or revise accordingly.

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.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

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).

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

1.3 POST APPROVAL REVISIONS

These comments will be addressed post approval (in the first labeling supplement review).
Click here to enter text.

2. LABELING REVIEW INFORMATION

2.1 REGULATORY INFORMATION

Are there any pending issues in DLR's SharePoint Drug Facts? NO If Yes, please explain.
Is the drug product listed in the Policy Alert Tracker on OGD's SharePoint? NO If Yes, please explain.
Is the drug product listed in the Susceptibility Test Interpretive Criteria web page? NO
Is there a mid-review cycle meeting (MRCM) task in Platform? Or, if filing review is not complete, was there a Product Development or Pre-ANDA Submission Project under the ANDA Program? NO If **YES** is answered, there is a potential for holding MRCM. What is the proposed agenda from DLR for

MRCM?

Click here to enter text.

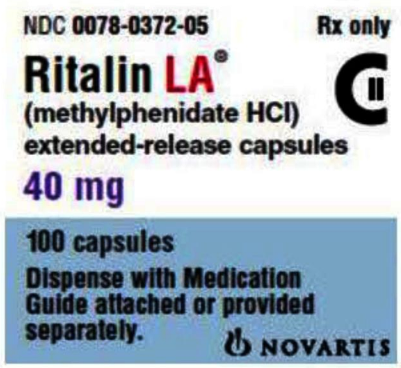
2.2 MODEL LABELING

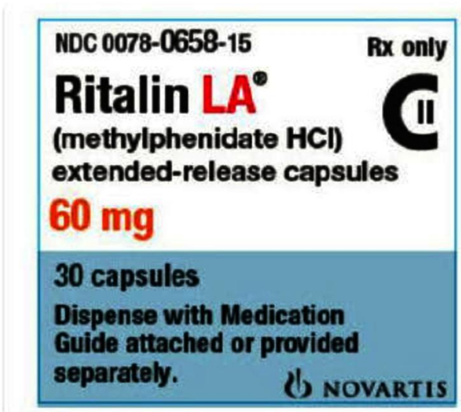
2.2.1 MODEL PRESCRIBING INFORMATION

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, indicate whether the application has been withdrawn and if so, enter the most recently approved ANDA labeling information as applicable.)* **NDA#/Supplement# (S-000 if original):** 021284/S-034 **Supplement Approval Date:** 1/4/2017 **Proprietary Name:** Ritalin LA **Established Name:** Methylphenidate Hydrochloride Extended-Release Capsules **Description of Supplement:** We also refer to our letter dated September 21, 2016, notifying you, under Section 505(o)(4) of the FDCA, 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, and the association between the use of methylphenidate products and severe hepatic injury.
☐ **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:** Click here to enter text.
☐ **TEMPLATE (e.g., BPCA, PREA, Carve-out):** Click here to enter text.
☐ **OTHER (Describe):**

2.2.2 MODEL CONTAINER LABELS

Model container/carton/blister labels (Source: NDA 021284/S-034 SPL)





2.3 UNITED STATES PHARMACOPEIA (USP)

The USP was searched on 6/11/2018.

Table 2: USP				
	YES or NO	Date	Monograph Title (NA if no monograph)	Packaging and Storage/Labeling Statements (NA if no monograph)

Official Monograph	NO		NA	NA
Pending Monograph Proposed	NO	Click here to enter the date when the monograph becomes official.	NA	NA

2.4 PATENTS AND EXCLUSIVITIES

The Orange Book was searched on 6/11/2018.

Table 3 provides Orange Book patents for the Model Labeling (NDA 021284) 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)
6228398	11/01/2019	U-472	TREATMENT OF ATTENTION DEFICIT HYPERACTIVITY DISORDER USING METHYLPHENIDATE BI-MODAL RELEASE PROFILE EXTENDED-RELEASE CAPSULES	PIII	4/2/2018	None

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)
NA					

2.5 MANUFACTURING FACILITY

Table 5: Comparison of Manufacturer/Distributor/Packer Labeling Statements

Name and Address of ANDA Manufacturer/Distributor/Packer (cite source as applicable)	Name and Address on ANDA Container/Carton	Name and Address on ANDA Prescribing Information
(b) (4) [redacted]	Manufactured by: **Granules Pharmaceuticals Inc.,** Chantilly, VA 20151	Manufactured by: **Granules Pharmaceuticals Inc.,** Chantilly, VA 20151

3. ASSESSMENT OF ANDA LABELING AND LABELS

Is this product Rx or OTC? Please check one.

☒ Rx Product (If Rx, skip 3.2 OTC DRUG PRODUCT.)
☐ OTC Product (If OTC, skip 3.1 RX DRUG PRODUCT.)

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**
Is the established name the same as the USP monograph title appearing in section 2.3? **NA**
Is the established name the same as the RLD's nonproprietary name? **YES**
If YES is answered to both questions, then continue with review.
If NO is answered to EITHER questions, then advise firm to revise to the USP name (if applicable) and include justification language under Reviewer Comments.
Does the Model Labeling have combined insert labeling for multiple NDAs or dosage forms? **NO**
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:
Click here to enter text.

3.1.1.1 RX: DESCRIPTION

Table 6: Comparison of Inactive Ingredients Contained in Model Product and ANDA Description Section	
Model Labeling Inactive Ingredients	**ANDA Labeling Inactive Ingredients**
Inactive ingredients: ammonio methacrylate copolymer, black iron oxide (10 and 40 mg capsules only), gelatin, methacrylic acid copolymer, polyethylene glycol, red iron oxide (10 and 40 mg capsules only), sugar spheres, talc, titanium dioxide, triethyl citrate, and yellow iron oxide (10, 30, and 40 mg capsules only).	(b) (4) [redacted]

Reviewer Assessment:
Are the inactive ingredients accurate? **PENDING CHEMISTRY REVIEW**
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? **YES**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **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:

4 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

3.1.1.2 RX: HOW SUPPLIED/STORAGE AND HANDLING

Table 7: Comparison of Model Labeling to ANDA Labeling	
Model Labeling	Ritalin LA capsules 10 mg: white/light brown (imprinted NVR R10) Bottles of 100.....................................NDC 0078-0424-05 Ritalin LA capsules 20 mg: white (imprinted NVR R20) Bottles of 100.....................................NDC 0078-0370-05 Ritalin LA capsules 30 mg: yellow (imprinted NVR R30) Bottles of 100.....................................NDC 0078-0371-05 Ritalin LA capsules 40 mg: light brown (imprinted NVR R40) Bottles of 100.....................................NDC 0078-0372-05 Ritalin LA capsules 60 mg: light brown/yellow (imprinted NVR R60) Bottles of 30.....................................NDC 0078-0658-15 Store at 25°C (77°F), excursions permitted 15°C-30°C (59°F-86°F). [See USP controlled room temperature] Dispense in tight container (USP)
ANDA Labeling	Methylphenidate hydrochloride extended-release capsules are supplied as: **10 mg:** Hard gelatin capsules, yellow opaque cap printed with "G 10mg" and white opaque body printed with "012" contains white to off-white pellets. Bottles of 100 NDC 70010-012-01 **20 mg:** Hard gelatin capsules, white opaque cap printed with "G 20mg" and white opaque body printed with "013" contains white to off-white pellets. Bottles of 100 NDC 70010-013-01 **30 mg**: Hard gelatin capsules, yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014" contains white to off-white pellets. Bottles of 100 NDC 70010-014-01 **40 mg**: Hard gelatin capsules, yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015" contains white to off-white pellets. Bottles of 100 NDC 70010-015-01 **60 mg**: Hard gelatin capsules, yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets. Bottles of 30 NDC 70010-016-03 Store at 20 to 25°C (68 to 77°F). [See USP Controlled Room Temperature] Dispense in a tight container as defined in the USP with a child-resistant closure.

Reviewer Assessment:

Are all of the submitted labels and labeling reflected in the How Supplied section? **YES**
Is the description (e.g., scoring, color, 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? **PENDING CHEMISTRY REVIEW**
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? **NA**
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? **NA**

Reviewer Comments:
Applicant will be requested to delete "USP" in the established name in the HOW SUPPLIED section of the Prescribing Information.

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**
Has the Applicant committed to provide a sufficient number of medication guides? **NO**
Is the phonetic spelling of the proprietary or established name present? **YES**
Is FDA 1-800-FDA-1088 phone number included? **YES**

Reviewer Comments:
Applicant will be requested to provide a sufficient number of medication guides for each package size.

3.1.3 <u>RX: OTHER PATIENT LABELING</u>

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? **CLICK HERE**
Is the patient labeling the same as the model labeling, except for allowable differences? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.1.4 <u>RX: CONTAINER LABEL</u>

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

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**
If the container label is too small to contain all required information, does it 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): **NO**
- Medication Guide Pharmacist instructions per 21 CFR 208.24(d): **YES**
- Controlled substance symbol: **NO**
- Usual Dosage statement: **NO**
- 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 USP recommendations and/or differences in test methods (e.g., organic impurities, assay) reflected on the label(s)? **NA**
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? **YES**
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 requirements met for the required label statements (21 CFR 201.15 and 21 CFR 201.100)? **YES**

Reviewer Comments:
[redacted] (b) (4)

(b) (4)

[redacted]

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 <7> Labeling **CLICK HERE**
If volume is less than 1 mL, is strength per fraction of a milliliter the only expression of strength? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

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? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

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? **CLICK HERE**
Is there a prominent, boxed declaration reading "Pharmacy Bulk Package – Not for Direct Infusion" on the principal display panel following the expression of strength? **CLICK HERE**
Does the container label include graduation marks? **CLICK HERE**
Are instructions for reconstitution and resultant concentration provided, if space permits? **CLICK HERE**
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? **CLICK HERE**
Is the quantity or proportion of all inactive ingredients listed on label as required under 21 CFR 201.100(b)(5)(iii)? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

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)? **CLICK HERE**
Do proprietary name, established name, strength, bar code, and manufacturer appear accurately on each blister cell? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

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? **CLICK HERE** 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? **CLICK HERE**
If country of origin is not on Container, does it appear on outer packaging labeling? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

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? **CLICK HERE**
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)? **CLICK HERE**
Did firm submit a Labeling Format Information Table to evaluate the font size? **CLICK HERE**
Is the applicant's "patent carve out" acceptable? **CLICK HERE**
Is the applicant's "exclusivity carve out" acceptable? **CLICK HERE**
Is the established name for this ANDA acceptable? **CLICK HERE**
Is title case used in expressing the established name? **CLICK HERE**
Are established name (proprietary name, if applicable) and strength the most prominent information on the Principal Display Panel? **CLICK HERE**
Is the following information properly displayed?

Pharmacological category: **CLICK HERE**
Net quantity statement: **CLICK HERE**
Route(s) of administration (other than oral): **CLICK HERE**
Warnings (if any) or cautionary statements (if any): **CLICK HERE**
NDC: **CLICK HERE**
Bar code per 21 CFR 201.25(c)(2): **CLICK HERE**
Is the Manufacturer/Distributor/Packager statement acceptable? **CLICK HERE**
For foreign manufacturers, does the labeling have the country of origin? **CLICK HERE**
Are the required USP recommendations and/or differences in test methods (e.g., dissolution, organic impurities, assay) reflected in the labeling? **CLICK HERE**
Is the storage statement acceptable? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
Are multiple strengths differentiated by use of different color or other acceptable means? **CLICK HERE**
Are the labels of related products differentiated to avoid selection errors? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.1 OTC: INACTIVE INGREDIENTS COMPARISON

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? **CLICK HERE**
Are the inactive ingredients listed in alphabetical order? **CLICK HERE**
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? **CLICK HERE**
Does any inactive ingredient require special warnings, precautions, or labeling statements? **CLICK HERE**
If the labeling includes a "Does not contain…" statement, is it acceptable/allowed? **CLICK HERE** Has the statement been verified by chemistry? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.1.2 OTC: HOW SUPPLIED AND STORAGE INFORMATION

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.

Table 9: Comparison of Model Labeling to ANDA finished product	
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? **CLICK HERE**
Is there any difference in scoring configuration between the ANDA and the Model Labeling? **CLICK HERE**
Are the packaging sizes and configurations acceptable as compared to the Model Labeling? **CLICK HERE**
If the packaging configuration is different than the Model Labeling, does it require addition or deletion of labeling statements? **CLICK HERE**
Is the storage statement acceptable as compared to the Model Labeling? **NA**
Is the storage statement acceptable as compared to USP? **CLICK HERE**

Reviewer Comments:
Click here to enter text.

3.2.2 OTC: PATIENT LABELING

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

Reviewer Assessment:

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

Reviewer Comments:
Click here to enter text.

3.3 CONTAINER/CLOSURE

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, Ophthalmic and Controlled Substances **CHEMISTRY REVIEW PENDING**

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 <7> Labeling? **NA**
What is the cap color? Click here to enter text.

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

Reviewer Comments: Bottles of 30 tablets (60 mg) and 100 tablets (10 mg, 20 mg, 30 mg, and 40 mg) have child-resistant caps.

(b) (4)

[redacted]

3.4 CALCULATIONS FOR CONTENTS AND VERIFICATION OF ALUMINUM CONTENT

Is calculation of ingredient(s) or verification of aluminum content required? **NO**

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.

Reviewer Assessment:

Are the stated contents in the table above acceptable? **CLICK HERE**

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? **CLICK HERE**

Are the labeling requirements met per 21 CFR 201.323? **CLICK HERE**

Reviewer Comments:

Click here to enter text.

3.5 STRUCTURED PRODUCT LABELING (SPL) DATA ELEMENTS

Was SPL submitted? **YES**

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 (Cite source: e.g., Chemistry Review, Product Specification in 3.2.P.5.1, and Commercial Batch Record in 3.2.P.3.3)**
10 mg, 20 mg, 30 mg, and 60 mg extended-release capsules	(b) (4) [redacted]	[redacted]

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? **PENDING CHEMISTRY REVIEW**
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: Please note that D&C Yellow No.10 is listed for the 10 mg, 20 mg, and 30 mg strengths; FD&C Yellow No. 5 is listed for the 20 mg and 40 mg strengths; and FD&C Yellow No. 6 is listed for 20 mg strength in the inactive ingredients section of the data elements of the SPL. (b) (4) [redacted]

(b) (4)

[redacted]

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5. SPECIAL CONSIDERATIONS

Please note that the RLD for this application is Ritalin LA; [redacted] (b) (4) Lastly, there is no USP monograph for this drug product.

6. OVERALL ASSESSMENT OF MATERIALS REVIEWED

Table 12: Review Summary of Container Label and Carton Labeling				
	Final or Draft or NA	**Packaging Sizes**	**Submission Received Date**	**Recommendation**
Container	Final	100's	4/2/2018	Revise
Blister	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
Carton	N A	Click here to enter text.	Click here to enter text.	Click here to enter text.
(Other – specify)	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
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	Draft *	Click here to enter text.	4/2/2018	Revise
Medication Guide	Draft*	Click here to enter text.	4/2/2018	Revise
Patient Information	NA	Click here to enter text.	Click here to enter text.	Click here to enter text.
SPL Data Elements	Click here to enter text.	1/2018	4/2/2018	Revise

*Prescribing information (PI) and Medication Guide (MG) were submitted in draft and final printed labeling. However, draft PI and MG were used to compare with the reference listed drug labeling.

Jeanne Skanchy

Digitally signed by Jeanne Skanchy
Date: 6/14/2018 05:55:11PM
GUID: 508da70800028bd836b811ba0ad71161

Angela Payne

Digitally signed by Angela Payne
Date: 6/25/2018 08:25:42AM
GUID: 508da70600028ab611d2ba935d5074a6

[redacted]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211796

<u>CHEMISTRY REVIEW(s)</u>

Recommendation: Approval

ANDA 211796
Review 2

Drug Name/Dosage Form	Methylphenidate Hydrochloride Extended-Release Capsules
Strength	10 mg, 20 mg, 30 mg, 40 mg, and 60 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Granules Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission/Response to CRL (eCTD 0009)	02/26/2019	Quality
Quality/Response to IR (eCTD 0008)	12/06/2018	Quality
Quality/Response to IR (eCTD 0007)	11/05/2018	Quality
Quality/Response to DRL (eCTD 0006)	10/22/2018	Quality
Quality/Response to IR (eCTD 0003)	06/27/2018	Quality
New application (eCTD 0001)	04/02/2018	All

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Oluyomi Bakare	David Skanchy
Drug Product	Jingwen Ma	Yanning Lin
Process	Zhong Li	Jiao Yang
Microbiology	N/A	N/A
Facility	Zhong Li	Zhihao Peter Qiu
Biopharmaceutics	Parnali Chatterjee	Om Anand
Regulatory Business Process Manager	Qinghua Ge	N/A
Application Technical Lead	Yanning Lin	N/A
Laboratory (OTR)	Michael Tollon	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) [redacted]	Type II	(b) (4) [redacted]		Adequate	10/24/2018	
	Type III *(if applicable)*					
	Type IV *(if applicable)*					
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is recommended for approval based on the adequate reviews of drug substance, drug product, process, facility and biopharmaceutics.

II. Summary of Quality Assessments

A. Product Overview

Methylphenidate hydrochloride extended-release capsules are a central nervous system stimulant prescription medicine. It is used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Methylphenidate hydrochloride extended-release capsules may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD. Methylphenidate hydrochloride extended-release capsules is a federally controlled substance (CII) because it can be abused or lead to dependence. Methylphenidate hydrochloride extended-release capsules should not be used in children less than 6 years old.

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

Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee	☒ 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 application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Methylphenidate hydrochloride extended-release capsules should not be used in children less than 6 years old.

Duration of Treatment	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.
Maximum Daily Dose	60 mg
Alternative Methods of Administration	To be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of applesauce.

B. Quality Assessment Overview

DMF [redacted], for drug substance, Methylphenidate Hydrochloride manufactured by [redacted]., is found adequate. [redacted]. The drug product is an extended release capsules, [redacted]. The review of drug product is found adequate. No labeling issue was found. The manufacturing process involves [redacted] [redacted] No deficiencies were identified in this review cycle. No facility issue was found. The control limits and method of dissolution of Methylphenidate Hydrochloride extended-release capsules are found adequate by the reviewer of Biopharmaceutics.

C. Special Product Quality Labeling Recommendations (NDA only)

D. Final Risk Assessment (see Attachment)

Final Risk Assessment of ANDA 211796 (Methylphenidate Hydrochloride Extended Release Capsules, USP, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg)

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2
Physical stability (solid state)	36 Medium	(b) (4) [redacted]	Low
Chemical Stability	12 Low	[redacted]	Low
Assay	36 Medium	[redacted]	Low
Content uniformity	36 Medium	[redacted]	Low
Microbial limits	9	[redacted]	

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2
	Low	(b) (4) [redacted]	Low
Dissolution	80 High		Low
Dose dumping from mechanical failure	20 Low		Low

Yanning Lin

Digitally signed by Yanning Lin
Date: 5/03/2019 02:58:37PM
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[redacted]

Adequate

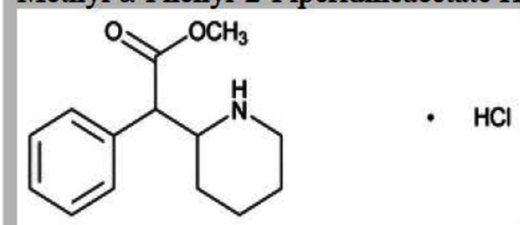
DRUG SUBSTANCE

IQA Review Guide Reference

Product Background: Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

NDA/ANDA (review cycle number): 2

Chemical Name and Structure:
Methyl α-Phenyl-2-Piperidineacetate Hydrochloride



DMF # (if applicable): [redacted] (b) (4)

Applicant Name/DMF Holder: [redacted] (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:
Methylphenidate hydrochloride USP is a white, fine crystalline powder, [redacted] (b) (4)

Maximum Daily Dose (MDD): 60 mg

	Reporting Threshold (RT)	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	0.2%	0.2%

List Submissions being reviewed (table):

	Submission Type	Submission Date

Previous	Original ANDA	04/02/2018
	Response to Information Request - Samples	06/27/2018
	Quality Information	10/22/2018

Highlight Key Outstanding Issues from Last Cycle: [redacted] (b) (4)

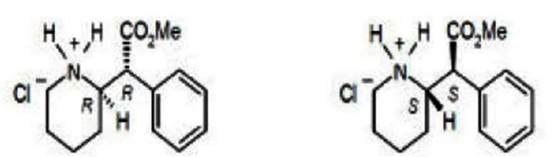
Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): None

S.1 General Information

Summary of the info provided. Information from Application

Below is the general information of the drug substance Methylphenidate Hydrochloride, USP.

Subject	Details
Recommended International Non-proprietary Name (INN)	Methylphenidate Hydrochloride
Chemical Name	Methyl α-Phenyl-2-Piperidineacetate Hydrochloride
Other Non-proprietary Names	Methylphenidate Hydrochloride
Compendia Name	Methylphenidate Hydrochloride, USP
Molecular Formula	$C_{14}H_{19}NO_2$ □HCI
Molecular Weight	269.77
CAS Number	298-59-9 [(±)-*threo*-isomer].
Structure	 (+)-*threo*-Methylphenidate (-)-*threo*-Methylphenidate
DEA Controlled Substance Schedule	II
Pharmacological Class	CNS Stimulant

Subject	Details
Description	White crystalline powder
Solubility Data	[redacted] (b) (4)
pKa	[redacted]
Melting Point	[redacted]
Hygroscopicity	[redacted]

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(b) (4)

[redacted]

Post-Approval Stability Protocol and Commitment

Reviewer's Assessment: ***N/A***

R Regional Information

Comparability Protocols

Reviewer's Assessment: ***N/A***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

Lifecycle Management Considerations

List of Deficiencies: None

Primary Drug Substance Reviewer Name and Date: Jingwen Ma, 08/27/2018, 12/12/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yanning Lin, 09/13/2018 and 12/20/2018

DRUG PRODUCT

IQA Review Guide Reference

Product Background:

NDA/ANDA (review cycle number): 1B

Drug Product Name / Strength: Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

Route of Administration: Oral

Applicant Name: Granules Pharmaceuticals Inc.

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:

List Submissions being reviewed (table):

	Submission Type	**Submission Date**
Previous	Original ANDA	04/02/2018
	Response to Information Request - Samples	06/27/2018
	Quality Information	10/22/2018
	Quality Information	11/05/2018
	Quality Information	12/06/2018
Current	Quality Information	02/26/2019

Highlight Key Outstanding Issues from Last Cycle: The Drug product section is inadequate with minor deficiencies. [redacted] (b) (4)

Concise Description Outstanding Issues Remaining: [redacted] (b) (4)

List Number of Comparability Protocols (ANDA only): None

P.1 Description and Composition

Component/composition table

Granules proposed drug product "Methylphenidate hydrochloride Extended-Release Capsules" is an Extended Release Capsule dosage form, consisting of five strengths (10 mg, 20 mg, 30 mg, 40 mg and 60 mg) and its quantitative composition, function of each excipient is provided in below Table 6 to 5. Refer Module 3.2.P.1 for further information.

Table 6. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 10 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	10.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)	[redacted]	[redacted]
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF ([redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Total Capsule Weight***	100.0	161.3	[redacted]

[redacted] (b) (4)

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 161.3 mg**	**Function**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Titanium Dioxide	[redacted]	[redacted]	[redacted] (b) (	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 10 mg			
Component	% w/w	mg/Capsule	Function
[redacted] (b) (4)			

Table 7. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 20 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 20 mg			
Component	% w/w	mg/Capsule	Function
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	20.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)		
[redacted]			
Cellaburate, NF ([redacted] (b) (4)			
Hypromellose Acetate Succinate, NF [redacted] (b) (4)			
Acetyltributyl Citrate, NF [redacted] (b) (4)			
Talc, USP [redacted] (b) (4)			
[redacted]			
Total Capsule Weight***	100.0	261.6	[redacted]

[redacted] (b) (4)

Component	% w/w per Total Empty Capsule weight of	Amount per Unit (mg/Capsule)	% w/w per Total capsule weight of	Function
[redacted]	[redacted] (b) (4)			[redacted] (b) (4)
Titanium Dioxide				
[redacted]				

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 20 mg				
Component		% w/w	mg/Capsule	Function
Total weight of hard gelatin capsule	100.0	[redacted] (b) (4)	23.3	N/A
[redacted] (b) (4)				

Table 8. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 30 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 30 mg			
Component	% w/w	mg/Capsule	Function
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	30.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4) [redacted] (b) (4)	[redacted] (b) (4)		
[redacted]			
Cellaburate, NF [redacted] (b) (4) [redacted] (b) (4)			
Hypromellose Acetate Succinate, NF [redacted] (b) (4)			
Acetyltributyl Citrate, NF [redacted] (b) (4)			
Talc, USP [redacted] (b) (4)			
[redacted]			
Total Capsule Weight*	100.0	377.0	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	Amount per Unit (mg/Capsule)	% w/w per Total capsule weight of 377.0 mg	Function
[redacted] (b) (4)				
Titanium Dioxide	[redacted] (b) (4)			
FD&C Yellow #5				Colorant
FD&C Yellow #6				Colorant

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 30 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
[redacted] (b) (4)			

Table 9. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 40 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 40 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	40.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)		
[redacted] (b) (4)			
Cellaburate, NF ([redacted] (b) (4)			
Hypromellose Acetate Succinate, NF [redacted] (b) (4)			
Acetyltributyl Citrate, NF [redacted] (b) (4)			
Talc, USP [redacted] (b) (4)			
[redacted]			
Total Capsule Weight*	100.0	497.4	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of** [redacted] (b) (4)	**Function**
[redacted]				[redacted] (b) (4)
Titanium Dioxide	[redacted]			
D&C Yellow #10				Colorant
FD&C Yellow #6				Colorant
[redacted] (b) (4)				

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 40 mg			
Component	% w/w	mg/Capsule	Function
[redacted]	[redacted]	[redacted]	[redacted]

Table 10. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 60 mg			
Component	% w/w	mg/Capsule	Function
Methylphenidate Hydrochloride, USP	[redacted]	60.00	Active ingredient
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]
Talc, USP ([redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total Capsule Weight***	100.0	720.0	[redacted]

[redacted]

Component	[redacted]	Amount per Unit (mg/Capsule)	% w/w per Total capsule weight of 720 mg	Function
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant

[redacted]

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 60 mg			
Component	% w/w	mg/Capsule	Function
[redacted]			

All inactive ingredients, utilized in the formulation as listed in the Inactive Ingredient Database (IID), are within or below the listed levels for orally administered products. Please refer from Table 11 to 10. Each excipient present in is within the potency limits listed for oral dosage forms in the most current FDA/CDER Inactive Ingredient Guide (IIG) as applicable.

Table 11. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted]	10.00	10.00	N/A	
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[1]*Maximum daily dosage per RLD label is one capsule per day as recommended size of dose* [2] *Refer* http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm					

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted] (b) (4)					

Table 12. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted] (b) (4)	20.00	20.00	N/A	
Polyethylene glycol, [redacted] (b) (4)	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Capsule	[redacted] (b) (4)
[redacted] (b) (4)					
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)					
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)					

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted] (b) (4)					

Table 13. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted] (b) (4)	30.00	30.00	N/A	
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)	[redacted]	[redacted]	Oral / Capsule	[redacted] (b) (4)
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF ([redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted] (b) (4)					

Table 14. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted] (b) (4)	40.00	40.00	N/A	
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)	[redacted]	[redacted]	Oral / Capsule	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted]					

Table 15. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted]	60.00	60.00	N/A	
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF ([redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]					
Maximum daily dosage per RLD label is one capsule per day as recommended size of dose Refer http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm					

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(b) (4)

[redacted]

R Regional Information

Environmental

Reviewer's Assessment: ***Adequate***
Categorical exclusion from the requirement of an Environmental Assessment Statement in accordance with Code of Federal Regulations 21 CFR 25.31(a).

Methods Verification Package

Reviewer's Assessment: ***See body of review***

Comparability Protocols

Reviewer's Assessment: ***N/A***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

Lifecycle Management Considerations

List of Deficiencies
None

Primary Drug Product Reviewer Name and Date: Jingwen Ma, 4/22/2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yanning Lin, 4/23/19

LABELING

IQA Review Guide Reference
{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

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

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

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? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable: N/A

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

If "No," explain.

For OTC Drugs and Controlled Substances: N/A

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
10 mg	17.73 mm	yellow opaque cap printed with "G 10mg" and white opaque body printed with "012"

20 mg	17.66 mm	white opaque cap printed with "G 20mg" and white opaque body printed with "013"
30 mg	19.22 mm	yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014"
40 mg	21.55 mm	yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015"
60 mg	23.15 mm	yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets.

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

List of Deficiencies:

Primary Drug Product Reviewer Name and Date: Jingwen Ma, 08/29/2018

Secondary Drug Product Reviewer Name and Date: Yanning Lin, 09/13/2018

Yanning Lin

Digitally signed by Yanning Lin
Date: 5/06/2019 02:48:22PM
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PROCESS

ANDA:	211796
Drug Product Name / Strength:	Methylphenidate Hydrochloride Extended-Release Capsules, 10mg, 20 mg, 30 mg, 40 mg and 60 mg
Route of Administration:	Oral
Applicant Name:	Granules Pharmaceuticals Inc. (GPI)

Review Recommendation: **Adequate**
Theme: **N/A**
Justification: N/A

Review Summary (Rev 03):
The proposed drug product "*Methylphenidate hydrochloride Extended-Release (ER) Capsules*" is an extended release capsule. [redacted] (b) (4) The basis of the application is the reference list drug (RLD), *Ritalin® LA, NDA 021284*, held by Novartis.

[redacted] (b) (4)

Following the review of the application's responses to the 9/25/2018 DRL and 11/30/2018 IR, there is no outstanding process risk that prevents approval of this application. The application is recommended for approval from a process perspective.

List Submissions being reviewed (table):

Submissions Reviewed	Document Date
Quality/Response To Information Request	12/4/2018
Unsolicited Amendment	11/3/2018
Quality/Response to DRL	10/22/2018
Original submission	4/2/2018
Quality/Response to Information Request	N/A

Highlight Key Outstanding Issues from Last Cycle: Inadequate process control strategy for [redacted] (b) (4)
Concise Description Outstanding Issues Remaining: None.
List Number of Comparability Protocols (ANDA only): N/A

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Reviewer's Assessment: ***N/A***

Lifecycle Management Considerations

Reviewer's Assessment: ***N/A***

List of Deficiencies:

None

Primary Process Reviewer Name and Date:

Zhong Li Ph.D.;	Review 01 7/30/2018;	Revised 7/31/2018
	Review 02 11/5/2018;	Revised 11/20/2018
	Review 03 12/6/2018;	Revised 12/7/2018

OQ/OPF/DIA/Branch I

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Jiao yang, Ph.D. December 07, 2018
OPQ/OPF/DPA1/Branch III

Zhong Li

Digitally signed by Zhong Li
Date: 12/07/2018 10:33:22AM
GUID: 5452326f000475beaec6af628762212a

Jiao Yang

Digitally signed by Jiao Yang
Date: 12/07/2018 10:43:38AM
GUID: 563249bd003b5a06d5a7a137f8bd3c53

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FACILITIES

ANDA:	**211796**
Drug Product Name / Strength:	**Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg**
Route of Administration:	**Oral**
Applicant Name:	**Granules Pharmaceuticals Inc.**

Review Summary:

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on the firm inspection history, PAI coverage, and EIR reviews, the manufacturing facilities listed for ANDA 211796 are found to be acceptable.

List Submissions being reviewed (table):	**ANDA-211796-ORIG-1**
Highlight Key Outstanding Issues from Last Cycle:	**N/A**
Concise Description Outstanding Issues Remaining:	**N/A**

3.2.S.2 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
[redacted] (b) (4)			Low	Acceptable

(b) (4)

[redacted]

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(b) (4)

[redacted]

Comparability Protocols

Reviewer's Assessment:	**N/A**

Post-Approval Commitments

Reviewer's Assessment:	**N/A**

Lifecycle Management Considerations

	N/A

List of Deficiencies: **None.**

Primary Facilities Reviewer Name and Date:

Zhong Li

Chemist, OPQ/OPF/DIA/IAB1

Date: 12/5/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur with the primary facility reviewer's recommendation.

Zhihao Peter Qiu, Ph.D.

Branch Chief, OPQ/OPF/DIA/IABI

Date: 12/5/2018

Zhong Li

Digitally signed by Zhong Li
Date: 12/05/2018 08:41:50PM
GUID: 5452326f000475beaec6af628762212a

Zhihao Peter Qiu

Digitally signed by Zhihao Peter Qiu
Date: 12/06/2018 01:21:13AM
GUID: 508da7480002bfb5825e149b2b4eb91d

[redacted]

Adequate

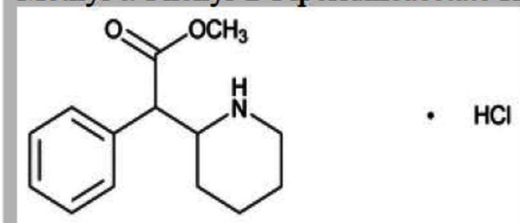
DRUG SUBSTANCE

IQA Review Guide Reference

Product Background: Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

NDA/ANDA (review cycle number): 2

Chemical Name and Structure:
Methyl α-Phenyl-2-Piperidineacetate Hydrochloride



DMF # (if applicable): [redacted] (b) (4)

Applicant Name/DMF Holder: [redacted] (b) (4)

Review Recommendation: **Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:
Methylphenidate hydrochloride USP is a white, fine crystalline powder. [redacted] (b) (4)

Maximum Daily Dose (MDD): 60 mg

	Reporting Threshold (RT)	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	0.2%	0.2%

List Submissions being reviewed (table):

	Submission Type	Submission Date

Previous	Original ANDA	04/02/2018
	Response to Information Request - Samples	06/27/2018
	Quality Information	10/22/2018

Highlight Key Outstanding Issues from Last Cycle: [redacted] (b) (4)

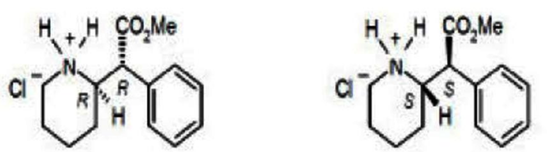
Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): None

S.1 General Information

Summary of the info provided. Information from Application

Below is the general information of the drug substance Methylphenidate Hydrochloride, USP.

Subject	Details
Recommended International Non-proprietary Name (INN)	Methylphenidate Hydrochloride
Chemical Name	Methyl α-Phenyl-2-Piperidineacetate Hydrochloride
Other Non-proprietary Names	Methylphenidate Hydrochloride
Compendia Name	Methylphenidate Hydrochloride, USP
Molecular Formula	$C_{14}H_{19}NO_2$ □HCI
Molecular Weight	269.77
CAS Number	298-59-9 [(±)-*threo*-isomer].
Structure	 (+)-*threo*-Methylphenidate (-)-*threo*-Methylphenidate
DEA Controlled Substance Schedule	II
Pharmacological Class	CNS Stimulant

Subject	Details
Description	White crystalline powder
[redacted] (b) (4)	

(b) (4)

[redacted]

Reviewer's Assessment: ***N/A***

R Regional Information

Comparability Protocols

Reviewer's Assessment: ***N/A***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

Lifecycle Management Considerations

List of Deficiencies: None

Primary Drug Substance Reviewer Name and Date: Jingwen Ma, 08/27/2018, 12/12/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yanning Lin, 09/13/2018 and 12/20/2018

DRUG PRODUCT

IQA Review Guide Reference

Product Background:

NDA/ANDA (review cycle number): 1B

Drug Product Name / Strength: Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

Route of Administration: Oral

Applicant Name: Granules Pharmaceuticals Inc.

***Review Recommendation:* Adequate**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:

List Submissions being reviewed (table):

	Submission Type	Submission Date
Previous	Original ANDA	04/02/2018
	Response to Information Request - Samples	06/27/2018
	Quality Information	10/22/2018
	Quality Information	11/05/2018
	Quality Information	12/06/2018
Current	Quality Information	02/26/2019

Highlight Key Outstanding Issues from Last Cycle: The Drug product section is inadequate with minor deficiencies. The main issues are related to (b) (4) [redacted]

Concise Description Outstanding Issues Remaining: (b) (4) [redacted]

List Number of Comparability Protocols (ANDA only): None

P.1 Description and Composition

Component/composition table

Granules proposed drug product "Methylphenidate hydrochloride Extended-Release Capsules" is an Extended Release Capsule dosage form, consisting of five strengths (10 mg, 20 mg, 30 mg, 40 mg and 60 mg) and its quantitative composition, function of each excipient is provided in below Table 6 to 5. Refer Module 3.2.P.1 for further information.

Table 6. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 10 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted]	10.00	Active ingredient
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]
Talc, USP [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total Capsule Weight***	100.0	161.3	[redacted]

[redacted]

Component	% w/w per Total Empty Capsule weight of	Amount per Unit (mg/Capsule)	% w/w per Total capsule weight of	Function
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 10 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
[redacted]			

Table 7. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 20 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 20 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted]	20.00	Active ingredient
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF ([redacted]	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]
Talc, USP [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total Capsule Weight***	100.0	261.6	[redacted]

[redacted]

Component	[redacted]	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 261.6 mg**	**Function**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 20 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
[redacted] (b) (4)			

Table 8. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 30 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 30 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	30.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4) [redacted]	[redacted] (b) (4)		
[redacted] (b) (4)			
Cellaburate, NF ([redacted] (b) (4) [redacted]			
Hypromellose Acetate Succinate, NF [redacted] (b) (4)			
Acetyltributyl Citrate, NF [redacted] (b) (4))			
Talc, USP [redacted] (b) (4)			
[redacted] (b) (4)			
Total Capsule Weight***	100.0	377.0	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 377.0 mg**	**Function**
[redacted] (b) (4)		[redacted] (b) (4)		[redacted] (b) (4)
Titanium Dioxide				
FD&C Yellow #5				Colorant
FD&C Yellow #6				Colorant

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 30 mg			
Component	% w/w	mg/Capsule	Function
[redacted] (b) (4)			

Table 9. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 40 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 40 mg			
Component	% w/w	mg/Capsule	Function
Methylphenidate Hydrochloride, USP	8.04	[redacted] (b) (4)	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4) [redacted]	[redacted] (b) (4)		
[redacted] (b) (4)			
Cellaburate, NF [redacted] (b) (4) [redacted]			
Hypromellose Acetate Succinate, NF [redacted] (b) (4)			
Acetyltributyl Citrate, NF [redacted] (b) (4)			
Talc, USP [redacted] (b) (4)			
[redacted] (b) (4)			
Total Capsule Weight* **	100.0	497.4	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	Amount per Unit (mg/Capsule)	% w/w per Total capsule weight of 497.4 mg	Function
[redacted] (b) (4)				
Titanium Dioxide	[redacted]			
D&C Yellow #10				Colorant
FD&C Yellow #6				Colorant
[redacted] (b) (4)				

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 40 mg			
Component	% w/w	mg/Capsule	Function
[redacted]	[redacted]	[redacted]	[redacted]

Table 10. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 60 mg			
Component	% w/w	mg/Capsule	Function
Methylphenidate Hydrochloride, USP	[redacted]	60.00	Active ingredient
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF ([redacted]	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF ([redacted]	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]
Talc, USP ([redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total Capsule Weight* **	100.0	720.0	[redacted]

[redacted]

Component	[redacted]	Amount per Unit (mg/Capsule)	% w/w per Total capsule weight of 720 mg	Function
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant

[redacted]

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 60 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
[redacted]			

All inactive ingredients, utilized in the formulation as listed in the Inactive Ingredient Database (IID), are within or below the listed levels for orally administered products. Please refer from Table 11 to 10. Each excipient present in is within the potency limits listed for oral dosage forms in the most current FDA/CDER Inactive Ingredient Guide (IIG) as applicable.

Table 11. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg					
Component	**% w/w**	**Amount per Unit (mg/Capsule)**	**Maximum amount per MDD (mg/MDD)[1]**	**IIG Limits as per database last updated on January 31, 2018[2]**	
				Route; Oral Dosage Form	**Maximum Potency (mg)**
Methylphenidate Hydrochloride, CII	[redacted]	10.00	10.00	N/A	
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP ([redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	1.6483	1.6483	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	0.0130	0.0130	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	0.0006	0.0006	Oral / Capsule	[redacted]
[redacted]					
[1]Maximum daily dosage per RLD label is one capsule per day as recommended size of dose [2] *Refer* http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm					

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted] (b) (4)					

Table 12. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted] (b) (4)	20.00	20.00	N/A	
Polyethylene glycol, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Capsule	[redacted] (b) (4)
[redacted] (b) (4)					
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)					
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)					

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted]					

Table 13. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted]	30.00	30.00	N/A	
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted]					

Table 14. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted]	40.00	40.00	N/A	
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted] (b) (4)					

Table 15. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted] (b) (4)	60.00	60.00	N/A	
Polyethylene glycol, NF [redacted] (b) (4) [redacted]	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Capsule	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Cellaburate, NF (Cellulose Acetate Butyrate [redacted] (b) (4) [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)					
			(b) (4)		
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)					

[1]*Maximum daily dosage per RLD label is one capsule per day as recommended size of dose* [2] *Refer* http://www.accessdata.fda.gov/scripts/cder/iig/index.Cfm

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(b) (4)

[redacted]

R Regional Information

Environmental

Reviewer's Assessment: ***Adequate***
Categorical exclusion from the requirement of an Environmental Assessment Statement in accordance with Code of Federal Regulations 21 CFR 25.31(a).

Methods Verification Package

Reviewer's Assessment: ***See body of review***

Comparability Protocols

Reviewer's Assessment: ***N/A***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

Lifecycle Management Considerations

List of Deficiencies
None

Primary Drug Product Reviewer Name and Date: Jingwen Ma, 4/22/2019

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yanning Lin, 4/23/19

LABELING

IQA Review Guide Reference
{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

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

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

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? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable: N/A

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

If "No," explain.

For OTC Drugs and Controlled Substances: N/A

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
10 mg	17.73 mm	yellow opaque cap printed with "G 10mg" and white opaque body printed with "012"

20 mg	17.66 mm	white opaque cap printed with "G 20mg" and white opaque body printed with "013"
30 mg	19.22 mm	yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014"
40 mg	21.55 mm	yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015"
60 mg	23.15 mm	yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets.

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

List of Deficiencies:

Primary Drug Product Reviewer Name and Date: Jingwen Ma, 08/29/2018

Secondary Drug Product Reviewer Name and Date: Yanning Lin, 09/13/2018

Yanning Lin

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Date: 5/06/2019 02:48:22PM
GUID: 508da704000288d616a99128e1dd2b45

[redacted]

Recommendation: Approval

ANDA 211796
Review 2

Drug Name/Dosage Form	Methylphenidate Hydrochloride Extended-Release Capsules
Strength	10 mg, 20 mg, 30 mg, 40 mg, and 60 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Granules Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Resubmission/Response to CRL (eCTD 0009)	02/26/2019	Quality
Quality/Response to IR (eCTD 0008)	12/06/2018	Quality
Quality/Response to IR (eCTD 0007)	11/05/2018	Quality
Quality/Response to DRL (eCTD 0006)	10/22/2018	Quality
Quality/Response to IR (eCTD 0003)	06/27/2018	Quality
New application (eCTD 0001)	04/02/2018	All

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Oluyomi Bakare	David Skanchy
Drug Product	Jingwen Ma	Yanning Lin
Process	Zhong Li	Jiao Yang
Microbiology	N/A	N/A
Facility	Zhong Li	Zhihao Peter Qiu
Biopharmaceutics	Parnali Chatterjee	Om Anand
Regulatory Business Process Manager	Qinghua Ge	N/A
Application Technical Lead	Yanning Lin	N/A
Laboratory (OTR)	Michael Tollon	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) [redacted]	Type II	(b) (4) [redacted]		Adequate	10/24/2018	
	Type III *(if applicable)*					
	Type IV *(if applicable)*					
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is recommended for approval based on the adequate reviews of drug substance, drug product, process, facility and biopharmaceutics.

II. Summary of Quality Assessments

A. Product Overview

Methylphenidate hydrochloride extended-release capsules are a central nervous system stimulant prescription medicine. It is used for the treatment of Attention-Deficit Hyperactivity Disorder (ADHD). Methylphenidate hydrochloride extended-release capsules may help increase attention and decrease impulsiveness and hyperactivity in patients with ADHD. Methylphenidate hydrochloride extended-release capsules is a federally controlled substance (CII) because it can be abused or lead to dependence. Methylphenidate hydrochloride extended-release capsules should not be used in children less than 6 years old.

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

Final recommended dissolution method/specification acknowledged by Firm?	DD, BC or designee	☒ 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 application compliant with USP <232/233> requirements or ICH Q3D (regarding elemental impurities)?	DD, BC or designee	☒ Yes ☐ No *(see comments) ☐ N/A

Proposed Indication(s) including Intended Patient Population	Indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD). Methylphenidate hydrochloride extended-release capsules should not be used in children less than 6 years old.

Duration of Treatment	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.
Maximum Daily Dose	60 mg
Alternative Methods of Administration	To be swallowed as whole capsules or alternatively may be administered by sprinkling the capsule contents on a small amount of applesauce.

B. Quality Assessment Overview

DMF [redacted] (b) (4), for drug substance, Methylphenidate Hydrochloride manufactured by [redacted] (b) (4) is found adequate. [redacted] (b) (4). The drug product is an extended release capsules, [redacted] (b) (4) The review of drug product is found adequate. No labeling issue was found. The manufacturing process involves [redacted] (b) (4). No deficiencies were identified in this review cycle. No facility issue was found. The control limits and method of dissolution of Methylphenidate Hydrochloride extended-release capsules are found adequate by the reviewer of Biopharmaceutics.

C. Special Product Quality Labeling Recommendations (NDA only)

D. Final Risk Assessment (see Attachment)

Final Risk Assessment of ANDA 211796 (Methylphenidate Hydrochloride Extended Release Capsules, USP, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg)

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2
Physical stability (solid state)	36 Medium	(b) (4) [redacted]	Low
Chemical Stability	12 Low	[redacted]	Low
Assay	36 Medium	[redacted]	Low
Content uniformity	36 Medium	[redacted]	Low
Microbial limits	9	[redacted]	

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #2
	Low	(b) (4) [redacted]	Low
Dissolution	80 High	[redacted]	Low
Dose dumping from mechanical failure	20 Low	[redacted]	Low

Yanning Lin

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[redacted]

Recommendation: Complete Response - Minor

ANDA 211796
Review 1B

Drug Name/Dosage Form	Methylphenidate Hydrochloride Extended-Release Capsules
Strength	10 mg, 20 mg, 30 mg, 40 mg, and 60 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Granules Pharmaceuticals Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Quality/Response to IR (eCTD 0008)	12/06/2018	Quality
Quality/Response to IR (eCTD 0007)	11/05/2018	Quality
Quality/Response to DRL (eCTD 0006)	10/22/2018	Quality
Quality/Response to IR (eCTD 0003)	06/27/2018	Quality
New application (eCTD 0001)	04/02/2018	All

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Oluyomi Bakare	David Skanchy
Drug Product	Jingwen Ma	Yanning Lin
Process	Zhong Li	Jiao Yang
Microbiology	N/A	N/A
Facility	Zhong Li	Zhihao Peter Qiu
Biopharmaceutics	Parnali Chatterjee	Om Anand
Regulatory Business Process Manager	Qinghua Ge	N/A
Application Technical Lead	Yanning Lin	N/A
Laboratory (OTR)	Michael Tollon	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) [redacted]	Type II	(b) (4) [redacted]		Adequate	7/28/2018	
	Type III *(if applicable)*					
	Type IV *(if applicable)*					
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics				
Pharmacology/Toxicology				
CDRH				
Clinical				
Other				

Abbreviated Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

The application is not recommended for approval due to quality related deficiencies summarized in Section II. OPQ recommends issuing a Complete Response Letter – **Minor**.

II. Quality Assessment Overview

A. Drug Substance, Drug Product, and Labeling: Inadequate-Minor

DMF [redacted] (b) (4), for drug substance, Methylphenidate Hydrochloride manufactured by [redacted] (b) (4)., is adequate. [redacted] (b) (4)

The drug product is an extended release capsules, [redacted] (b) (4). One minor deficiency was identified [redacted] (b) (4).

No labeling issue was found.

B. Process: Adequate

The manufacturing process involves [redacted] (b) (4) [redacted] No deficiencies were identified in this review cycle.

C. Facility: Adequate

No facility issue was found.

D. Biopharmaceutics: Inadequate-Minor

The proposed in vitro dissolution method is the FDA recommended method. Minor deficiencies were identified related to the proposed dissolution specification.

E. Microbiology (if applicable): NA

List of Deficiencies for Complete Response

I. Drug Substance Deficiencies
None

II. Drug Product Deficiencies

1) (b) (4) [redacted]

2) Please submit the following drug product samples:
  a. Your 60 mg capsules from the 3 exhibit batches
  b. Unexpired 60 mg RLD

To
Attn: Qinghua Ge PQRPM

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
WO75 RM4621A
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

III. Environmental Deficiencies
None

IV. Labeling Deficiencies
None

V. Process Deficiencies
None

VI. Facilities Deficiencies
None

VII. Biopharmaceutics Deficiencies

1) You mentioned the pH of the FDA recommended Dissolution Method as pH 6.8 (page # 5 of the dissolution report comparison). Please clarify the pH of the phosphate buffer in the FDA dissolution method used for dissolution testing of your proposed drug product.

2) Based on the dissolution data available, we determined that your proposed dissolution acceptance criteria for the proposed product are [redacted]. Therefore, implement the following dissolution method and acceptance criteria for each strength of your proposed product, Methylphenidate Hydrochloride Extended-Release Capsules.

Method: Acid Stage: 500 mL of 0.01 N HCl (deaerated) for 2 hours; Buffer Stage: 500 mL of pH 6.8 Phosphate buffer (deaerated) using USP Apparatus 1 (basket) at 100 rpm

Acceptance Criteria:

Time (hrs)	Percent (%) Release
Acid Stage	
0.5 hr	NLT [redacted]%
2.0 hrs	NMT [redacted]%
Buffer Stage (after 2 hours in acid stage)	
3.0 hrs*	[redacted]%
6.0 hrs*	NLT [redacted]%

[redacted]

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

VIII. Microbiology Deficiencies
None

IX. Other Deficiencies (specify discipline)
None

Application Technical Lead Name and Date: Yanning Lin and 1/4/2019

Yanning Lin

Digitally signed by Yanning Lin
Date: 1/04/2019 02:53:46PM
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[redacted]

BE inadequate major, data analysis issue (9/17/2018), response 10/04/2018
Process Adequate (12/7/2018)
Facility Adequate (12/5/2018)
Biopharm pending

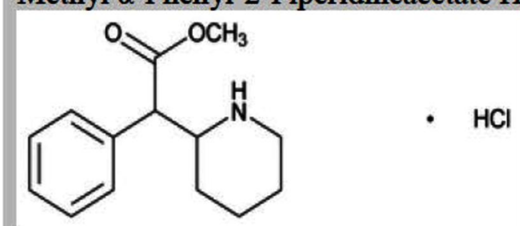
DRUG SUBSTANCE

IQA Review Guide Reference

Product Background: Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

NDA/ANDA (review cycle number): 1B

Chemical Name and Structure:
Methyl α-Phenyl-2-Piperidineacetate Hydrochloride



DMF # (if applicable): [redacted] (b) (4)

Applicant Name/DMF Holder: [redacted] (b) (4)

Review Recommendation: **Inadequate - Minor**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:
Methylphenidate hydrochloride USP is a white, fine crystalline powder, [redacted] (b) (4).

Maximum Daily Dose (MDD): 60 mg

	Reporting Threshold (RT)	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	0.2%	0.2%

List Submissions being reviewed (table):

	Submission Type	Submission Date
Previous	Original ANDA	04/02/2018
	Response to Information Request - Samples	06/27/2018
Current	Quality Information	10/22/2018

Highlight Key Outstanding Issues from Last Cycle: [redacted] (b) (4)

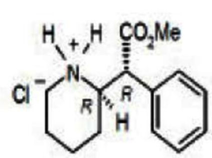
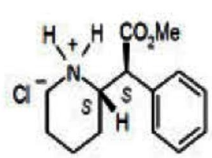
Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): None

S.1 General Information

Summary of the info provided. Information from Application

Below is the general information of the drug substance Methylphenidate Hydrochloride, USP.

Subject	Details
Recommended International Non-proprietary Name (INN)	Methylphenidate Hydrochloride
Chemical Name	Methyl α-Phenyl-2-Piperidineacetate Hydrochloride
Other Non-proprietary Names	Methylphenidate Hydrochloride
Compendia Name	Methylphenidate Hydrochloride, USP
Molecular Formula	C14H19NO2 □HCl
Molecular Weight	269.77
CAS Number	298-59-9 [(±)-*threo*-isomer].
Structure	 (+)-*threo*-Methylphenidate  (-)-*threo*-Methylphenidate
DEA Controlled Substance Schedule	II
Pharmacological Class	CNS Stimulant

Subject	Details
Description	White crystalline powder

[redacted] (b) (4)

10 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

Lifecycle Management Considerations

List of Deficiencies: None

Primary Drug Substance Reviewer Name and Date: Jingwen Ma, 08/27/2018, 12/12/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yanning Lin, 09/13/2018 and 12/20/2018

DRUG PRODUCT

IQA Review Guide Reference

Product Background:

NDA/ANDA (review cycle number): 1B

Drug Product Name / Strength: Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

Route of Administration: Oral

Applicant Name: Granules Pharmaceuticals Inc.

Review Recommendation: **Inadequate - Minor**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:

List Submissions being reviewed (table):

	Submission Type	Submission Date
Previous	Original ANDA	04/02/2018
	Response to Information Request - Samples	06/27/2018
Current	Quality Information	10/22/2018
	Quality Information	11/05/2018
	Quality Information	12/06/2018

Highlight Key Outstanding Issues from Last Cycle: The Drug product section is inadequate with minor deficiencies. The main issues are related to [redacted] (b) (4)

Concise Description Outstanding Issues Remaining: [redacted] (b) (4)

List Number of Comparability Protocols (ANDA only): None

P.1 Description and Composition

Component/composition table

Granules proposed drug product "Methylphenidate hydrochloride Extended-Release Capsules" is an Extended Release Capsule dosage form, consisting of five strengths (10 mg, 20 mg, 30 mg, 40 mg and 60 mg) and its quantitative composition, function of each excipient is provided in below Table 6 to 5. Refer Module 3.2.P.1 for further information.

Table 6. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 10 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	10.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4) [redacted]	[redacted]	[redacted] (b) (4)	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Cellaburate, NF ([redacted] (b) (4) [redacted]	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF ([redacted] (b) (4) [redacted]	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Total Capsule Weight***	100.0	161.3	[redacted]

[redacted] (b) (4)

****Components of hard gelatin capsule shell Size 2**				
Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 161.3 mg**	**Function**
[redacted]	[redacted]	[redacted]	[redacted] (b) (4)	[redacted] (b) (4)
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant

[redacted] (b) (4)

Table 7. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 20 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 20 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	20.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4) [redacted]	[redacted]	[redacted]	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Cellaburate, NF [redacted] (b) (4) [redacted]	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total Capsule Weight* **	100.0	261.6	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of** [redacted] (b) (4)	**Function**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)

Table 8. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 30 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 30 mg			
Component	**% w/w**	**mg/Capsule**	**Function**

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 30 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted]	30.00	Active ingredient
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF ([redacted]	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]
Talc, USP ([redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total Capsule Weight***	100.0	377.0	[redacted]

[redacted]

Component	[redacted]	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 377.0 mg**	**Function**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant

[redacted]

Table 9. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 40 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 40 mg			
Component	**% w/w**	**mg/Capsule**	**Function**

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 40 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	40.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)	[redacted]	[redacted]
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4))	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Total Capsule Weight* **	100.0	497.4	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 497.4 mg**	**Function**
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]

Table 10. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 60 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	8.33	60.00	Active ingredient

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 60 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)	6.00	Binder
[redacted] (b) (4)			
Cellaburate, NF ([redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
[redacted] (b) (4)			
Total Capsule Weight*	100.0	720.0	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 720 mg**	**Function**
Gelatin	[redacted] (b) (4)	[redacted]	[redacted]	[redacted] (b) (4)
[redacted] (b) (4)				
D&C Yellow #10	[redacted]	[redacted]	[redacted]	
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant

[redacted] (b) (4)

All inactive ingredients, utilized in the formulation as listed in the Inactive Ingredient Database (IID), are within or below the listed levels for orally administered products. Please refer from Table 11 to 10. Each excipient present in is within the potency limits listed for oral dosage forms in the most current FDA/CDER Inactive Ingredient Guide (IIG) as applicable.

Table 11. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg

Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	(b) (4) [redacted]	10.00	10.00	N/A	
Polyethylene glycol, NF (b) (4) [redacted]	[redacted]	[redacted]	(b) (4) [redacted]	Oral / Capsule	(b) (4) [redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(b) (4) [redacted]
Cellaburate, NF (b) (4) [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF (b) (4) [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF (b) (4) [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP (b) (4) [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(b) (4) [redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(b) (4) [redacted]

Table 12. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	(b) (4) [redacted]	20.00	20.00	N/A	
Polyethylene glycol, NF (b) (4) [redacted]	[redacted]	[redacted]	(b) (4) [redacted]	Oral / Capsule	(b) (4) [redacted]

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 13. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted] (b) (4)	30.00	30.00	N/A	
Polyethylene glycol, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Capsule	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP ([redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 14. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted]	40.00	40.00	N/A	
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Tablet	[redacted] (b) (4)
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted] (b) (4)	60.00	60.00	N/A	
Polyethylene glycol, NF [redacted] (b) (4) [redacted]	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Capsule	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Cellaburate, NF [redacted] (b) (4) [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (b) (4)

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted]					
Titanium Dioxide	[redacted]				
D&C Yellow #10					
FD&C Yellow #5					
FD&C Yellow #6					
[redacted]					

(b) (4)

(b) (4)

(b) (4)

GPI used same excipients as Reference standard formulation 60 mg used. GPI used different excipients than RLD formulation strengths (10 mg, 20 mg, 30 mg and 40 mg) used. These differences will not expect to have potential concerns with respect to the therapeutic equivalence and are just excipients. The following Table 16 lists the ingredients and the function of Granules Pharmaceuticals Inc. (GPI) and Reference Drug Products. Please refer 3.2.P.1 for further information.

Table 16. Comparison between GPI and RLD formulation

Ingredients of GPI's Methylphenidate HCl ER Capsules	Ingredients of RS (60 mg) and RLD (10 mg, 20 mg, 30 mg, 40 mg)[1]	Function
[redacted]		

(b) (4)

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R Regional Information

Environmental

Reviewer's Assessment: ***Adequate***
Categorical exclusion from the requirement of an Environmental Assessment Statement in accordance with Code of Federal Regulations 21 CFR 25.31(a).

Methods Verification Package

Reviewer's Assessment: ***See body of review***

Comparability Protocols

Reviewer's Assessment: ***N/A***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

Lifecycle Management Considerations

List of Deficiencies

1. [redacted] (b) (4)

2. Please submit the following drug product samples:
   - Your 60 mg capsules from the 3 exhibit batches
   - Unexpired 60 mg RLD

To
Attn: Qinghua Ge PQRPM

Office of Pharmaceutical Quality
Center for Drug Evaluation and Research
WO75 RM4621A
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Primary Drug Product Reviewer Name and Date: Jingwen Ma, 9/10/2018, 9/17/2018, 12/18/2018, 12/31/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yanning Lin, 09/15/2018 and 12/20/2018

LABELING

IQA Review Guide Reference
{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

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

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

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? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable: N/A

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

If "No," explain.

For OTC Drugs and Controlled Substances: N/A

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
10 mg	17.73 mm	yellow opaque cap printed with "G 10mg" and white opaque body printed with "012"
20 mg	17.66 mm	white opaque cap printed with "G

		20mg" and white opaque body printed with "013"
30 mg	19.22 mm	yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014"
40 mg	21.55 mm	yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015"
60 mg	23.15 mm	yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets.

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

List of Deficiencies:

Primary Drug Product Reviewer Name and Date: Jingwen Ma, 08/29/2018

Secondary Drug Product Reviewer Name and Date: Yanning Lin, 09/13/2018

Yanning Lin

Digitally signed by Yanning Lin
Date: 1/02/2019 02:52:54PM
GUID: 508da704000288d616a99128e1dd2b45

[redacted]

PROCESS

ANDA:	211796
Drug Product Name / Strength:	Methylphenidate Hydrochloride Extended-Release Capsules, 10mg, 20 mg, 30 mg, 40 mg and 60 mg
Route of Administration:	Oral
Applicant Name:	Granules Pharmaceuticals Inc. (GPI)

Review Recommendation: **Adequate**
Theme: **N/A**
Justification: N/A

Review Summary (Rev 03):
The proposed drug product "*Methylphenidate hydrochloride Extended-Release (ER) Capsules*" is an extended release capsule, [redacted] (b) (4) The basis of the application is the reference list drug (RLD), *Ritalin® LA, NDA 021284*, held by Novartis.

[redacted] (b) (4).

Following the review of the application's responses to the 9/25/2018 DRL and 11/30/2018 IR, there is no outstanding process risk that prevents approval of this application. The application is recommended for approval from a process perspective.

List Submissions being reviewed (table):

Submissions Reviewed	Document Date
Quality/Response To Information Request	12/4/2018
Unsolicited Amendment	11/3/2018
Quality/Response to DRL	10/22/2018
Original submission	4/2/2018
Quality/Response to Information Request	N/A

Highlight Key Outstanding Issues from Last Cycle: [redacted] (b) (4)

Concise Description Outstanding Issues Remaining: None.
List Number of Comparability Protocols (ANDA only): N/A

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Reviewer's Assessment: ***N/A***

Lifecycle Management Considerations

Reviewer's Assessment: ***N/A***

List of Deficiencies:

None

Primary Process Reviewer Name and Date:

Zhong Li Ph.D.;	Review 01	7/30/2018;	Revised 7/31/2018
	Review 02	11/5/2018;	Revised 11/20/2018
	Review 03	12/6/2018;	Revised 12/7/2018

OQ/OPF/DIA/Branch I

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Jiao yang, Ph.D. December 07, 2018
OPQ/OPF/DPA1/Branch III

Zhong Li

Digitally signed by Zhong Li
Date: 12/07/2018 10:33:22AM
GUID: 5452326f000475beaec6af628762212a

Jiao Yang

Digitally signed by Jiao Yang
Date: 12/07/2018 10:43:38AM
GUID: 563249bd003b5a06d5a7a137f8bd3c53

[redacted]

FACILITIES

ANDA:	**211796**
Drug Product Name / Strength:	**Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg**
Route of Administration:	**Oral**
Applicant Name:	**Granules Pharmaceuticals Inc.**

Review Summary:

Following a review of the application and inspectional documents, there are no significant, outstanding manufacturing risks that prevent approval of this application. Based on the firm inspection history, PAI coverage, and EIR reviews, the manufacturing facilities listed for ANDA 211796 are found to be acceptable.

List Submissions being reviewed (table):	**ANDA-211796-ORIG-1**
Highlight Key Outstanding Issues from Last Cycle:	**N/A**
Concise Description Outstanding Issues Remaining:	**N/A**

3.2.S.2 Manufacture

Summary of Facility Information:

Establishment Name and Address	FEI Number	Responsibilities and profile codes	Initial Risks Identified	Final Recommendation
[redacted]	[redacted]	[redacted]	[redacted] (b) (4)	Acceptable

(b) (4)

[redacted]

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(b) (4)

[redacted]

Comparability Protocols

Reviewer's Assessment:	**N/A**

Post-Approval Commitments

Reviewer's Assessment:	**N/A**

Lifecycle Management Considerations

N/A

List of Deficiencies: **None.**

Primary Facilities Reviewer Name and Date:

Zhong Li

Chemist, OPQ/OPF/DIA/IAB1

Date: 12/5/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

I concur with the primary facility reviewer's recommendation.

Zhihao Peter Qiu, Ph.D.

Branch Chief, OPQ/OPF/DIA/IABI

Date: 12/5/2018

Zhong Li | Digitally signed by Zhong Li
Date: 12/05/2018 08:41:50PM
GUID: 5452326f000475beaec6af628762212a

Zhihao Peter Qiu | Digitally signed by Zhihao Peter Qiu
Date: 12/06/2018 01:21:13AM
GUID: 508da7480002bfb5825e149b2b4eb91d

[redacted]

PROCESS

ANDA:	211796
Drug Product Name / Strength:	Methylphenidate Hydrochloride Extended-Release Capsules, 10mg, 20 mg, 30 mg, 40 mg and 60 mg
Route of Administration:	Oral
Applicant Name:	Granules Pharmaceuticals Inc. (GPI)

Review Recommendation: **Inadequate - Minor**
Theme: **Inadequate supporting data/information**
Justification: N/A

Review Summary (Rev 02):

The proposed drug product "*Methylphenidate hydrochloride Extended-Release (ER) Capsules*" is an extended release capsule, [redacted] (b) (4). The basis of the application is the reference list drug (RLD), *Ritalin® LA, NDA 021284*, held by Novartis.

[redacted] (b) (4)

Following the review of the application's responses to the 9/25/2018 DRL, minor deficiencies have been identified for the proposed commercial manufacturing process and in-process controls as shown in the *List of Deficiencies*.

List Submissions being reviewed (table):

Submissions Reviewed	Document Date
Unsolicited Amendment	11/3/2018
Quality/Response to DRL	10/22/2018
Original submission	4/2/2018
Quality/Response to Information Request	N/A

Highlight Key Outstanding Issues from Last Cycle: [redacted] (b) (4)

Concise Description Outstanding Issues Remaining: see *List of Deficiencies*.
List Number of Comparability Protocols (ANDA only): N/A

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Reviewer's Assessment: ***N/A***

Lifecycle Management Considerations

Reviewer's Assessment: ***N/A***

List of Deficiencies:

1. (b) (4) [redacted]
2. (b) (4) [redacted]

Primary Process Reviewer Name and Date:

Zhong Li Ph.D.; Review 01 7/30/2018; Revised 7/31/2018

Review 02 11/5/2018; Revised 11/20/2018

OQ/OPF/DIA/Branch I

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Jiao yang, Ph.D. November 20, 2018
OPQ/OPF/DPA1/Branch III

Zhong Li

Digitally signed by Zhong Li
Date: 11/20/2018 10:07:23AM
GUID: 5452326f000475beaec6af628762212a

Jiao Yang

Digitally signed by Jiao Yang
Date: 11/20/2018 10:42:33AM
GUID: 563249bd003b5a06d5a7a137f8bd3c53

[redacted]

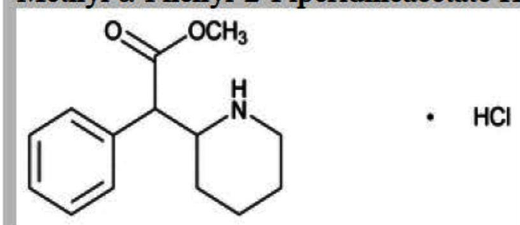
DRUG SUBSTANCE

IQA Review Guide Reference

Product Background: Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

NDA/ANDA (review cycle number): 211796

Chemical Name and Structure:
Methyl α-Phenyl-2-Piperidineacetate Hydrochloride



DMF # (if applicable): [redacted] (b) (4)

Applicant Name/DMF Holder: [redacted] (b) (4)

Review Recommendation: **Inadequate - Minor**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:
Methylphenidate hydrochloride is a white, fine crystalline [redacted] (b) (4).

Maximum Daily Dose (MDD): 60 mg

	Reporting Threshold (RT)	Identification Threshold (IT)	Qualification Threshold (QT)
Drug Substance	0.05%	0.10%	0.15%
Drug Product	0.1%	0.2%	0.2%

List Submissions being reviewed (table):

	Submission Type	Submission Date
Current	Original ANDA	04/02/2018

	Response to Information Request - Samples	06/27/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

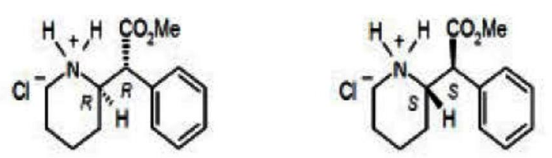
Concise Description Outstanding Issues Remaining: Particle size specification and analytical method validation

List Number of Comparability Protocols (ANDA only): None

S.1 General Information

Summary of the info provided. Information from Application

Below is the general information of the drug substance Methylphenidate Hydrochloride, USP.

Subject	Details
Recommended International Non-proprietary Name (INN)	Methylphenidate Hydrochloride
Chemical Name	Methyl α-Phenyl-2-Piperidineacetate Hydrochloride
Other Non-proprietary Names	Methylphenidate Hydrochloride
Compendia Name	Methylphenidate Hydrochloride, USP
Molecular Formula	$C_{14}H_{19}NO_2 \cdot HCl$
Molecular Weight	269.77
CAS Number	298-59-9 [(±)-*threo*-isomer].
Structure	 (+)-*threo*-Methylphenidate (-)-*threo*-Methylphenidate
DEA Controlled Substance Schedule	II
Pharmacological Class	CNS Stimulant

Subject	Details
Description	White crystalline powder
Solubility Data	[redacted] (b) (4)
pKa	[redacted]

11 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

R Regional Information

Comparability Protocols

Reviewer's Assessment: ***N/A***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***{Adequate/Inadequate}***

Lifecycle Management Considerations

List of Deficiencies:

1. [redacted] (b) (4)

2. [redacted] (b) (4)

Primary Drug Substance Reviewer Name and Date: Jingwen Ma, 08/27/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yanning Lin, 09/13/2018

DRUG PRODUCT

IQA Review Guide Reference

Product Background:

NDA/ANDA (review cycle number): 211796

Drug Product Name / Strength: Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

Route of Administration: Oral

Applicant Name: Granules Pharmaceuticals Inc.

Review Recommendation: **Inadequate - Minor**

Theme (ANDA only): Choose an item.

Justification (ANDA only): Choose an item.

Review Summary:

List Submissions being reviewed (table):

	Submission Type	Submission Date
Current	Original ANDA	04/02/2018
	Response to Information Request - Samples	06/27/2018

Highlight Key Outstanding Issues from Last Cycle: N/A

Concise Description Outstanding Issues Remaining: The Drug product section is inadequate with minor deficiencies. [redacted] (b) (4)

List Number of Comparability Protocols (ANDA only): None

P.1 Description and Composition

Component/composition table

Granules proposed drug product "Methylphenidate hydrochloride Extended-Release Capsules" is an Extended Release Capsule dosage form, consisting of five strengths (10 mg, 20 mg, 30 mg, 40 mg and 60 mg) and its quantitative composition, function of each excipient is provided in below Table 8 to 5. Refer Module 3.2.P.1 for further information.

Table 8. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 10 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	10.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted] (b) (4)
[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF ([redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted] (b) (4)
Total Capsule Weight*	100.0	161.3	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 161.3 mg**	**Function**
[redacted]	[redacted]	[redacted]	[redacted] (b) (4)	[redacted] (b) (4)
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]

Table 9. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 20 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 20 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	20.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Total Capsule Weight***	100.0	261.6	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 261.6 mg**	**Function**
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted] (b) (4)	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 10. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 30 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 30 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	30.00	Active ingredient

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 30 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Polyethylene glycol, [redacted] (b) (4)	[redacted] (b) (4)	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF ([redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]
Total Capsule Weight***	100.0	377.0	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 377.0 mg**	**Function**
[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant

[redacted] (b) (4)

Table 11. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 40 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 40 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted] (b) (4)	40.00	Active ingredient

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 40 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)		
[redacted] (b) (4)			
Cellaburate, NF [redacted] (b) (4)			
Hypromellose Acetate Succinate, NF [redacted] (b) (4)			
Acetyltributyl Citrate, NF [redacted] (b) (4)			
Talc, USP ([redacted] (b) (4)			
[redacted] (b) (4)			
Total Capsule Weight***	100.0	497.4	[redacted]

[redacted] (b) (4)

Component	[redacted] (b) (4)	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 497.4 mg**	**Function**
[redacted] (b) (4)				
Titanium Dioxide	[redacted]			
D&C Yellow #10	[redacted]			Colorant
FD&C Yellow #6	[redacted]			Colorant

[redacted] (b) (4)

Table 12. Components, composition and functions of Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 60 mg			
Component	[redacted] (b) (4)	**mg/Capsule**	**Function**
Methylphenidate Hydrochloride, USP	[redacted]	60.00	Active ingredient
Polyethylene glycol, NF [redacted] (b) (4)	[redacted]	[redacted] (b) (4)	

Granules Drug Product: Methylphenidate hydrochloride Extended-Release Capsules, 60 mg			
Component	**% w/w**	**mg/Capsule**	**Function**
[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]
Talc, USP [redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
Total Capsule Weight***	100.0	720.0	[redacted]

[redacted]

Component	[redacted]	**Amount per Unit (mg/Capsule)**	**% w/w per Total capsule weight of 720 mg**	**Function**
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

All inactive ingredients, utilized in the formulation as listed in the Inactive Ingredient Database (IID), are within or below the listed levels for orally administered products. Please refer from Table 13 to 10. Each excipient present in is within the potency limits listed for oral dosage forms in the most current FDA/CDER Inactive Ingredient Guide (IIG) as applicable.

Table 13. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 10 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	(b) (4) [redacted]	10.00	10.00	N/A	
Polyethylene glycol, NF (b) (4) [redacted] r	[redacted]	[redacted]	(b) (4) [redacted]	Oral / Capsule	(b) (4) [redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(b) (4) [redacted]
Cellaburate, NF [redacted] (b) (4) [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF (b) (4) [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(b) (4) [redacted]
Titanium Dioxide	[redacted]	[redacted]	(b) (4) [redacted]	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	(b) (4) [redacted]

Table 14. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride,	(b) (4) [redacted]	20.00	20.00	N/A	

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 20 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 15. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted]	30.00	30.00	N/A	
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 30 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Table 16. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted]	40.00	40.00	N/A	
Polyethylene glycol, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Cellaburate, NF [redacted]	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 40 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Tablet	[redacted] (b) (4)
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)					
Titanium Dioxide	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
D&C Yellow #10	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]
[redacted] (b) (4)					

Table 17. Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
Methylphenidate Hydrochloride, CII	[redacted] (b) (4)	60.00	60.00	N/A	
Polyethylene glycol, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted] (b) (4)	Oral / Capsule	[redacted] (b) (4)
[redacted] (b) (4)					
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Tablet	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	Oral / Capsule	[redacted]

Inactive ingredients and amounts as per IIG limit for Methylphenidate hydrochloride ER Capsules, 60 mg					
Component	% w/w	Amount per Unit (mg/Capsule)	Maximum amount per MDD (mg/MDD)[1]	IIG Limits as per database last updated on January 31, 2018[2]	
				Route; Oral Dosage Form	Maximum Potency (mg)
[redacted]					
Titanium Dioxide	[redacted]			Oral / Capsule	[redacted]
D&C Yellow #10				Oral / Capsule	
FD&C Yellow #5				Oral / Capsule	
FD&C Yellow #6				Oral / Capsule	
[redacted]					

(b) (4)

GPI used same excipients as Reference standard formulation 60 mg used. GPI used different excipients than RLD formulation strengths (10 mg, 20 mg, 30 mg and 40 mg) used. These differences will not expect to have potential concerns with respect to the therapeutic equivalence and are just excipients. The following Table 18 lists the ingredients and the function of Granules Pharmaceuticals Inc. (GPI) and Reference Drug Products. Please refer 3.2.P.1 for further information.

(b) (4)

[redacted]

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Deficiency
10. [redacted]

R Regional Inform

Environmental

Reviewer's Assessment: ***Adeq***
Categorical exclusion from the
in accordance with Code of Fe

Methods Verification Pack

[redacted]

(b) (4)

[redacted]

Primary Drug Product Reviewer Name and Date: Jingwen Ma, 9/10/2018, 9/17/2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Yanning Lin, 09/15/2018

LABELING

IQA Review Guide Reference
{For ANDA only}

R Regional Information

1.14 Labeling

Labeling & Package Insert

DESCRIPTION section

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

Is the drug product subject of a USP monograph? ☐ Yes ☒ No
If "Yes," state if labeling needs a special USP statement in the Description. (e.g., USP test pending. Meets USP assay test 2. Meets USP organic impurities test 3.)

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? ☒ Yes ☐ No
If "No," explain.

ii) Are the storage conditions acceptable? ☒ Yes ☐ No
If "No," explain.

DOSAGE AND ADMINISTRATION section, for injectables, and where applicable: N/A

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

If "No," explain.

For OTC Drugs and Controlled Substances: N/A

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
10 mg	17.73 mm	yellow opaque cap printed with "G 10mg" and white opaque body printed with "012"
20 mg	17.66 mm	white opaque cap printed with "G

		20mg" and white opaque body printed with "013"
30 mg	19.22 mm	yellow opaque cap printed with "G 30mg" and yellow opaque body printed with "014"
40 mg	21.55 mm	yellow opaque cap printed with "G 40mg" and yellow opaque body printed with "015"
60 mg	23.15 mm	yellow opaque cap printed with "G 60mg" and yellow opaque body printed with "016" contains white to off-white pellets.

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

The 10 mg, 20 mg and 60 mg drug products contain FD&C #5 in the capsule shells. See deficiency #1.

List of Deficiencies:

Primary Drug Product Reviewer Name and Date: Jingwen Ma, 08/29/2018

Secondary Drug Product Reviewer Name and Date: Yanning Lin, 09/13/2018

PROCESS

ANDA:	211796
Drug Product Name / Strength:	Methylphenidate Hydrochloride Extended-Release Capsules, 10mg, 20 mg, 30 mg, 40 mg and 60 mg
Route of Administration:	Oral
Applicant Name:	Granules Pharmaceuticals Inc. (GPI)

Review Recommendation: **Inadequate - Minor**
Theme: **Inadequate supporting data/information**
Justification: N/A

Review Summary:

The proposed drug product "*Methylphenidate hydrochloride Extended-Release (ER) Capsules*" is an extended release capsule, [redacted] (b) (4) The basis of the application is the reference list drug (RLD), *Ritalin® LA, NDA 021284*, held by Novartis.

[redacted] (b) (4)

Following the review of the application, minor deficiencies have been identified for [redacted] (b) (4) as shown in the *List of Deficiencies*.

List Submissions being reviewed (table):

Submissions Reviewed	Document Date
Original submission	4/2/2018
Quality/Response to Information Request	N/A

Highlight Key Outstanding Issues from Last Cycle: N/A
Concise Description Outstanding Issues Remaining: see *List of Deficiencies*.
List Number of Comparability Protocols (ANDA only): N/A

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(b) (4)

[redacted]

Summary of Process Validation Studies Conducted

Reviewer's Assessment: ***N/A***

Comparability Protocols:

Reviewer's Assessment: ***N/A***

Post-Approval Commitments (For NDA only)

Reviewer's Assessment: ***N/A***

Lifecycle Management Considerations

Reviewer's Assessment: ***N/A***

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(b) (4)

[redacted]

Primary Process Reviewer Name and Date:

Zhong Li Ph.D.; Review 01 7/30/2018; Revised 7/31/2018

OPQ/OPF/DIA/Branch I

Secondary Reviewer Name and Date (and Secondary Summary, as needed):

Jiao yang, Ph.D. July 31, 2018
OPQ/OPF/DPA1/Branch III

Zhong Li

Digitally signed by Zhong Li
Date: 7/31/2018 02:30:07PM
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Jiao Yang

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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: 5/22/2018

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 on-site inspection**

RE: ANDA [redacted] (b) (4)
ANDA [redacted] (b) (4)

The Division of Generic Drug Bioequivalence Evaluation (DGDBE) within the Office of Study Integrity and Surveillance (OSIS) recommends accepting data without on-site inspection. The rationale for this decision is noted below.

Rationale

OSIS recently inspected the site listed below. The inspectional outcome from the inspection was classified as No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Analytical	[redacted]	[redacted] (b) (4)

Timely Consults and Early IR Checklist for Type II API DMFs

Result: TCIR-NAI

ANDA#:211796

Drug Product: METHYLPHENIDATE HYDROCHLORIDE, CAPSULE, EXTENDED RELEASE, 10mg || 30mg || 40mg || 60mg || 20mg

DMF#: (b) (4) [redacted]

DMF Subject (API name): METHYLPHENIDATE HYDROCHLORIDE

1. Does the Type II API DMF list any manufacturing facilities or testing facilities for routine release or stability testing that are not listed in the facility profile and/or on the 356h form for the referencing ANDA? ☐Yes ☒No

   If yes, include the information identifying each facility and its function below:

Facility Name and Address	**Function***	**FEI/DUNS#**

* CSN: Non-Sterile API by Chemical Synthesis
CSS: Sterile API by Chemical Synthesis
CSP: Chemical Sterilization
CTL: Control Testing Laboratories
CTB: Control Testing Laboratories “Also”
CTX: Control Testing Laboratories “ Also” (Drugs)
CXA: Plant/Animal Extraction Purified API
CFN: Non –Sterile API by Fermentation
CFS: Sterile API by Fermentation

RBPM to include the following comment in the early-IR sent to the applicant:

N/A

2. Does the DMF include any data (e.g. Ames study or cited literature studies) that requires a pharm/tox consult?
   ☐Yes ☒No

   If yes, prepare the consult and send to DCR in Panorama and enter date sent below.

Consult form date:

3. After examining the labelling for the drug product:

   Is a DCR consult required to establish the Maximum Daily Dose (MDD)? ☐Yes ☒No

   Is a DCR consult required to establish the product use (i.e. duration and frequency of use, patient population)? ☐Yes ☒No

   The following question applies to drug products indicated for the treatment of cancer.

   Is a consult required to determine if the drug product is indicated for the treatment of advanced cancer in the context of ICH S9? ☐Yes ☐No

   Is a DCR consult required to determine that the drug substance is carcinogenic? ☐Yes ☐No

   If yes to any of the above prepare the appropriate consult and send to DCR in Panorama and enter date sent below.

   Consult form date:

David Skanchy

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Date: 4/18/2018 07:20:36AM
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[redacted]

Initial Risk Assessment of ANDA 211796 (Methylphenidate Hydrochloride Extended Release Capsules, USP, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg)

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments*
Physical stability (solid state)	36 Medium	(b) (4) [redacted]		(b) (4) [redacted]
Chemical Stability	12 Low	[redacted]		[redacted]
Assay	36 Medium	[redacted]		[redacted]

Drug Product CQAs	Initial Risk Ranking	Comments	Updated Risk Ranking after Review Cycle #1	Comments*
Content uniformity	**36** **Medium**	(b) (4) [redacted]		(b) (4) [redacted]
Microbial limits	**9** **Low**	[redacted]		[redacted]
Dissolution	**80** **High**	[redacted]		[redacted]
Dose dumping from mechanical failure	**20** **Low**	[redacted]		[redacted]

ANDA 211796

Methylphenidate Hydrochloride Extended-Release Capsules 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

Granules Pharmaceuticals Inc.

ATTACHMENT II: List of Deficiencies for Discipline Review Letter

A. Drug Substance Deficiencies

1.

B. Drug Product Deficiencies

1.

C. Environmental Analysis Deficiencies

1.

D. Labeling Deficiencies

1.

E. Process Deficiencies

(b) (4)

[redacted]

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(b) (4)

[redacted]

F. Facilities Deficiencies

None

G. Biopharmaceutics Deficiencies

1.

H. Microbiology Deficiencies

1.

OVERALL ASSESSMENT AND SIGNATURES:

Application Technical Lead Name and Date:

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
ANDA 211796

BIOEQUIVALENCE REVIEW(s)

BIOPHARMACEUTICS ANDA REVIEW

Application No.	ANDA-211796-ORIG-1-Amend-9
Applicant	Granules Pharmaceuticals Inc.
Product Name/Strength	Methylphenidate Hydrochloride Extended-Release Capsules/10 mg, 20 mg, 30 mg, 40 mg, and 60 mg
Dosage Form/ Route of Administration	Extended-Release Capsules /Oral
Indication	For treatment of Attention Deficit Hyperactivity Disorder
Submission Date(s)	03/30/2018, Original Submission 02/26/2019, Reply to Complete Response comments, SDN 009
RLD/RS	RLD: Ritalin LA®, 60[1] mg [NDA 021284; Approval:10/27/2014] RS: Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg [ANDA 078458; Approval:12/01/2011]
Primary Reviewer	Parnali Chatterjee, Ph.D.
Secondary Reviewer	Om Anand, Ph.D.
Recommendation	**ADEQUATE**

***EXECUTIVE SUMMARY*:**

The Applicant submitted the current amendment to address the deficiencies identified in the FDA Complete Response (CR) letter, dated 01/29/2019. The objective of this review is to evaluate the Applicant's response to the ***Biopharmaceutics comments 3 and 4*** in the CR letter.

The original Biopharmaceutics Review is located in Panorama[2]. The Applicant proposed their own dissolution method [redacted] (b) (4) for dissolution testing of the proposed Methylphenidate Extended-Release Tablets. The proposed dissolution method was found adequate for batch release and stability testing of the proposed drug product in the previous review cycle.

The Applicant noted the pH of the phosphate buffer in the FDA dissolution database method as pH 6.8 (page 5 of the dissolution comparison report). In the CR letter, the FDA requested the Applicant to clarify the pH of the phosphate buffer in the FDA dissolution database method used for dissolution testing of the proposed drug product. Additionally, the FDA recommended the Applicant to implement new dissolution acceptance criteria for batch release and stability testing of the proposed drug product. Further, the FDA requested the Applicant to update the

[2] http://panorama.fda.gov/document/view?ID=5c2d185d0126c9c775dde3c90545457c

drug product release and stability specifications accordingly.

In their response to the Biopharmaceutics comments, the Applicant [redacted]

Further, the Applicant accepted the FDA recommended dissolution acceptance criteria for the batch release and stability testing of the proposed drug product. Additionally, the Applicant updated the finished product specification and release report in eCTD Modules.

RECOMMENDATION:

From the Biopharmaceutics perspective, the ANDA 211796-ORIG-1-Amend-09 for the proposed Methylphenidate Hydrochloride Extended-Release Tablets, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg strength is recommended for **APPROVAL**.

The approved dissolution method and acceptance criteria for the proposed product are presented below:

<table>
<tr><th>Method Source</th><th>USP Apparatus/Speed</th><th>Medium</th><th>Volume/Temp (mL/°C)</th></tr>
<tr><td>In-house</td><td>USP Apparatus I (basket)/
100 rpm</td><td><u>Acid Stage:</u>
0.01N HCl (deaerated)
for 2 hrs

<u>Buffer Stage:</u>
pH 6.8 phosphate buffer for
2-10 hrs</td><td>500 mL
/37° C</td></tr>
<tr><th colspan="4">Acceptance Criteria</th></tr>
<tr><td colspan="2">Time (hrs)</td><td colspan="2">Percent (%) Release</td></tr>
<tr><td colspan="4">Acid Stage</td></tr>
<tr><td colspan="2">0.5 hrs</td><td colspan="2">NLT [redacted]%</td></tr>
<tr><td colspan="2">2 hrs</td><td colspan="2">NMT [redacted]%</td></tr>
<tr><td colspan="4">Buffer Stage
(after 2 hrs in acid stage)</td></tr>
<tr><td colspan="2">3.0 hrs</td><td colspan="2">[redacted]%</td></tr>
<tr><td colspan="2">6.0 hrs</td><td colspan="2">NLT [redacted]%</td></tr>
</table>

1. REVIEW SUMMARY:

The Applicant responded to the Complete Response Letter on 02/25/2019:
(Refer to: \\cdsesub1\evsprod\anda211796\0009\m1\us\1-2-cover-letter-0009.pdf)

Biopharmaceutics Comment 1.
You mentioned the pH of the FDA recommended Dissolution Method as pH 6.8 (page # 5 of the dissolution report comparison). Please clarify the pH of the phosphate buffer in the FDA dissolution method used for dissolution testing of your proposed drug product.

Applicant's Response to Biopharmaceutics Comment 1.
In their reply (02/25/2019) to the **Biopharmaceutics Comment 1** in the CRL, the Applicant noted [redacted] (b) (4) The Applicant revised the pH of the phosphate buffer in the dissolution comparison report [redacted] (b) (4)

Biopharmaceutics Comment 2.
Based on the dissolution data available, we determined that your proposed dissolution acceptance criteria for the proposed product are [redacted] (b) (4). Therefore, implement the following dissolution method and acceptance criteria for each strength of your proposed product, Methylphenidate Hydrochloride Extended-Release Capsules.

Method: Acid Stage: 500 mL of 0.01 N HCl (deaerated) for 2 hours; Buffer Stage: 500 mL of pH 6.8 Phosphate buffer (deaerated) using USP Apparatus 1 (basket) at 100 rpm

Acceptance Criteria:

Time (hrs)	Percent (%) Release
Acid Stage	
0.5 hr	NLT [redacted] (b) (4)%
2.0 hrs	NMT [redacted] (b) (4)%
Buffer Stage (after 2 hours in acid stage)	
3.0 hrs*	[redacted] (b) (4)%
6.0 hrs*	NLT [redacted] (b) (4)%

*include two hours in acid stage

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

Applicant's Response to Biopharmaceutics Comment 2.

The Applicant accepted the FDA recommended dissolution acceptance criteria for batch release and stability testing of the proposed drug product. Additionally, the Applicant updated the finished product specification and release report in eCTD Module 3.2.P.5.1. The Applicant also updated the stability protocol and stability data in Modules 3.2.P.8.1. Hence, the Applicant adequately addressed the Information Request comment in the Complete Response Letter.

The Applicant's responses are adequate and acceptable.

Parnali Chatterjee

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Om Anand

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Yanning Lin

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BIOPHARMACEUTICS ANDA REVIEW		
Application No.	ANDA-211796-ORIG-1	
Applicant	Granules Pharmaceuticals Inc.	
Product Name/Strength	Methylphenidate Hydrochloride Extended-Release Capsules/10 mg, 20 mg, 30 mg, 40 mg, and 60 mg	
Dosage Form/ Route of Administration	Extended-Release Capsules /Oral	
Indication	For treatment of Attention Deficit Hyperactivity Disorder	
Submission Date(s)	03/30/2018, Original Submission 10/22/2018, Response to Information Request comments, SDN 006	
RLD/RS	RLD: Ritalin LA®, 60[1] mg [NDA 021284; Approval:10/27/2014] RS: Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg [ANDA 078458; Approval:12/01/2011]	
Primary Reviewer	Parnali Chatterjee, Ph.D.	01/02/2019
Secondary Reviewer	Om Anand, Ph.D.	01/02/2019
Recommendation	**Inadequate - Minor**	

1. EXECUTIVE SUMMARY:

The objective of this review is to evaluate and provide a recommendation for the adequacy of the dissolution data for the (1) dissolution method and (2) dissolution acceptance criteria for Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg strength.

Dissolution Method: The Applicant proposed their own dissolution method [redacted] (b) (4) However, in the original submission (03/30/2018), the Applicant provided limited dissolution data supporting the discriminating ability of the proposed dissolution method.

In response to an IR comment (09/25/2018), the Applicant provided a list of critical material attributes (CMA) and critical process parameters (CPP) [redacted] (b) (4)

Based on the totality of evidence, the proposed dissolution method is acceptable as a quality control tool for batch release and stability testing of the proposed drug product.

[1] 60 mg strength is discontinued now

Dissolution Acceptance Criteria: The Applicant proposed [redacted] as the dissolution acceptance criteria for each strength of the Methylphenidate Hydrochloride Extended-Release Capsules. The dissolution profile data for each strength of the drug product supports *NLT* [redacted] *% in 0.5 hrs; NMT* [redacted] *% in 2.0 hrs;* [redacted] *%in 3.0 hrs; and NLT* [redacted] *% in 6 hrs'* as the dissolution acceptance criteria for batch release and stability testing of the proposed drug product.

Recommendation

The Biopharmaceutics recommendation for ANDA-211796-ORIG-1 is **pending** due to the outstanding deficiencies regarding the dissolution method. The Applicant will be requested to provide additional information to address the deficiencies listed in Section 3.

2. REVIEW SUMMARY:

Solubility: [redacted] (b) (4)

The proposed drug product is an extended-release (ER) capsule of methylphenidate hydrochloride [redacted] (b) (4).

3. Dissolution method and dissolution acceptance criteria:

Method Source	USP Apparatus	Speed (RPMs)	Medium	Volume/Temp (mL/°C)	Acceptance Criteria
[redacted] (b) (4)					

The Applicant provided dissolution profile data in [redacted] (b) (4) to justify the proposed dissolution medium for dissolution testing of the proposed drug product. Because the proposed dissolution method is not the FDA dissolution database method, the Applicant will be recommended to provide the dissolution method development report.

[redacted] (b) (4)

Other formulation and manufacturing process parameters that can be used to support the discriminating ability of the proposed dissolution method include [redacted] (b) (4)

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(b) (4)

[redacted]

5. Biopharmaceutics Comments:

List of Biopharmaceutics Information Request comments to be conveyed to the Applicant:

1. You mentioned the pH of the FDA recommended Dissolution Method as pH 6.8 (page # 5 of the dissolution report comparison). Please clarify the pH of the phosphate buffer in the FDA dissolution method used for dissolution testing of your proposed drug product.

2. Based on the dissolution data available, we determined that your proposed dissolution acceptance criteria for the proposed product are [redacted] (b) (4) Therefore, implement the following dissolution method and acceptance criteria for each strength of your proposed

product, Methylphenidate Hydrochloride Extended-Release Capsules.

Method: Acid Stage: 500 mL of 0.01 N HCl (deaerated) for 2 hours; Buffer Stage: 500 mL of pH 6.8 Phosphate buffer (deaerated) using USP Apparatus 1 (basket) at 100 rpm

Acceptance Criteria:

Time (hrs)	Percent (%) Release
Acid Stage	
0.5 hr	NLT [redacted]%
2.0 hrs	NMT [redacted]%
Buffer Stage (after 2 hours in acid stage)	
3.0 hrs*	[redacted]%
6.0 hrs*	NLT [redacted]%

*include two hours in acid stage

Update your drug product release and stability specifications accordingly. In addition, please be advised, that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

APPENDIX I

(b) (4)

[redacted]

APPENDIX II

List of Biopharmaceutics Information Request comments conveyed to the Applicant on 09/25/2018:

1) *The proposed dissolution method* [redacted] (b) (4) *is not acceptable at this stage because the discriminating ability of the method has not been adequately investigated. Described below are our recommendations with respect to proper investigation for the discriminating ability of the proposed dissolution method:*

   - *Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting the dissolution and establish that your method is discriminating with regard to those CMAs and CPPs which affect dissolution. In general, the testing conducted to demonstrate the discriminating ability of the dissolution method should compare the dissolution profiles of the proposed drug product(target) and the formulations/product that are intentionally manufactured with meaningful variations, i.e., aberrant formulations and manufacturing conditions with* **± *10-20%*** *change to the specification-ranges of these variables for the most relevant CMA's and CPPs.*

In addition, if available, data can be submitted showing that the selected dissolution method is able to reject batches that are not bioequivalent. Supportive dissolution data may also be submitted showing that the selected dissolution method can detect the change(s) in the drug product occurring during the accelerated and stress conditions.

2) *Provide complete dissolution profile data (individual, mean, ranges, % CV) for all strengths of your proposed test product including dissolution data for the earlier time points during the stage-1 (e.g., at 10 minutes, 15 minutes and 20 minutes) and stage-2 (e.g., at 2.25, 2.5 and 3 hrs) dissolution testing using the proposed dissolution method and the dissolution method recommended in the FDA dissolution methods database* [redacted] (b) (4)

The Applicant responded to the Biopharmaceutics Information request comment on 10/22/2018, SDN 006
(refer to: \\cdsesub1\evsprod\anda211796\0006\m1\us\1-2-cover-letter-0006.pdf)

Comment #1. In response to the biopharmaceutics Information Request comment, the Applicant provided a list of critical material attributes (CMA) and critical process parameters (CPP) that could have an impact on the dissolution profile of the proposed drug product. Based on the Applicant's response, the Information Request comment #1 is adequately addressed.

Comment #2. The Applicant provided complete dissolution profile data for all strengths of the proposed drug product at the earlier time points of 10 minutes, 15 minutes and 20 minutes during the stage-1 and at 2.25, 2.5 and 3 hrs for stage-2 dissolution testing using the proposed dissolution method [redacted] (b) (4)

The dissolution profile data at 12 month stability time-point on long-term stability conditions using the proposed dissolution method [redacted] (b) (4) [redacted] for one batch for all strengths of the proposed drug product is provided in **Table B-Table F**.

Based on the Applicant's response, the Information Request comment #2 is adequately addressed.

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Parnali Chatterjee

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Om Anand

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[redacted]

DIVISION OF BIOEQUIVALENCE REVIEW

ANDA No.	211796			
Drug Product Name	Methylphenidate Hydrochloride Extended-Release Capsules			
Strength(s)	10 mg, 20 mg, 30 mg, 40 mg, and 60 mg			
Applicant Name	Granules Pharmaceuticals Inc.			
Applicant Address	3701 Concorde Parkway Chantilly, Virginia 20151			
Applicant's Contact Name and Mailing Address	Vamsi Nama, Director Regulatory Affairs			
Applicant's Contact Telephone Number	[redacted] (b) (6)			
Applicant's Contact Fax Number	703-378-1578			
Applicant's Contact Email Address	vamsi.nama@granulesindia.com			
Original Submission Date(s)	04/02/2018			
Submission Date(s) of Amendment(s) Under Review	05/18/2018, applicant's response to Filing Information Request (IR) with re-submitted bioequivalence (BE) summary tables			
Primary Reviewer	Dapeng Cui, Ph.D.			
Secondary Reviewer	Tao Bai, Ph.D.			
Tertiary Reviewer	Utpal Munshi, Ph.D.			
Study Number(s)	2018-4413	2017-4351	2018-4455	2017-4358
Study Type(s)	Pivotal Fasting	Pivotal Fed	Pivotal Fasting Sprinkle	Pilot Fed
Strength(s)	1 × 60 mg	1 × 60 mg	1 × 60 mg	1 × 60 mg
Clinical Site	[redacted] (b) (4)			
Clinical Site Address				
Analytical Site				
Analytical Site Address				
Office of Study Integrity and Surveillance (OSIS) status	**Backlog, Year 1 and Year 2 ANDAs** ☐ **Pending** ☐ **Complete**		**Post October 1, 2014 ANDAs** ☐ **To Be Determined by OSIS**	

	☐ N/A (Waiver/Deem Bioequivalent)		☐ Pending For Cause Inspection ☒ Complete ☐ N/A (Waiver/Deem Bioequivalent)
Waiver/Deem Bioequivalent	☐ 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/IR ☐ N/A (Review is Adequate)		
Major Deficiency Theme	Bioanalytical (sample reanalysis) deficiency		
Justification for Major Designation	Review of deficiency requires a substantial expenditure of FDA resources.		
Overall Review Result	☐ Adequate ☒ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	*Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)* ☒ Recommended/Latest Revision Date: __Mar 2015_ RLD Number: __NDA 021284__ https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf ☐ N/A (no PSG available at time of review)		
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	Pivotal Fasting	60 mg	☐ Adequate ☒ Inadequate
1, 2	Pivotal Fed	60 mg	☒ Adequate ☐ Inadequate
1, 2	Pivotal Fasting Sprinkle	60 mg	☒ Adequate ☐ Inadequate
1, 2	Pilot Fed	60 mg	☐ Adequate ☐ Inadequate ☒ N/A (For information)
1, 2	Waiver	10, 20, 30, 40 mg	☐ Adequate ☒ Inadequate
1, 2	Alcohol Dose Dumping	10, 20, 30, 40 and 60 mg	☒ Adequate ☐ Inadequate

1 EXECUTIVE SUMMARY

This application contains the results of fasting, fed, and fasting sprinkle bioequivalence (BE) studies comparing a test product, Granules Pharmaceuticals Inc.'s Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg, to the corresponding Reference Standard (RS) product, Mayne Pharma LLC.'s Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg (ANDA 078458, approved on 06/23/2016)[1]. Each of the BE studies was designed as a single-dose, two-way crossover study in healthy male and female subjects. The results of the three studies are summarized in the tables below (reviewer calculated):

Methylphenidate (No of subjects completed = 24) Dose 60 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasted Bioequivalence Study (2018-4413)							
Parameter	**Unit**	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC_{inf}	ng hr/mL	203.82	24	197.83	24	1.03	99.59-106.58
C_{max}	ng/mL	25.87	24	25.61	24	1.01	94.67-107.79
AUC_{0-3}	ng hr/mL	37.37	24	37.83	24	0.99	90.72-107.55
AUC_{3-7}	ng hr/mL	76.26	24	74.58	24	1.02	95.80-109.16
AUC_{7-12}	ng hr/mL	55.27	24	52.33	24	1.06	97.19-114.77

Methylphenidate (No of subjects completed = 39) Dose 60 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (2017-4351)							
Parameter	**Unit**	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC_{inf}	ng hr/mL	226.26	39	229.27	37*	0.99	95.76-101.70
C_{max}	ng/mL	20.71	39	20.80	39	1.00	96.17-102.98
AUC_{0-4}	ng hr/mL	46.52	39	46.51	39	1.00	92.34-108.31
AUC_{4-8}	ng hr/mL	60.06	39	56.01	39	1.07	102.16-112.53
AUC_{8-12}	ng hr/mL	50.03	39	49.84	39	1.00	96.20-104.73

* AUCi of two subjects [redacted] (b) (6) were not calculated due to increasing concentration at the last time point

Methylphenidate (No of subjects completed = 24) Dose 60 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Sprinkle Bioequivalence Study (2018-4455)							
Parameter	**Unit**	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC_{inf}	ng hr/mL	204.09	24	203.42	24	1.00	97.18-103.58
C_{max}	ng/mL	23.86	24	23.77	24	1.00	95.80-105.18
AUC_{0-3}	ng hr/mL	38.39	24	38.92	24	0.99	93.69-103.85
AUC_{3-7}	ng hr/mL	73.21	24	70.83	24	1.03	97.57-109.50
AUC_{7-12}	ng hr/mL	53.37	24	51.77	24	1.03	96.96-109.64

[1] Orange Book, ANDA 078458, Last accessed on 08/16/2018: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=078458

The pivotal fed (#2017-4351) and pivotal fasting sprinkle (#2018-4455) BE studies are **adequate** (please refer to Sections **4.1.2** and **4.1.3**), however, the pivotal fasting BE study (#2018-4413) is **inadequate** due to a deficiency in the bioanalytical repeat assay (please refer to Section **4.1.1**).

The applicant also submitted summary tables of a pilot fed study #2017-4358. The test product used in the pilot fed study was the same exhibit batch used in the three pivotal BE studies. The pilot fed study was designed as single-dose, two-way crossover study in healthy male and female subjects. The 90% confidence intervals (CIs) of T/R ratios for Cmax, AUCinf, AUC4-8, and AUC8-12 were within the BE acceptance range. The upper limit of 90% CI for AUC0-4 was out of the BE acceptance range, likely due to the small sample size (N=9). There was no serious adverse event in the pilot study (please refer to Section **4.1.4**).

The test product formulation is adequate. All inactive ingredients are below the acceptance levels for the FDA approved drug products of oral dosage forms. The 10 mg, 20 mg, 30 mg and 40 mg test product formulations are proportionally similar to that of the 60 mg strength which underwent in vivo BE studies (please refer to Section **4.2**).

At the time of current BE review, the Biopharmaceutics review of the applicant's dissolution testing method is not available[2]. The applicant's dissolution data are evaluated by the current BE reviewer from a waiver perspective only. The applicant conducted dissolution testing using a method [redacted] (b) (4) The dissolution profiles for the bio-strength (60 mg) of the test product are comparable to those of the lower strengths, 10 mg, 20 mg, 30 mg, and 40 mg (please refer to Section **4.3**).

The applicant conducted multi-media dissolution testing in multi-pH media (0.1N HCl [pH1.2], pH 4.5 Acetate buffer, and pH 6.8 phosphate buffer) using USP Apparatus I (basket) at 100 rpm. The dissolution profiles for the bio-strength (60 mg) of the test product are similar to those of the lower strengths, 10 mg, 20 mg, 30 mg, and 40 mg in all pH media.

The applicant also submitted data for alcohol dose-dumping studies. The risk of dose-dumping from each strength of the test product is not higher compared to the corresponding strength of the reference product at each alcohol concentration level.

Due to the deficiency in the pivotal BE studies, the Division of Bioequivalence I (DBI) does not deem the 10 mg, 20 mg, 30 mg and 40 mg strengths of the test product to be bioequivalent to the corresponding strengths of the reference product based on criteria set forth in under 21 CFR § 320.24 (b) (6).

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[2] GDRP, ANDA-211796-ORIG-1, Biopharmaceutics Quality Review is pending as of 09/05/2018

[3] [redacted] (b) (4)

The Office of Study Integrity and Surveillance (OSIS) recently inspected both the analytical and clinical sites and the outcomes were No Action Indicated (NAI) for both sites. Therefore, OSIS recommended accepting the submitted data from the current application without an on-site inspection[4,5]. Although there is a deficiency related to repeat assays in the pivotal fasting study, the in vivo BE studies submitted in the current ANDA do not indicate any conduct issues and no data integrity deficiencies were identified by the reviewer. As such, the OSIS status for the clinical and analytical sites is complete and adequate.

The application is **inadequate**.

[4] GDRP ANDA-211796-ORIG-1, Documents, [redacted] (b) (4)

[5] GDRP ANDA-211521-ORIG-1, Documents, [redacted] (b) (4)., 06/06/2018

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3 SUBMISSION SUMMARY

3.1 Drug Product Information

Test Drug Product and Strength(s)	Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg
Reference Standard (RS) and Strength(s)	Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg
RS Holder; NDA/ANDA Number; Approval Date[6]	Mayne Pharma LLC.; ANDA 078458 (60 mg strength); 06/23/2016[a]
Reference Listed Drug (RLD) and Strength(s)	Ritalin LA®, (methylphenidate hydrochloride) Extended-Release capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg
RLD Holder; NDA/ANDA Number; Approval Date[7]	Novartis Pharmaceuticals Corp.; NDA 021284; 10 mg strength: approved on 04/10/2004, 20 mg, 30 mg and 40 mg strengths: approved on 06/05/2002 60 mg strength: approved on 10/27/2014 and withdrew on 03/23/2016[b]

Reviewer's Note:

[a]: There are four strengths (20 mg, 30 mg, 40 mg and 60 mg) under ANDA 078458 Methylphenidate Hydrochloride ER Capsules. The 60 mg strength is designated as the RS per Orange Book. The applicant used RS product, Methylphenidate Hydrochloride ER Capsules 60 mg (ANDA 078458) in the vivo bioequivalence (BE) studies for current ANDA.

[b]: The Orange Book has the following message for Ritalin LA® (methylphenidate hydrochloride) ER Capsules, 60 mg, "*Federal Register determination that product was not discontinued or withdrawn for safety or efficacy reasons*'. The RLD (NDA 021284) applicant voluntarily discontinued manufacture of the 60 mg strength as a business decision on 03/23/2016.[8]

3.2 PK/PD Information[9,10]

Most recent RLD label (provide embedded document) Please check if an NG/G/J tube study needed.	021284s034lbl.pdf
Indication	Ritalin LA (methylphenidate hydrochloride) Extended-Release Capsules is indicated for the treatment of Attention Deficit Hyperactivity Disorder (ADHD).
Boxed warning	N/A
Bioavailability	The absolute oral bioavailability of methylphenidate in children was 22±8% for d-methylphenidate and 5±3% for l-methylphenidate, suggesting pronounced presystemic metabolism

[6] Electronic Orange Book, Last accessed on 08/16/2018: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=A&Appl_No=078458

[7] Electronic Orange Book, Last accessed on 08/16/2018: https://www.accessdata.fda.gov/scripts/cder/ob/results_product.cfm?Appl_Type=N&Appl_No=021284

[8] EDR, NDA 021284, Sequence 0061, 03/23/2016, Module 1.2 Cover Letter: \\cdsesub1\evsprod\nda021284\0061\m1\us\cover.pdf

[9] Drugs@FDA: RLD Labeling (NDA 021284), version approved date 01/04/2017: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021284s034lbl.pdf

[10] Drugs@FDA: RS Labeling (ANDA 078458), version approved date 06/23/2016: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/078458Orig1s010lbl.pdf

Food Effect	Administration times relative to meals and meal composition may need to be individually titrated. When Ritalin LA was administered with a high fat breakfast to adults, Ritalin LA had a longer lag time until absorption began and variable delays in the time until the first peak concentration, the time until the interpeak minimum, and the time until the second peak. The first peak concentration and the extent of absorption were unchanged after food relative to the fasting state, although the second peak was approximately 25% lower. The effect of a high fat lunch was not examined. There were no differences in the pharmacokinetics of Ritalin LA when administered with applesauce, compared to administration in the fasting condition. There is no evidence of dose dumping in the presence or absence of food. For patients unable to swallow the capsule, the contents may be sprinkled on applesauce and administered
Tmax	Ritalin LA produces a bi-modal plasma concentration-time profile (i.e., 2 distinct peaks approximately 4 hours apart) when orally administered to children diagnosed with ADHD and to healthy adults. The initial rate of absorption for Ritalin LA is similar to that of Ritalin tablets as shown by the similar rate parameters between the 2 formulations, i.e., initial lag time (Tlag), first peak concentration (Cmax1), and time to the first peak **(Tmax1)**, which is reached in 1-3 hours. The mean time to the interpeak minimum (Tminip), and time to the second peak **(Tmax2)** are also similar for Ritalin LA given once daily and Ritalin tablets given in 2 doses 4 hours apart.
Metabolism	The absolute oral bioavailability of methylphenidate in children was 22±8% for d-methylphenidate and 5±3% for l-methylphenidate, suggesting pronounced presystemic metabolism. Biotransformation of methylphenidate by the carboxylesterase CES1A1 is rapid and extensive leading to the main, de-esterified metabolite α-phenyl-2-piperidine acetic acid (ritalinic acid). Only small amounts of hydroxylated metabolites (e.g., hydroxymethylphenidate and hydroxyritalinic acid) are detectable in plasma. Therapeutic activity is principally due to the parent compound.
Excretion	In studies with Ritalin LA and Ritalin tablets in adults, methylphenidate from Ritalin tablets is eliminated from plasma with an average half-life of about 3.5 hours, (range 1.3-7.7 hours).
Half-life	In studies with Ritalin LA and Ritalin tablets in adults, methylphenidate from Ritalin tablets is eliminated from plasma with an average half-life of about 3.5 hours, (range 1.3-7.7 hours). In children the average half-life is about 2.5 hours, with a range of about 1.5-5.0 hours. The rapid half-life in both children and adults may result in unmeasurable concentrations between the morning and mid-day doses with Ritalin tablets.
Maximum Daily Dose	60 mg

3.3 OGD Recommendations for Drug Product

Source of most recent recommendations or provide the embedded document to the current draft guidance[11]	UCM281454.pdf	
Summary of OGD or DB History	Approved ANDAs:[12]	Yes, A078458 (20 mg, 30 mg, 40 mg and 60 mg [RS]) and A200886 (10 mg) (Note: both A078458 and A200886 are held by Mayne Pharma LLC)
	Pending ANDAs: [13]	Yes, [redacted] (b) (4) and current A211796
	Controls:[15,16]	Yes, (See below, three are from the current applicant).
	Protocols:[17]	No
	Pending Citizen Petitions and other legal and regulatory issues:[18]	☐ Yes ☒ No

Discussion on individual PK parameter T/R ratio analysis

Per PSG of the product[19], BE study may be conducted as a four-period reference replicate design. Per the associated guidance revision document[20], this option may be recommended if there are substantial numbers of outliers or if the RLD and test formulation designs are substantially different. Specifically, "*Due to the simple formulation (similar mechanism of release compared to RLD) and no safety signals were observed for the approved generic products, the subject-by-formulation interaction variance test is not recommended at this time for Ritalin LA generics. However, during review, if a generic is using a completely new design and/or significance percentage of T/R outliers are observed, it may be prudent to recommend a fully replicate study*".

Based on above rationale, the reviewer calculated and summarized individual PK parameter T/R ratios for each of the in vivo BE studies of the current ANDA, i.e., fasting

[11] Draft Guidance on Methylphenidate Hydrochloride ER Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg, Recommended Nov 2011, Revised Mar 2015: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf
[12] Electronic Orange Book, search: Methylphenidate Hydrochloride; Last accessed 08/16/2018
[13] DARRTS search as of 08/16/2018
[14] [redacted] (b) (4)
[15] OGD Controls Documents Tracking, accessed on 08/16/2018: http://cdsogd1/controls/Doc.Asp
[16] GDRP Controls Project Search as of 08/16/2018
[17] OGD DB Protocols Tracking, accessed on 08/16/2018: http://ogd.fda.gov/seltrack/Protocols.asp
[18] DLRS policy update, accessed on 08/16/2018: http://sharepoint.fda.gov/orgs/CDER-OGD/OGDP/DLRS/SitePages/Home.aspx
[19] Draft Guidance on Methylphenidate Hydrochloride ER Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg, Recommended Nov 2011, Revised Mar 2015: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf
[20] GDRP; Methylphenidate Hydrochloride ER Capsules, RLD 021284 BE Guidance Revision; http://panorama.fda.gov/project/view?ID=547479a00016605a845e69631dd015b6; last accessed on 09/13/2018

(refer to Section 4.1.1.4), fed (refer to Section **Error! Reference source not found.**), and fasting sprinkle (refer to Section **Error! Reference source not found.**) studies. In all three studies, the reviewer noted parts of subjects that had test to reference ratios outside of the range of 0.8 to 1.25 for specific partial AUCs (25-33.33% subjects in fasting study, 17.95-35.90% subjects in fed study, and 12.5-20.83% subjects in fasting sprinkle study). However, these results of the individual T/R ratio analysis are presented in the current BE review for information purpose only and will not be communicated to the sponsor due to below reasons:

- The formulation designs regarding release controlling mechanism are similar between the test and RLD products in current application (refer to Section 4.2).

- In the past, there were two problematic ANDAs for Methylphenidate Extended Release Tablets; i.e. ANDA 202608 from Mallinckrodt and ANDA 091695 from Kudco, which were subsequently downgraded by changing the TE code from "AB" to "BX" [21]. So far as we are aware, there is no similar issue identified in post marking reports for the drug product of the current ADNA, i.e., Methylphenidate Hydrochloride ER Capsules referencing RLD Ritalin LA® (NDA 021284).

- The individual subject PK profiles are similar between test and reference treatments in the fasting, fed and fasting sprinkle BE studies, i.e., generally overlapping PK profiles for all individual subjects (Module 5.3.1.2, Appendix 16.2.6).

OGD Controls Database Search and Mercado Search, as of 08/16/2018[22]:

Ctl No	Title	Description	Status/Date	From
[redacted]				

(b) (4)

[21] [redacted] (b) (4)

[22] OGD Controls Documents Tracking, accessed on 08/16/2018: http://cdsogd1/controls/Doc.Asp

(b) (4)

[redacted]

Panorama Controls Project Search as of 08/16/2018[23]:

Reference Number	FDA Received Date	Project Name	Discipline	Discipline Cat.	Assignment Cat.	Company Name	Status
(b) (4) [redacted]							
10018547 (from applicant of current ANDA 211796)	9/2/16	Controlled Correspondence for number of ANDA Batches for Granules Generic product Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg	OPQ	Stability/Batch/Matrixing	Correspondence	Granules Pharmaceuticals, Inc.	Complete
12770541 (from applicant of current ANDA 211796)	1/24/17	Controlled Correspondence-Granules Methylphenidate HCl ER Capsules 10, 20, 30, 40, 60 mg-RLD 021284-Ritalin LA-60 mg unavailability	Bioequivalence	Bioequivalence Questions	Correspondence	Granules Pharmaceuticals, Inc.	Complete

[23] GDRP Controls Project Search as of 06/15/2018

(b) (4)

[redacted]

17762932 (from applicant of current ANDA 211796)	9/21/17	Controlled Correspondence: Methylphenidate HCl ER Capsules- 10,20,30,40,60 mg- RLD N021284 - invitro dissolution	Bioequivalence	Dissolution / specification	Correspondence	Granules Pharmaceuticals, Inc.	Complete

(b) (4)

[redacted]

The three control correspondences submitted by the applicant of current ANDA 211796, Granules Pharmaceuticals Inc., are summarized below:

CC #10018547[24]

On 09/02/2016, Granules Pharmaceuticals Inc., submitted CC #10018547 requesting the Agency to comment regarding the appropriateness of the proposed batch size for their proposed generic drug product, Methylphenidate Hydrochloride Capsules, 10, 20, 30, 40, and 60 mg ER.

On 10/26/2016, the Office of Pharmaceutical Quality (OPQ) responded the control and recommended that "*This proposal will be acceptable if (i) you include testing for the BE strength, or clarify in the ANDA application that one of the tested strengths is the*

[24] GDRP, Control Project 10018547, Documents, CC 10018547 Granules Batch Size Methylphenidate CC, 10/26/2016

strength used in BE studies. (ii) If the biobatch is not one of the two extreme strengths, three batches of the bioequivalent batch strength, manufactured using at least 2 distinct lots of API, should be included in the study. (iii) You have not disclosed if there are process aids used in filling such as lubricants and glidants and if they are used in a dose proportional manner."

CC #12770541[25]

On 01/24/2017, Granules Pharmaceuticals Inc. submitted CC #12770541 requesting the Agency to evaluate the proposed strategy to conduct in vivo BE studies using Ritalin LA®, 40 mg because the 60 mg strength of RLD was not available in the US market.

On 03/21/2017, the Division of Bioequivalence III (DBIII) responded the control and clarified that Ritalin LA®, 60 mg was to be moved to the discontinued section of the Orange Book and Methylphenidate Hydrochloride Extended-release Capsules, 60 mg under ANDA 078458 was to be designated as the new Reference Standard (RS). The DBIII also clarified that the 60 mg strength (RS under ANDA 078458) should be used in the BE studies, and waiver of lower strengths should be based on (i) acceptable BE studies on the 60 mg strength, (ii) acceptable in vitro dissolution testing of all strengths, and (iii) proportional similarity of the formulations across all strengths.

CC #17762932[26]

On 09/21/2017, Granules Pharmaceuticals Inc. submitted CC #17762932 requesting the Agency's further clarification on the waiver request for its Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg. The applicant proposed to perform in vitro dissolution testing comparing their 60 mg test product vs. the RS, 60 mg under ANDA 078458. The firm proposed to compare the in vitro dissolution of the 10 mg, 20 mg, 30 mg, and 40 mg strengths of the test product vs. the Reference Listed Drug (RLD), Ritalin LA®, 10 mg, 20 mg, 30 mg, and 40 mg, respectively, under NDA 021284.

On 10/30/2017, the DBII responded the control that the applicant's proposed in vitro dissolution testing comparing their 60 mg test product vs. the RS, 60 mg, under ANDA 078458 and to compare the waiver strengths (10 mg, 20 mg, 30 mg, and 40 mg) vs. the RLD, Ritalin LA®, 10 mg, 20 mg, 30 mg, and 40 mg is acceptable.

[25] GDRP, Control Project 12770541, Documents, C12770541DB_CC01242017, 03/13/2017
[26] GDRP, Control Project 17762932, Documents, C17762932DB-Review01, 10/30/2017

3.4 Pre-Study Bioanalytical Method Validation

Information Requested	Data
Bioanalytical method validation report location	Module 5.3.1.4, *2017-4351-validation-report*, *2018-4413-validation report,* and *2018-4455-validation-report*, pages 2 to 248
Analyte	Methylphenidate
Internal standard (IS)	Methylphenidate-d_9
Method description	Liquid-liquid extraction; liquid chromatographic tandem mass spectrometric method
Limit of quantitation	0.100 ng/mL
Average recovery of drug (%) and CV(%)	Average: 91.4% (1.3%) QC A (0.300 ng/mL): 92.7% (5.9%) QC B (15.0 ng/mL): 90.1% (1.3%) QC C (24.0 ng/mL): 91.5% (3.0%)
Average recovery of IS (%) and CV(%)	91.3% (0.7%)
Standard curve concentrations (ng/mL)	0.100, 0.200, 0.500, 1.50, 4.00, 9.00, 18.0 and 30.0
QC concentrations (ng/mL)	0.300, 15.0 , 24.0 and 7.50
QC Intraday precision range (%)	0.5 to 5.1
QC Intraday accuracy range (%)	93.8 to 107.3
QC Interday precision range (%)	2.6 to 4.5
QC Interday accuracy range (%)	99.6 to 100.0
Bench-top stability (hrs)	6.00 @ room temperature 6.00 in ice-water bath
Stock stability (days)	53 hrs @ 5 ± 3 ºC for Methylphenidate 45 @ 5 ± 3 ºC for the internal standard
Processed stability (hrs)	70.25 hrs @ approximately 5ºC (served as autosampler stability)
Freeze-thaw stability (cycles)	3 cycles @ -25 ± 10 ºC
Long-term storage stability (days)	127 days @ -25 ± 10 ºC
Dilution integrity	48.0 ng/mL diluted 2-fold and 120 ng/mL diluted 5-fold
Selectivity	No interfering peaks noted in blank plasma samples

Data source:
Module 2.7.1, Clinical Summary, Table 4
Module 5.3.1.4, Attachment 16.6, Method Validation Report (#BVP-PMRI-1640-16) Version 1.1 and Amendments 1, 2, 3, 4 and 5

SOP for bioanalytical method validation submitted?	☒ Yes ☐ No Module 5.3.1.4, Bioanalytical Report Amend 1, Appendix3, SOP [redacted] (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: adequate

Per the RLD labeling[27], methylphenidate is a racemic mixture comprised of the d- and l-threo enantiomers, and the d-enantiomer is more pharmacologically active than the l-enantiomer. The applicant developed [redacted] method for the measurement of methylphenidate racemate in plasma using Liquid Chromatography-Tandem Mass Spectrometry (LC-MS/MS) method with Methylphenidate-d9 as the internal standard (IS). The Guidance for Industry; Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA (revised December 2013)[28] states that "*for BE studies, we recommend using an achiral assay to measure the racemate. We only recommend measuring individual enantiomers in BE studies when all of the following conditions have been met: (1) the enantiomers exhibit different pharmacodynamic characteristics, (2) the enantiomers exhibit different pharmacokinetic characteristics, (3) primary efficacy and safety activity reside with the minor enantiomer, and (4) nonlinear absorption is present (as expressed by a change in the enantiomer concentration ratio with change in the input rate of the drug) for at least one of the enantiomers. In such cases where all of these conditions are met, we recommend that applicants apply BE analysis to the enantiomers separately*". Per the RLD label and Clinical Pharmacology review of NDA 021284[29], there is no evidence that the above criteria 3 and 4 are met for the d- and l-enantiomers of methylphenidate. The current applicant's use of [redacted] is acceptable. Additionally, the analytical method for ANDA 078458 (current RS) is also an [redacted]

K_2EDTA (Di-potassium Ethylenediaminetetraacetic Acid) was used as the anticoagulant for the preparation of the calibration curves and quality control samples in the validation study, which was the same anticoagulant used in subject sample collection in the pivotal fasting, fed, and fasting sprinkle BE studies.

The storage time for the LTSS samples in plasma (127 days at -25°C ± 10 °C) is sufficient to cover the maximum storage period of the study samples from the pivotal fasting (19 days at -25°C ± 10 °C), fed (33 days at -25°C ± 10 °C), and fasting sprinkle BE study (15 days at -25°C ± 10 °C).

The applicant's pre-study method validation is **adequate**.

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[27] Drugs@FDA: RLD Labeling (NDA 021284), version approved date 01/04/2017: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021284s034lbl.pdf
[28] https://www.fda.gov/downloads/drugs/guidances/ucm377465.pdf
[29] DARRTS NDA021284 REV-CLINPHARM-01 (General Review), 09/07/2001
[30] [redacted]

3.5 In Vivo Studies

Summary of all in vivo Bioequivalence Studies

Pivotal Fasting Study #2018-4413

Methylphenidate (No of subjects completed = 24)											
					Mean Parameters (CV%)						
Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Product ID, Dosage Form, Route)	Subjects (No. M/F) Age:mean(range)	Cmax (ng/mL)	Tmax (h)	AUC_{0-3} (ng.h/mL)	AUC_{3-7} (ngh/mL)	AUC_{7-12} (ngh/mL)	AUC_{inf} (ngh/mL)	Study Report Location
2018-4413	A Single-Dose, Bioequivalence Study of Two Formulations of Methylphenidate HCl 60 mg Extended-Release Capsules under Fasted Conditions	Open-label, single-dose, randomized, two period, two treatment, two sequence, crossover, bioequivalence study.	Dose: 60 mg A: Methylphenidate hydrochloride Extended-Release Capsules, CII 60 mg , Lot No.: GPI17176A (Granules Pharmaceuticals, Inc., USA) p.o.	24 healthy subjects (11 M/13 F) 39 years (23-59)	26.725 (26)	Median 5.50 (1.50-7.00)	39.476 (34)	78.210 (23)	58.827 (39)	212.340 (31)	2018-4413-study-report, section 14.2 Mean Concentration and Pharmacokinetic Data
			Dose: 60 mg B: Methylphenidate Hydrochloride Extended-Release Capsules (LA) CII 60 mg , Lot No.: 634151 (Mayne Pharma, USA) p.o.		26.442 (27)	Median 5.00 (1.00-6.50)	39.364 (27)	78.027 (29)	57.653 (47)	208.995 (34)	

Data source: Module 2.7.1, Clinical Summary, Table 2c

Pivotal Fed Study #2017-4351

Methylphenidate (No of subjects completed = 39)											
				Mean Parameters (CV%)							
Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Product ID, Dosage Form, Route)	Subjects (No. M/F) Age:mean(range)	Cmax (ng/mL)	Tmax (h)	AUC_{0-4} (ng.h/mL)	AUC_{4-8} (ngh/mL)	AUC_{8-12} (ngh/mL)	AUC_{inf} (ngh/mL)	Study Report Location
2017-4351	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Methylphenidate HCl 60 mg Extended-Release Capsules under Fed Conditions	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover, bioequivalence study.	Dose: 60 mg A: Methylphenidate hydrochloride Extended-Release Capsules, CII 60 mg , Lot No.: GPI17176A (Granules Pharmaceuticals, Inc., USA) p.o.	39 healthy subjects (26 M/13 F) 40 years (19-60)	22.885 (72)	Median 3.00 (1.00-10.00)	51.429 (58)	67.348 (76)	59.428 (110)	274.416 (124)	2017-4351-study-report, section 14.2 Mean Concentration and Pharmacokinetic Data
			Dose: 60 mg B: Methylphenidate Hydrochloride Extended-Release Capsules (LA) CII 60 mg , Lot No.: 634151 (Mayne Pharma, USA) p.o.		23.008 (74)	Median 3.00 (1.50-10.00)	52.103 (77)	66.103 (96)	60.459 (110)	283.170 (136)	

Data source: Module 2.7.1, Clinical Summary, Table 2b

Pivotal Sprinkle Fasting Study #2018-4455

Methylphenidate (No of subjects completed = 24)											
					Mean Parameters (CV%)						
Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Product ID, Dosage Form, Route)	Subjects (No. M/F) Age: mean(range)	Cmax (ng/mL)	Tmax (h)	AUC_{0-3} (ng.h/mL)	AUC_{3-7} (ngh/mL)	AUC_{7-12} (ngh/mL)	AUC_{inf} (ngh/mL)	Study Report Location
2018-4455	A Single-Dose, Bioequivalence Study of Two Formulations of Methylphenidate HCl 60 mg Extended-Release Capsules Sprinkled on Applesauce under Fasting Conditions	Open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study.	Dose: 60 mg A: Methylphenidate hydrochloride Extended-Release Capsules, CII 60 mg, Lot No.: GPI17176A (Granules Pharmaceuticals, Inc., USA) p.o.	24 healthy subjects (11 M/13 F) 41 years (23-59)	26.729 (75)	Median 5.50 (1.50-7.00)	43.223 (71)	82.051 (77)	67.247 (125)	261.596 (135)	2018-4455-study-report, section 14.2 Mean Concentration and Pharmacokinetic Data
			Dose: 60 mg B: Methylphenidate Hydrochloride Extended-Release Capsules (LA) CII 60 mg, Lot No.: 634151 (Mayne Pharma, USA) p.o.		26.946 (84)	Median 5.03 (1.02-6.50)	43.731 (71)	80.592 (85)	67.122 (135)	268.284 (148)	

Data source: Module 2.7.1, Clinical Summary, Table 2d

4 APPENDIX

4.1 Individual Study Reviews

4.1.1 Single-Dose Pivotal Fasting Bioequivalence Study

4.1.1.1 Study Design

4.1.1.1.1 Study Information

Study Number	2018-4413
Study Title	A Single-Dose, Bioequivalence Study of Two Formulations of Methylphenidate HCl 60 mg Extended-Release Capsules under Fasting Conditions
Study Type	☑In Vivo BE ☐In Vitro BE ☐Permeability ☐Other
Submission Location: **Study Report** **Validation Report** **Bioanalytical Report**	Module 5.3.1.2, *2018-4413-study-report* Module 5.3.1.4, *2018-4413-validation-report* Module 5.3.1.4, *2018-4413-bioanalytical-report*
Clinical Site (Name, Address, Phone #, Fax#)	(b) (4) [redacted]
Principal Clinical Investigator (Name, Email)	[redacted]
Dosing Dates	Period 1: November 03, 2017 Period 2: November 10, 2017
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4) [redacted]
Principal Analytical Investigator (Name, Email)	[redacted]
Analytical Dates	Nov 16, 2017 to Nov 22, 2017
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) Nineteen (19) days (November 03, 2017 - November 22, 2017) b) -35 to -15 °C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	This period is covered by the established Long Term Stability of one hundred and twenty seven (127) days at -25 ± 10°C.
LTSS Data Location	2018-4413-validation-report.pdf, page 469 and page 472

Data source:
Module 2.7.1, Clinical Summary, Table 10c
Module 5.3.1.2, Fasting Study Report (Study #2018-4413)

4.1.1.1.2 Product (Bio-batch) Information

Product	Test	Reference
Treatment ID	A	B
Product Name	Methylphenidate hydrochloride Extended-Release Capsules, CII 60 mg	Methylphenidate Hydrochloride Extended-Release Capsules (LA) CII 60 mg
Manufacturer	Granules Pharmaceuticals, Inc., USA	[redacted] (b) (4)
Lot No.	GPI17176A	634151
Manufacture Date	06/09/2017	N/A
Expiration Date	N/A	08/2018
Strength	60 mg	60 mg
Dosage Form	Extended-release capsule	Extended-release capsule
Bio-batch Size	[redacted] (b) (4)	N/A
Production Batch Size		N/A
Potency	99.0%	100.0%
Content Uniformity (min, max, mean)	100.1%	N/A
Dose Administered	1 x 60 mg	1 x 60 mg
Route of Administration	Oral	Oral

Data source:
Module 2.7.1, Clinical Summary, Table 11
Module 3.2.P.5.4, Batch Analyses

Are the test and reference products expired at the time of study? If Yes, please comment.	☐ Yes ☒ No
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
Is difference of the potency values for the Test and RLD within 5%? If No, please comment.	☒ Yes ☐ No

4.1.1.1.3 Study Design, Single-Dose Fasting Bioequivalence Study

Number of Subjects	Enrolled: 24 Dosed: 24 Completed: 24 Samples Analyzed: 24 Statistically Analyzed: 24
No. of Sequences	2
No. of Periods	2
No. of Treatments	2

No. of Groups	1
Washout Period	7 days
Randomization	☒ Yes ☐ No Module 5.3.1.2, Appendix 16.1.7, Randomization Scheme
Blood Sampling Times	Pharmacokinetic samples were collected prior to dosing (0-hour), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 14, 16, 18, and 24 hours after drug administration, total 25 samples in each period.
IRB Approval	☒ Yes Date: 30 Oct 2017 ☐ No
Informed Consent	☒ Yes Date: 30 Oct 2017 ☐ No
Length of Fasting	Subjects fasted from at least 10 hours prior to drug administration until at least 4 hours post-dose.
Length of Confinement	Subjects were confined in-house from at least 10 hours prior to drug administration until at least 24 hours post-dose in each period.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Data Source: Module 5.3.1.2, Fasting Study Report (Study #2018-4413)

Comments on Study Design: Adequate

Per the RLD label[31], Ritalin LA produces a bi-modal plasma concentration-time profile (i.e., 2 distinct peaks approximately 4 hours apart) with the first peak reached in 1-3 hours. The PK sampling times in the current study are sufficient to capture the Cmax/Tmax.

Per the RLD label, an average half-life of Ritalin LA is about 3.5 hours. The mean half-life in current study is 4.1 hours for Test treatment and 3.9 hours for Reference treatment, respectively. The sampling duration of 24 hours (> 3-fold half-lives) and washout period of 7 days (> 5-fold half-lives) in the current study are sufficient to characterize the half-life and complete elimination.

The fasting study design is acceptable.

[31] Drugs@FDA: RLD Labeling (NDA 021284), version approved date 01/04/2017: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021284s034lbl.pdf

4.1.1.2 Clinical Results

4.1.1.2.1 Demographic Profile of Subjects

Study No. 2018-4413			
		Treatment Groups	
		Trt A N = 24	Trt B N = 24
Age (years)	Mean ± SD	39 ± 13	39 ± 13
	Range	23 - 59	23 - 59
Age Group	<18	0 (0%)	0 (0%)
	18 - 40	13 (54.2%)	13 (54.2%)
	41 - 64	11 (45.8%)	11 (45.8%)
	65 - 75	0 (0%)	0 (0%)
	>75	0 (0%)	0 (0%)
Sex	Female	13 (54.2%)	13 (54.2%)
	Male	11 (45.8%)	11 (45.8%)
Race	White	8 (33.3%)	8 (33.3%)
	Black or African American	11 (45.8%)	11 (45.8%)
	Asian	1 (4.2%)	1 (4.2%)
	Other*	4 (16.7%)	4 (16.7%)
Ethnicity	Hispanic or Latino	1 (4.2%)	1 (4.2%)
	Not Hispanic or Latino	23 (95.8%)	23 (95.8%)
BMI	Mean ± SD	26.0 ± 3.5	26.0 ± 3.5
	Range	21.4 - 31.8	21.4 - 31.8
Other Factors		N/A	N/A

Data source: Module 2.7.1, Clinical Summary, Table 7c

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

There were no discontinued subjects in this study.

Data source: Module 2.7.1, Clinical Summary, Table 12c

Are dropouts appropriate? If no, please comment.	☐ Yes ☐ No ☒ N/A

4.1.1.2.3 Study Adverse Events

System Organ Class Term Preferred Term	Reported Incidence by Treatment Group n (%) of Subjects		
	A N =24	**B** N =24	**Total** N =24
Subjects with One or More TEAEs	**12 (50.0%)**	**8 (33.3%)**	**16 (66.7%)**
Subjects with No TEAEs	12 (50%)	16 (66.7%)	8 (33.3%)
Cardiac disorders	**5 (20.8%)**	**3 (12.5%)**	**7 (29.2%)**
Cardiac flutter	1 (4.2%)	0 (0%)	1 (4.2%)
Tachycardia	4 (16.7%)	3 (12.5%)	6 (25.0%)
Gastrointestinal disorders	**2 (8.3%)**	**3 (12.5%)**	**5 (20.8%)**
Abdominal discomfort	0 (0%)	2 (8.3%)	2 (8.3%)
Nausea	1 (4.2%)	1 (4.2%)	2 (8.3%)
Toothache	1 (4.2%)	0 (0%)	1 (4.2%)
General disorders and administration site conditions	**3 (12.5%)**	**1 (4.2%)**	**4 (16.7%)**
Feeling jittery	3 (12.5%)	0 (0%)	3 (12.5%)
Vessel puncture site pain	0 (0%)	1 (4.2%)	1 (4.2%)
Investigations	**2 (8.3%)**	**0 (0%)**	**2 (8.3%)**
Eosinophil count increased	1 (4.2%)	0 (0%)	1 (4.2%)
Heart rate increased	1 (4.2%)	0 (0%)	1 (4.2%)
Metabolism and nutrition disorders	**1 (4.2%)**	**1 (4.2%)**	**2 (8.3%)**
Decreased appetite	1 (4.2%)	1 (4.2%)	2 (8.3%)
Musculoskeletal and connective tissue disorders	**1 (4.2%)**	**1 (4.2%)**	**2 (8.3%)**
Pain in extremity	1 (4.2%)	1 (4.2%)	2 (8.3%)
Nervous system disorders	**2 (8.3%)**	**2 (8.3%)**	**4 (16.7%)**
Depressed level of consciousness	1 (4.2%)	0 (0%)	1 (4.2%)
Headache	1 (4.2%)	2 (8.3%)	3 (12.5%)
Psychiatric disorders	**2 (8.3%)**	**1 (4.2%)**	**2 (8.3%)**
Change in sustained attention	0 (0%)	1 (4.2%)	1 (4.2%)
Euphoric mood	1 (4.2%)	0 (0%)	1 (4.2%)
Insomnia	1 (4.2%)	0 (0%)	1 (4.2%)
Skin and subcutaneous tissue disorders	**1 (4.2%)**	**1 (4.2%)**	**2 (8.3%)**
Hyperhidrosis	1 (4.2%)	0 (0%)	1 (4.2%)
Skin irritation	0 (0%)	1 (4.2%)	1 (4.2%)
Vascular disorders	**1 (4.2%)**	**0 (0%)**	**1 (4.2%)**
Peripheral coldness	1 (4.2%)	0 (0%)	1 (4.2%)

Data source: Module 2.7.1, Clinical Summary, Table 8c

Subjects Experiencing Emesis (Include in eCTD)

N/A

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 (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
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

Comments on Adverse Events: Adequate

Overall there were 33 Treatment-emergent adverse event (TEAEs) affecting 16 subjects (66.7% of subjects dosed). Of these, 29 TEAEs affecting 15 subjects (62.5%) were considered treatment-related. All TEAEs were mild in severity. No SAEs were reported during the conduct of the study as determined by the clinical investigator (per the fasting study report Section 12).

The reviewer confirmed that majority of the TEAEs are common AEs of the RLD product per the RLD labeling. The AE profile is comparable for the Test and Reference products. There is no safety concern of the test product from BE perspective.

4.1.1.2.4 Protocol Deviations

There were no protocol deviations in this study.
Data source: Module 2.7.1, Clinical Summary, Table 13c

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 ☒ N/A No dropout; No protocol deviation

Comments on Concomitant medications: Adequate

Per the fasting study report Section 12.2.1, no concomitant medications were given during the study except cold (ice) pack and hot pack were used to treat pain in extremity, pain in puncture site, and headache.

Table 12-2 Summary of Concomitant Non-Drug Therapy

Subject	Period	Treatment	NDT	Adverse Event (PT)	Relationship to Study Drug
(b) (6) [redacted]	1	A	Hot Pack	Pain in extremity	POSSIBLE
	1	B	Hot Pack	Vessel puncture site pain	UNRELATED
	1	B	Cold (Ice) Pack	Headache	POSSIBLE

NDT, non-drug therapy; PT, preferred term.

Data source: Module 5.3.1.2, Fasting Study Report Table 12-2

Reviewer's Overall Comments on Dropout/Adverse Events/Protocol Deviations:

- There is no dropout subject in the fasting study.
- AE profile is comparable between the test and reference treatments. There is no safety concern of the test product.
- There is no protocol deviation in the fasting study.
- There is no concomitant medications in the fasting study.

The clinical results of the fasting study are **adequate.**

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
[redacted]		Repeat Sample Analysis Procedure and Acceptance Criteria
		Calibration Standards, Quality Control Samples and Analytical Run Acceptance Criteria

Data source:
Module 2.7.1, Clinical Summary, Table 15
Module 5.3.1.4, Bioanalytical Report, Section 17

All necessary SOPs submitted?	☒ Yes ☐ No

4.1.1.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. 2018-4413 Methylphenidate								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.100	0.200	0.500	1.50	4.00	9.00	18.0	30.0
Inter day Precision (%CV)	4.1	4.8	3.8	2.2	2.7	1.6	2.0	1.2
Inter day Accuracy (%Actual)	92.9	101.5	102.0	102.0	101.0	101.4	100.0	99.3
Linearity	0.9992 to 0.9998							
Linearity Range (ng/mL)	0.100 to 30.0							
Sensitivity/LOQ (ng/mL)	0.100							

Bioequivalence Study No. 2018-4413 Methylphenidate			
Parameter	**Quality Control Samples**		
Concentration (ng/mL)	0.300	15.0	24.0
Inter day Precision (%CV)	3.6	2.5	2.5
Inter day Accuracy (%Actual)	101.3	100.7	100.4

Data source: Module 2.7.1, Clinical Summary, Table 14c

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No Concentration data are provided in Module 5.3.1.2 as SAS dataset and in Appendix 16.2.5. Most subject samples are within 0.3 to 25 ng/mL (calibration rage: 0.100 ng/mL to 30 ng/mL) and QCs are well distributed (0.3, 15, and 24 ng/mL)
Are there any concerns related to sample analysis (including rejected runs, reinjection, sample dilution, etc.)? If yes,	☐ Yes ☒ No

comment below or consult TL/tertiary reviewer for additional actions	
Were 20% of chromatograms included?	☒ Yes ☐ No Module 5.3.1.4, Bioanalytical Report, Appendix 6
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly Subjects #01-08
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 Module 5.3.1.4, Bioanalytical Report, Appendix 7

4.1.1.3.3 Reanalysis of Study Samples

Study No.: 2018-4413 Additional information, *2018-4413-bioanalytical-report*, Pages 27-34 Analyte: Methylphenidate								
	Nr. of samples reanalyzed				Nr. of recalculated values used after reanalysis			
	Actual Nr.		% of assays		Actual Nr.		% of assays	
Reason why assay was repeated	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Pharmacokinetic	0	0	0	0	0	0	0	0
AULOQ	21	19	3.50	3.17	21	19	3.50	3.17
CP	4	4	0.67	0.67	3	4	0.50	0.67
UISR	5	3	0.83	0.50	3	3	0.50	0.50
Total	**30**	**26**	**5.00**	**4.33**	**27**	**26**	**4.50**	**4.33**

Code	Definition
AULOQ	Above the Upper Limit of Quantitation
CP	Confirm presence of peak in pre-dose
UISR	Unacceptable Internal Standard Response.

Data source: Module 2.7.1, Clinical Summary, Table 9c

Does the reviewer agree with the reanalysis of study samples: analytical and/or PK repeat?	☐ Yes ☒ No See comments below
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: Inadequate

A total of 9 batches were generated during study sample analysis (fasting bioanalytical report Table 5). Eight (8) were accepted and 1 batch was not completed due to sample processing error, and was re-extracted in a new batch (the applicant did not submit sufficient information for the re-extracted run - please see comments below).

Above the Upper Limit of Quantitation (AULOQ)

Forty (40) samples were repeated due to Above the Upper Limit of Quantitation (code: AULOQ). The reviewer spot checked the numerical raw data and confirmed that these samples were correctly identified for repeat per the applicant's SOP [redacted] (b) (4) ('Repeat Sample Analysis Procedure and Acceptance Criteria') Section 2.2.6, i.e., "*Samples that are AULOQ are repeated with an appropriate validated dilution factor using the appropriate blank matrix. A set of dilution QCs with the same dilution factor as the diluted samples are included*". For example as shown below from the 100% numerical raw data, [redacted] (b) (4), (b) (6)

[redacted] (b) (4), (b) (6)

Per SOP [redacted] (b) (4) Section 2.2.6.2, *the dilution QCs are not included in the overall acceptance criteria of the batch, however in order to accept the results of the diluted samples, two-thirds (two out of three) of the dilution QCs should meet the acceptance criteria*. [redacted] (b) (4), (b) (6)

For all 40 samples, the repeated values were at least 96% the upper limit of quantitation after correction for dilution (fasting bioanalytical report Table 3). In addition, the dilution integrity has been established in the pre-study method validation. The bioanalytical repeats for these samples are acceptable.

Confirm Presence of Peak in Pre-dose (CP)

From the total of 48 pre-dose samples, 8 were repeated for "confirm presence of peak in pre-dose (code: CP)".

Per SOP [redacted] (b) (4) Section 2.2.9, *Samples are identified for CP if one or more of the following apply:*

- *A peak that is present at the retention time of the analyte in the blank of the pre-dose is >20% of the analyte peak area of the STD A within the batch.*
- *The analyte/ISTD area ratio of a peak that is present at the retention time of the pre-dose with ISTD sample is >20% of the analyte/ISTD area ratio of the STD A within the batch.*

The reviewer spot checked the 100% numerical raw data and confirmed these samples were correctly identified for repeat per the applicant's SOP [redacted] (b) (4). For example, [redacted] (b) (4)

(b) (4), (b) (6)

[redacted]

It should be noted that for all 8 samples coded as "CP", although there were peak at the retention time of the analyte in the original run, the concentrations were BLQ from both the original and repeated runs, as shown below:

(b) (4), (b) (6)

[redacted]

The bioanalytical repeats for these samples are acceptable.

Unacceptable Internal Standard Response (UISR)

Eight (8) samples were repeated due to "Unacceptable Internal Standard Response (code: UISR)". The reviewer spot checked the numerical raw data and confirmed that these samples were correctly identified for repeat per the applicant's SOP [redacted] (b) (4) Section 2.2.8. For example, [redacted] (b) (4), (b) (6). Therefore, this sample was identified as "UISR" and repeated per SOP [redacted] (b) (4) 2 Section 2.2.8, i.e., *Study samples with internal standard response outside ±40% of the average ISTD response within a batch are repeated as UISR.* The repeated values met the acceptance criteria and were used as final sample values. The bioanalytical repeats for these samples are acceptable.

Whole Batch Repeat

Run [redacted] (b) (6) was "incomplete" due to "Sample processing error" and was re-extracted and re-injected as a new batch run [redacted] (b) (6) The 100% numerical raw data are provided for both the original and re-extracted runs. The original run may have stopped in the middle of the run because the raw data only included 142 samples; the repeated run included 236 samples. However, the fasting bioanalytical report does not provide further details of the "sample processing error". SOP [redacted] (b) (4) ('Repeat Sample Analysis Procedure and Acceptance Criteria') does not specify criteria for "sample processing error". The applicant will be requested to provide a detailed explanation of the reason for re-extraction of the original run [redacted] (b) (6) in the pivotal fasting BE study with supporting document.

Incurred Sample Reanalysis (ISR)

The applicant provided a report for its incurred sample reanalysis (ISR) in fasting bioanalytical report Section 16.3 and Table 4.

The ISR was conducted using 89 subject samples for methylphenidate (7.4% of the total 1200 samples analyzed) as per its SOP [redacted] (b) (4) Section 2.3, i.e., *Approximately 10% of the first 1000 samples and 5% of the remaining number of samples, or 7 % of the total number of samples is selected for incurred sample reanalysis.* For each selected subject, within each period, two samples were selected. One was close to the Cmax, and the second sample was selected from the elimination phase.
87 out of 89 samples (97.8%) were found to be within ±20% bias. Thus, ISR were within acceptance criteria specified in its SOP [redacted] (b) (4) Section 2.3:

[redacted] (b) (4)

Additionally, the applicant's ISR approach (# of samples chose, nature of samples chose, calculation approach for % difference, and acceptance criteria) is consistent with the FDA Guidance for Industry: Bioanalytical Method Validation (May2018)[32], as shown below

In-Study Analysis Recommendations
Elements: • Sample size: o 10% reanalysis of the first 1000 samples, and o 5% reanalysis of the remaining samples • Sample selection: o Around C_{max} and in the elimination phase **Acceptance Criteria:** • CC: 67% should be ± 20% of the mean • LBA: 67% should be ± 30% of the mean

Source: FDA Guidance Bioanalytical Method Validation (May 2018) Table 2

Reviewer's Overall Comments on Bioanalytical Results:

The applicant's bioanalytical results for the fasting study are inadequate.

[32] https://www.fda.gov/downloads/drugs/guidances/ucm070107.Pdf

4.1.1.4 Pharmacokinetic Results

4.1.1.4.1 Arithmetic Mean Pharmacokinetic Parameters – Reviewer calculated

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
cmax	ng/mL	26.725	25.69	13.10	43.90	26.442	27.09	15.70	49.20	1.01
tmax	hr	5.500	.	1.50	7.00	5.000	.	1.00	6.50	1.10
AUCINF	ng hr/mL	212.300	30.59	130.86	373.07	208.885	34.30	111.03	380.84	1.02
KE	hr-1	0.175	19.04	0.12	0.23	0.184	17.34	0.14	0.27	0.95
THALF	hr	4.118	20.61	3.04	6.01	3.865	16.04	2.52	4.98	1.07
Auc0-3	ng hr/mL	39.465	33.72	19.42	69.13	39.360	26.81	19.49	57.34	1.00
Auc3-7	ng hr/mL	78.231	22.97	47.35	113.50	78.024	29.20	34.80	128.30	1.00
Auc7-12	ng hr/mL	58.793	38.69	28.81	113.75	57.594	46.84	21.75	134.33	1.02

4.1.1.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Methylphenidate (No of subjects completed = 24) Dose 60 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasted Bioequivalence Study (2018-4413)							
Parameter	Contrast	Test	N	RLD	N	Ratio (%)	90% C.I.
AUC_{inf}	A vs B	203.865	24	197.936	24	103.00	99.56-106.55
C_{max}	A vs B	25.867	24	25.607	24	101.02	94.67-107.79
AUC_{0-3}	A vs B	37.375	24	37.833	24	98.79	90.74-107.56
AUC_{3-7}	A vs B	76.242	24	74.572	24	102.24	95.78-109.14
AUC_{7-12}	A vs B	55.304	24	52.379	24	105.58	97.15-114.74

Data source: Module 2.7.1, Clinical Summary, Table 3A

4.1.1.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Methylphenidate (No of subjects completed = 24) Dose 60 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasted Bioequivalence Study (2018-4413)							
Parameter	Unit	Test	N	RLD	N	Ratio	90% C.I.
AUC_{inf}	ng hr/mL	203.82	24	197.83	24	1.03	99.59-106.58
C_{max}	ng/mL	25.87	24	25.61	24	1.01	94.67-107.79
AUC_{0-3}	ng hr/mL	37.37	24	37.83	24	0.99	90.72-107.55
AUC_{3-7}	ng hr/mL	76.26	24	74.58	24	1.02	95.80-109.16
AUC_{7-12}	ng hr/mL	55.27	24	52.33	24	1.06	97.19-114.77

4.1.1.4.4 Additional Information for the Study

Root Mean Square Error	Not calculated in the output of DB SAS code of partial AUC analysis
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 ☒ No Minor difference in median Tmax (Test 5.5h vs Reference 5.0h) is acceptable. See comments below
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

AUCt/AUCi ratios are not calculated because AUCt is not a recommended PK parameter per the PSG. Based on the individual PK profiles (Module 5.3.1.2, Appendix 16.2.6), the terminal phase of methylphenidate is well characterized in the fasting study.

Comments on PK results: Inadequate

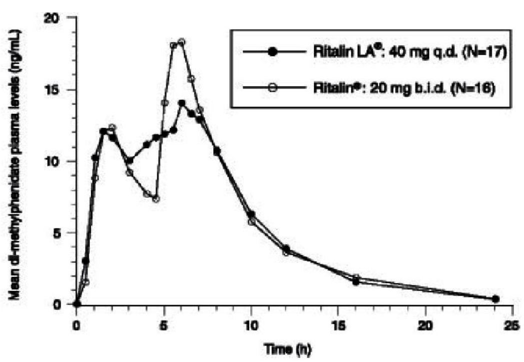
Since this is an ER product and there is deficiency in the repeat assay, the reviewer conducted a confirmative SAS analysis using the partial AUC (pAUC) SAS program (pAUC_macro) with the SAS datasets submitted by the applicant. The applicant used actual sampling time and the DB pAUC SAS program used nominal sampling time in the analysis. The results indicate that the geometric mean ratios and 90% CIs of Cmax calculated by the reviewer are the same as that by the applicant. There are marginal differences in the results of AUC0-3, AUC3-7, AUC7-12, and AUCi between the applicant and reviewer's analyses likely due to different sampling time used in the analysis (actual vs nominal) and different selection of data points for the determination of the terminal phase.

For both the applicant and reviewer's calculations, the 90% CIs for least squares geometric mean of LnCmax, LnAUC0-3, LnAUC3-7, LnAUC7-12, and LnAUCI in the fasting study are within the BE acceptable range of 80.00-125.00%.

The median Tmax of methylphenidate in current study is 5.5 hours for Test (range: 1.5-7.0 hours) and 5.0 hours for Reference (range: 1.0-6 hours) treatments. The minor difference is acceptable for the indication, i.e., treatment of Attention Deficit Hyperactivity Disorder (ADHD), of the drug product.

Per the RLD labeling, Ritalin LA PK profile has 2 distinct peaks approximately 4 hours apart. The reviewer confirmed that double peak profiles were observed in all individual subjects and consistent between the Test and Reference treatment (Module 5.3.1.2, Appendix 16.2.6, Individual PK Data). For majority of subjects, the Tmax occurred at the 2nd peak. This is consistent with the PK information stated in the RLD labeling[33], i.e., Cmax1 is generally lower than Cmax 2, also shown below:

Figure 1. Mean Plasma Concentration Time-Profile of Methylphenidate After a Single Dose of Ritalin LA 40 mg q.d. and Ritalin 20 mg Given in Two Doses Four Hours Apart



[33] Drugs@FDA: RLD Labeling (NDA 021284), version approved date 01/04/2017: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021284s034lbl.pdf

Table 1. Mean ± SD and Range of Pharmacokinetic Parameters of Methylphenidate After a Single Dose of Ritalin LA and Ritalin Given in Two Doses 4 Hours Apart

Population	Children		Adult Males	
Formulation Dose	Ritalin 10 mg & 10 mg	Ritalin LA 20 mg	Ritalin 10 mg & 10 mg	Ritalin LA 20 mg
N	21	18	9	8
T_{lag} (h)	0.24 ± 0.44	0.28 ± 0.46	1.0 ± 0.5	0.7 ± 0.2
	0 - 1	0 - 1	0.7 - 1.3	0.3 - 1.0
T_{max1} (h)	1.8 ± 0.6	2.0 ± 0.8	1.9 ± 0.4	2.0 ± 0.9
	1 - 3	1 - 3	1.3 - 2.7	1.3 - 4.0
C_{max1} (ng/mL)	10.2 ± 4.2	10.3 ± 5.1	4.3 ± 2.3	5.3 ± 0.9
	4.2 - 20.2	5.5 - 26.6	1.8 - 7.5	3.8 - 6.9
T_{minip} (h)	4.0 ± 0.2	4.5 ± 1.2	3.8 ± 0.4	3.6 ± 0.6
	4 - 5	2 - 6	3.3 - 4.3	2.7 - 4.3
C_{minip} (ng/mL)	5.8 ± 2.7	6.1 ± 4.1	1.2 ± 1.4	3.0 ± 0.8
	3.1 - 14.4	2.9 - 21.0	0.0 - 3.7	1.7 - 4.0
T_{max2} (h)	5.6 ± 0.7	6.6 ± 1.5	5.9 ± 0.5	5.5 ± 0.8
	5 - 8	5 - 11	5.0 - 6.5	4.3 - 6.5
C_{max2} (ng/mL)	15.3 ± 7.0	10.2 ± 5.9	5.3 ± 1.4	6.2 ± 1.6
	6.2 - 32.8	4.5 - 31.1	3.6 - 7.2	3.9 - 8.3
$AUC_{(0-\infty)}$	102.4 ± 54.6	86.6 ± 64.0[a]	37.8 ± 21.9	45.8 ± 10.0
(ng/mL x h-1)	40.5 - 261.6	43.3 - 301.44	14.3 - 85.3	34.0 - 61.6
$t_{1/2}$ (h)	2.5 ± 0.8	2.4 ± 0.7[a]	3.5 ± 1.9	3.3 ± 0.4
	1.8 - 5.3	1.5 - 4.0	1.3 - 7.7	3.0 - 4.2

Source: RLD labeling, Clinical Pharmacology section

Analysis of Individual T/R Ratios

The reviewer evaluated the distribution of individual Test/Reference (T/R) ratios for the PK parameters as given below. The results are presented for information only and will not be communicated to the applicant (please see discussion in Section 3.3)

Subject#	T/R Cmax	T/R TMAX	T/R AUCi	T/RAUC0-3	T/R AUC3-7	TRAUC7-12
(b) (6) [redacted]	1.33	1.20	1.29	1.10	1.24	1.59
	1.01	5.50	0.93	0.88	0.92	1.01
	0.76	1.00	0.77	0.85	0.75	0.77
	1.11	0.77	1.06	1.17	1.17	0.86
	1.23	1.00	0.97	0.71	0.97	1.18
	1.20	0.77	1.18	1.42	1.34	0.90
	1.19	1.00	1.11	1.21	1.03	1.12
	1.09	1.86	1.07	1.13	0.92	1.31
	0.84	1.20	1.01	0.90	0.89	1.34
	0.96	1.10	1.03	1.19	0.98	0.98
	0.89	0.85	0.97	0.92	0.89	0.96
	0.83	0.25	1.03	1.67	0.66	0.88
	1.15	0.30	0.99	1.03	0.95	1.00
	0.92	1.09	1.13	1.00	1.04	1.31
	1.13	1.63	1.23	0.72	1.05	2.18
	0.82	1.00	0.94	1.01	0.92	0.93
	1.08	1.00	0.99	1.09	1.10	0.93
	1.50	0.77	1.16	1.08	1.51	0.92

Subject#	T/R Cmax	T/R TMAX	T/R AUCi	T/RAUC0-3	T/R AUC3-7	TRAUC7-12
(b) (6) [redacted]	0.90	1.27	1.06	0.82	0.95	1.38
	0.89	0.92	0.87	0.94	0.88	0.84
	1.01	1.00	0.90	0.56	1.02	0.97
	0.74	4.00	1.12	0.76	1.36	1.10
	0.82	1.10	1.00	0.95	0.91	1.11
	1.25	0.69	1.07	1.27	1.57	0.64
Not within range	4	11	2	7	6	8
Total # of subjects (n =)	24	24	24	24	24	24
% not within range	16.67	45.83	8.33	29.17	25.00	33.33

Note: The values of T/R ratio not within 0.8 – 1.25 are highlighted

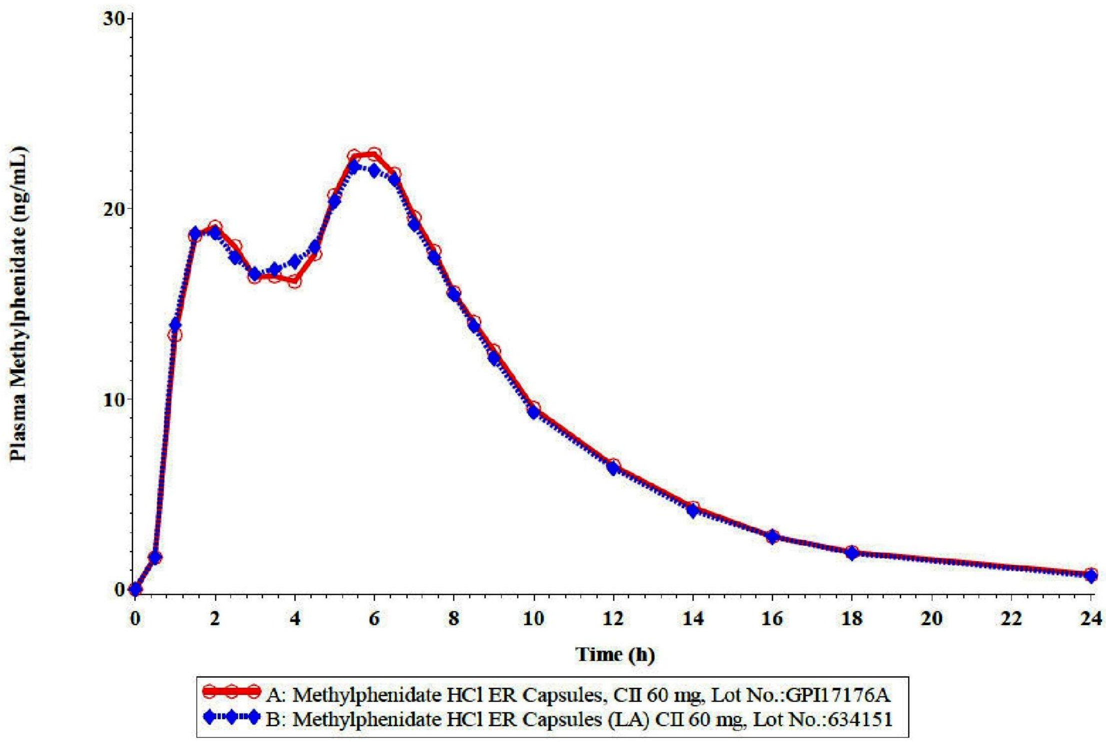
The applicant's *in vivo* fasting BE study is **inadequate** due to deficiency in the repeat assay.

4.1.1.5 Overall Comment

Was the fasting bioequivalence study acceptable? Inadequate

Mean Plasma Concentration Profile, Single-Dose Fasting Bioequivalence Study (Firm generated)

Figure 11-1 Mean Plasma Methylphenidate Concentration-Time Profiles (A: n = 24 / B: n = 24)



4.1.2 Single-Dose Pivotal Fed Bioequivalence Study

4.1.2.1 Study Design

4.1.2.1.1 Study Information

Study Number	2017-4351			
Study Title	A Single-Dose, Bioequivalence Study of Two Formulations of Methylphenidate HCl 60 mg Extended-Release Capsules under Fed Conditions			
Study Type	☑In Vivo BE	☐In Vitro BE	☐Permeability	☐Other
Submission Location: **Study Report** **Validation Report** **Bioanalytical Report**	Module 5.3.1.2, *2017-4351-study-report* Module 5.3.1.4, *2017-4351-validation-report,* Module 5.3.1.4, *2017-4351-bioanalytical-report*			
Clinical Site (Name, Address, Phone #, Fax#)	(b) (4) [redacted]			
Principal Clinical Investigator (Name, Email)	[redacted]			
Dosing Dates	Period 1: December 10, 2017 Period 2: December 22, 2017			
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4) [redacted]			
Principal Analytical Investigator (Name, Email)	[redacted]			
Analytical Dates	December 29, 2017 to January 13, 2018			
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) 33 days (December 10, 2017 to January 12, 2018) (b) -35 to -15 °C			
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	127 days @ -25 ± 10 °C			
LTSS Data Location	Module 5.3.1.4, *2017-4351-validation-report.pdf,* pages 469 and 472 Module 5.3.1.4, *2017-4351-validation-report.pdf,* pages 716 and 725			

Data source:
Module 2.7.1, Clinical Summary, Table 10b
Module 5.3.1.2, Fed Study Report (Study #2017-4351)

4.1.2.1.2 Product Information

Same as the fasting study (Section **4.1.1.1.2**)

4.1.2.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 40 Dosed: 39* Completed: 39 Samples Analyzed: 39 Statistically Analyzed: 39
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	12 days
Randomization	☒ Yes ☐ No Module 5.3.1.2, Appendix 16.1.7, Randomization Scheme
Blood Sampling Times	Pharmacokinetic samples were collected prior to dosing (0-hour), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 14, 16, 18, and 24 hours after drug administration, total 25 samples in each period.
IRB Approval	☒ Yes Date: 06 Dec 2017 ☐ No
Informed Consent	☒ Yes Date: 06 Dec 2017 ☐ No
Length of Fasting	After an overnight fast of at least 10 hours, subjects consumed a high-fat, high-calorie breakfast starting 30 minutes prior to drug administration. Subjects fasted for at least 4 hours postdose.
Length of Confinement	Subjects were confined in-house from at least 10.5 hours prior to drug administration until at least 24 hours post-dose in each period.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

Data Source: Module 5.3.1.2, Fed Study Report (Study #2017-4351)
* One subject discontinued prior to Period II check-in (please see Section 4.1.2.2.2)

Standard FDA Meal* Used?	☑ Yes ☐ No				
If No, then meal components and composition is listed in the tables below					
Composition of Non-standard FDA Meal Used in Fed Bioequivalence Study					
Ingredients	**Amount (g)**	**Energy (kcal)**	**Protein (kcal)**	**Fat (kcal)**	**Carbohydrate (kcal)**

TOTAL					
PERCENTAGE					

Data source: Module 2.7.1, Clinical Summary, Table 16

Comments on Study Design: Adequate

The PK sampling times in the current study are sufficient to capture the Cmax/Tmax.

Per the RLD label, an average half-life of Ritalin LA is about 3.5 hours. The mean half-life in current study is 4.8 hours for Test treatment and 4.6 hours for Reference treatment, respectively. The sampling duration of 24 hours (> 3-fold half-lives) and washout period of 12 days (> 5-fold half-lives) in the current study are sufficient to characterize the half-life and complete elimination.

The fed study design is acceptable.

4.1.2.2 Clinical Results

4.1.2.2.1 Demographic Profile of Subjects

Study No. 2017-4351			
		Treatment Groups	
		Trt A N = 40	**Trt B** N = 39
Age (years)	**Mean ± SD**	40 ± 11	40 ± 11
	Range	19 - 60	19 - 60
Age Group	**<18**	0 (0%)	0 (0%)
	18 - 40	24 (60.0%)	23 (59.0%)
	41 - 64	16 (40.0%)	16 (41.0%)
	65 - 75	0 (0%)	0 (0%)
	>75	0 (0%)	0 (0%)
Sex	**Female**	13 (32.5%)	13 (33.3%)
	Male	27 (67.5%)	26 (66.7%)
Race	**White**	14 (35.0%)	13 (33.3%)
	Black or African American	25 (62.5%)	25 (64.1%)
	Asian	0 (0%)	0 (0%)
	Other	1 (2.5%)	1 (2.6%)
Ethnicity	**Not Hispanic or Latino**	40 (100%)	39 (100%)

Study No. 2017-4351			
		Treatment Groups	
		Trt A N = 40	**Trt B** N = 39
BMI	**Mean ± SD**	27.3 ± 3.8	27.4 ± 3.9
	Range	18.3 - 32.9	18.3 - 32.9
Other Factors		N/A	N/A

Data source: Module 2.7.1, Clinical Summary, Table 7b

4.1.2.2.2 Dropout Information

Study No. 2017-4351				
Subject No.	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
[redacted] (b) (6)	**Reason:** Withdrawal by subject (personal) **Time Dropped-out:** N/V **Date Dropped-out:** [redacted] (b) (6) **Treatment:** Test	1	No	N/A

Data source: Module 2.7.1, Clinical Summary, Table 12b

Table 10-2 Discontinued Subjects

Subject	Reason for Discontinuation	Details	Period	Last Treatment Received	Time From Last Dosing (h)
[redacted] (b) (6)	WITHDRAWAL BY SUBJECT	Per phone conversation with emergency contact; subject withdrew participation prior to period 2 check in due to personal reasons.	1	A	~255.93

NV, not available.
Source: Listing 16.2.1

Data Source: Module 5.3.1.2, Fed Study Report (Study #2017-4351), Table10-2

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No

One subject, Subject [redacted] (b) (6) withdrew consent due to personal reason prior to Period II check in.

The fed protocol Section 15.0 states that *Samples from subjects included in the PK dataset will be assayed.*

Per the fed protocol Section 14.2, *Data from the following subjects will be included in the PK dataset:*

- *Subjects from whom the estimation of Cmax and AUC (AUC0-4, AUC4-8, AUC8-12, and AUCinf) parameters will be* ***possible for both periods****; and*
- *Subjects who complied with all protocol requirements or encountered protocol deviations that do not impact the estimation of the PK parameters.*

Therefore, Period I PK samples of Subject 04 were not assayed per the protocol. The applicant's handling of dropout subject is consistent with its protocol.

4.1.2.2.3 Study Adverse Events

System Organ Class Term Preferred Term	Reported Incidence by Treatment Group n (%) of Subjects		
	A N = 40	B N = 39	Total N = 40
Subjects with One or More TEAEs	**5 (12.5%)**	**9 (23.1%)**	**12 (30.0%)**
Subjects with No TEAEs	35 (87.5%)	30 (76.9%)	28 (70%)
Cardiac disorders	**1 (2.5%)**	**2 (5.1%)**	**2 (5.0%)**
Tachycardia	1 (2.5%)	2 (5.1%)	2 (5.0%)
Eye disorders	**1 (2.5%)**	**0 (0%)**	**1 (2.5%)**
Photophobia	1 (2.5%)	0 (0%)	1 (2.5%)
Gastrointestinal disorders	**3 (7.5%)**	**4 (10.3%)**	**7 (17.5%)**
Abdominal discomfort	0 (0%)	1 (2.6%)	1 (2.5%)
Abdominal pain upper	1 (2.5%)	0 (0%)	1 (2.5%)
Diarrhoea	0 (0%)	3 (7.7%)	3 (7.5%)
Dry mouth	1 (2.5%)	0 (0%)	1 (2.5%)
Nausea	1 (2.5%)	1 (2.6%)	2 (5.0%)
General disorders and administration site conditions	**1 (2.5%)**	**0 (0%)**	**1 (2.5%)**
Fatigue	1 (2.5%)	0 (0%)	1 (2.5%)
Investigations	**0 (0%)**	**2 (5.1%)**	**2 (5.0%)**
Blood bilirubin increased	0 (0%)	1 (2.6%)	1 (2.5%)
Heart rate increased	0 (0%)	1 (2.6%)	1 (2.5%)
Nervous system disorders	**1 (2.5%)**	**2 (5.1%)**	**3 (7.5%)**
Dizziness	0 (0%)	1 (2.6%)	1 (2.5%)
Headache	1 (2.5%)	1 (2.6%)	2 (5.0%)
Psychiatric disorders	**1 (2.5%)**	**1 (2.6%)**	**2 (5.0%)**
Anxiety	1 (2.5%)	0 (0%)	1 (2.5%)
Euphoric mood	0 (0%)	1 (2.6%)	1 (2.5%)
Vascular disorders	**0 (0%)**	**1 (2.6%)**	**1 (2.5%)**
Hypertension	0 (0%)	1 (2.6%)	1 (2.5%)

Data source: Module 2.7.1, Clinical Summary, Table 8b

Subjects Experiencing Emesis (Include in eCTD)

N/A

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 (IR products) or the labeled dosing interval (MR products)? Please comment.	☐ Yes ☐ No ☒ N/A
Was the adverse event profile observed comparable for the test and reference product?	☒ Yes ☐ No
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

Comments on Adverse Events: Adequate

Overall, there were 21 TEAEs affecting 12 subjects (30.0% of subjects dosed). Of these, 18 AEs affecting 10 subjects (25.0%) were considered treatment-related. All TEAEs were mild in severity and resolved prior to the end of the study. No subject discontinued from the study due to a TEAE. No SAEs were reported during the conduct of the study as determined by the clinical investigator (per the fed study report Section 12).

The reviewer confirmed that majority of the TEAEs are common AEs of the RLD per the RLD labeling. The AE profile is comparable for the Test and Reference products. There is no safety concern of the test product from BE perspective.

4.1.2.2.4 Protocol Deviations

Study No. 2017-4351		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
In Period 1, the scheduled 4-hour electrocardiogram was measured 15 minutes earlier than the protocol-specified 30 minute time frame.	[redacted]	(b) (6)
In Period 2, Time Point 7-hour PK blood sample, staff missed to document sample collection details.		
In Period 2, staff documented a collection time inconsistent with the scheduled collection time at the 6.5-hour Time Point PK blood sample, such that the actual time of collection cannot be verified.		
In Period 1, staff documented an unverifiable pulse rate at the 2-hour vital signs measurement. Pulse measurements before and after this time point were within normal limits.		

Study No. 2017-4351		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Staff inadvertently ordered additional, unnecessary lab tests along with the required post-study panel.	[redacted]	[redacted]
In Period 2, Time Point 7-hour sample, staff missed to capture aliquot and storage details.	[redacted]	[redacted]

Data source: Module 2.7.1, Clinical Summary, Table 13b

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

For the missing or inconsistent PK collection time for Subjects [redacted], the applicant used nominal time in its PK analysis. Since the problematic time points were not Tmax, and the 90% CIs for AUC are not marginal, the reviewer considers that the deviations do not impact study outcome.

Other deviations related to electrocardiogram (ECG) monitoring, vital sign measurement, sample storage documentation and end-of-study lab tests are not considered to have impact on study outcome.

Comments on Concomitant medications: Adequate

Per the fed study report Section 12.2.1, no concomitant medications were given during the study except non-drug therapy as shown below.

Table 12-2 Summary of Concomitant Nondrug Therapy

Subject	Period	Treatment	NDT	Adverse Event (PT)	Relationship to Study Drug
[redacted]	2	B	Gingerale	Abdominal discomfort	PROBABLE
	2	A	Other, Specify: Refresh Optive Mega 3 eye drops	Photophobia	UNLIKELY
	2	A	Gingerale	Nausea	PROBABLE

NDT, non-drug therapy; PT, preferred term.

Data source: Module 5.3.1.2, Fed Study Report Table 12-2

Per the CRF, Subject [redacted] received ginger ale at 12:35 on [redacted], i.e., 4 hours and 22 minutes after Period II dosing (8:13 on [redacted], reference product); Subject [redacted] received ginger ale at 12:35 on [redacted], i.e., 4 hours and 19 minutes after Period II dosing (8:16 on 1[redacted], test product); Subject [redacted] received Refresh Optive Mega 3 Eye Drops[34] at 10:00 on 12/23/2017, i.e., 25 hours and 45 minutes after Period II dosing (8:15 on [redacted], test product).

Per fed protocol Section 10.4, *water will be restricted from 1 hour prior to drug administration until 1 hour postdose (except the water administered with the drug). Access to water will otherwise be freely available to subjects*. The reviewer does not consider that carbonated soft drink flavoured with ginger administered 4 hours after dosing have an impact on the PK of the drug. Also, the Refresh Optive Mega 3 Eye Drops is not considered to impact PK of the drug.

Reviewer's Overall Comments on Dropout/Adverse Events/Protocol Deviations:

- Handling of dropout subjects is consistent with the protocol.
- AE profile is comparable between the test and reference treatments. There is no safety concern of the test product.
- Protocol deviation did not compromise the integrity of the fed study.
- There is no concomitant medication in the fed study.

The clinical results of the fed study are **adequate.**

4.1.2.3 Bioanalytical Results

4.1.2.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Same as that for the fasting study.

4.1.2.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. 2018-4455 Methylphenidate								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.100	0.200	0.500	1.50	4.00	9.00	18.0	30.0
Inter day Precision (%CV)	5.1	5.0	3.5	1.4	2.5	1.9	1.0	0.7
Inter day Accuracy (%Actual)	93.9	100.5	98.6	103.3	103.0	100.7	101.1	98.7
Linearity	0.9992 to 1.0000							
Linearity Range (ng/mL)	0.100 to 30.0							
Sensitivity/LOQ (ng/mL)	0.100							

Bioequivalence Study No. 2018-4455 Methylphenidate

[34] https://www.drugs.com/cdi/refresh-optive-mega-3.html

Parameter	Quality Control Samples			
Concentration (ng /mL)	0.300	7.5	15.0	24.0
Inter day Precision (%CV)	5.0	2.5	1.9	2.5
Inter day Accuracy (%Actual)	99.7	99.7	98.0	99.2

Data source: Module 2.7.1, Clinical Summary, Table 14b

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No Concentration data are provided in Module 5.3.1.2 as SAS dataset and in Appendix 16.2.5. Most subject samples are within 0.3 to 25 ng /mL (calibration rage: 0.100 ng/mL to 30 ng/mL) and QCs are well distributed (0.3, 7.5, 15, and 24 ng/mL)
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 Module 5.3.1.4, Bioanalytical Report, Appendix 6
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly Subjects [redacted]
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 Module 5.3.1.4, Bioanalytical Report, Appendix 7

4.1.2.3.3 Reanalysis of Study Samples

Study No.: 2017-4351 Additional information, *2017-4351-bioanalytical-report*, Pages 31-40 Analyte: Methylphenidate								
	Nr. of samples reanalyzed				**Nr. of recalculated values used after reanalysis**			
	Actual Nr.		**% of assays**		**Actual Nr.**		**% of assays**	
Reason why assay was repeated	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Pharmacokinetic	0	0	0	0	0	0	0	0
AULOQ	28	24	2.87	2.46	28	24	2.87	2.46
CP	5	2	0.51	0.21	5	1	0.51	0.10
UISR	6	2	0.62	0.21	6	2	0.62	0.21
Total	**39**	**28**	**4.00**	**2.87**	**39**	**27**	**4.00**	**2.77**

Code	Definition
AULOQ	Above the Upper Limit of Quantitation ({0} {1}).
CP	Confirm presence of peak in pre-dose
UISR	Unacceptable Internal Standard Response.

Data source: Module 2.7.1, Clinical Summary, Table 9b

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 Although the reviewer agrees with the repeat assay, a confirmative PK analysis was conducted by the reviewer because the drug product is a modified release dosage form
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: adequate

A total of seventeen (17) batches were generated during study sample analysis. Fourteen (14) were accepted, 1 failed the acceptance criteria, 1 was rejected, and 1 batch was not completed (fed bioanalytical report Table 5).

Above the Upper Limit of Quantitation (AULOQ)

Fifty-two (52) samples were repeated due to Above the Upper Limit of Quantitation (code: AULOQ). The reviewer spot checked the numerical raw data and confirmed that these samples were correctly identified for repeat per the applicant's SOP [redacted] (b) (4) ('Repeat Sample Analysis Procedure and Acceptance Criteria') Section 2.2.6, i.e., "*Samples that are AULOQ are repeated with an appropriate validated dilution factor using the appropriate blank matrix. A set of dilution QCs with the same dilution factor as the diluted samples are included*". [redacted] (b) (4), (b) (6)

(b) (4), (b) (6)
[redacted]

Per SOP [redacted] Section 2.2.6.2, *in order to accept the results of the diluted samples, two-thirds (two out of three) of the dilution QCs should meet the acceptance criteria*. The reviewer checked the three repeated batch runs [redacted] and confirmed that at least 2/3 of dilution QCs in these repeat batch runs met the acceptance criteria (±15% nominal value).

For all 52 samples repeated under code AULOQ, the repeated values were at least 93% the upper limit of quantitation after correction for dilution (fed bioanalytical report Table 3). In addition, the dilution integrity has been established in the pre-study method validation. The bioanalytical repeats for these samples are acceptable.

Confirm Presence of Peak in Pre-dose (CP)

From the total of 78 pre-dose samples, 7 were repeated for "confirm presence of peak in pre-dose (code: CP)".

Per SOP [redacted] Section 2.2.9, *Samples are identified for CP if one or more of the following apply:*

- *A peak that is present at the retention time of the analyte in the blank of the pre-dose is >20% of the analyte peak area of the STD A within the batch.*
- *The analyte/ISTD area ratio of a peak that is present at the retention time of the pre-dose with ISTD sample is >20% of the analyte/ISTD area ratio of the STD A within the batch.*

The reviewer spot checked the 100% numerical raw data and confirmed these samples were correctly identified for repeat per the applicant's SOP [redacted]. For example, as shown below, pre-dose sample [redacted]

[redacted]

It should be noted that for all 7 samples coded as "CP", although there were peak at the retention time of the analyte in the original run, the concentrations were BLQ from both the original and repeated runs, as shown below:

Sample Name	% of LLOQ in the original run	% of LLOQ in the repeat run	Reported result (ng/mL)
[redacted] (b) (6)	21.4	0.0	BLQ
	50.0	0.0	BLQ
	22.6	0.0	BLQ
	27.2	0.0	BLQ
	25.7	16.8	BLQ
	27.6	0.0	BLQ
	35.2	0.0	BLQ

Data source: Fed Bioanalytical Report, Section 16.2

The bioanalytical repeats for these samples are acceptable.

Unacceptable Internal Standard Response (UISR)

Eight (8) samples were repeated due to "Unacceptable Internal Standard Response (code: UISR)". The reviewer spot checked the numerical raw data and confirmed that these samples were correctly identified for repeat per the applicant's SOP [redacted] (b) (4) Section 2.2.8. For example, the IS area of sample [redacted] (b) (4), (b) (6) Therefore, this sample was identified as "UISR" and repeated per SOP [redacted] (b) (4) 2 Section 2.2.8, i.e., *Study samples with internal standard response outside ±40% of the average ISTD response within a batch are repeated as UISR.* The repeated values met the acceptance criteria and were used as final sample values. The bioanalytical repeats for these samples are acceptable.

<u>Whole Batch Repeat</u>

- Run [redacted] (b) (6) failed due to "Calibration curve failed acceptance criteria". This batch was re-extracted as [redacted] (b) (6). The reviewer confirmed that the standard STD-A1 (accuracy% 78.97%) of the original run did not meet SOP [redacted] (b) (4) ('Calibration Standards, Quality Control Samples and Analytical Run Acceptance Criteria') Section 2.5 "*The back-calculated concentration of STD-A (LLOQ) must be within ±20.0% of the nominal value.*" The repeated batch run [redacted] (b) (6) met the batch acceptance criteria. The whole batch repeat for this run is acceptable.

- Run [redacted] (b) (6) failed due to "analyte interference in the CO-BLK". The reviewer confirmed that the original did not meet the batch run acceptance criteria per SOP [redacted] (b) (4) Section 2.5 "*If peaks at the retention times of the analyte(s) or the ISTD(s) are present in the CO-BLKs, they must be less than 20.0% of the CO-LLOQ analyte(s) peak area and less than 5.0% of the CO-LLOQ ISTD peak area.*" As shown below, the original run did not meet the above batch run acceptance criteria, i.e., peak at the retention time of the analyte for [redacted]

[redacted]

This batch was re-extracted as [redacted]. The repeated batch run [redacted] met the batch acceptance criteria. The whole batch repeat for this run is acceptable.

- Run [redacted] was "incomplete" due to "Batch stopped at sample #16 to correct sample positions". This batch was re-injected as [redacted] per [redacted] Section 2.2.4., instrument error (INE). Based on the 100% raw data, the original run stopped at the 16th sample at the time [redacted], 16:05:27. The re-injected run started at time [redacted], 16:54:57. Additionally, the time between the last sample and the start of re-injection (49 minutes) was covered by the stability of extract (6 hours @ room temperature or ice-water bath) and the duration of the whole batch run (34 hours) was also covered by the auto-sampler stability (70.25 hrs @ approximately 5ºC) established in the pre-study method validation. The re-injection of this run is acceptable.

Incurred Sample Reanalysis (ISR)

The applicant provided a report for its incurred sample reanalysis (ISR) in fed bioanalytical report Section 16.3 and Table 4.

The ISR was conducted using 142 subject samples for methylphenidate (7.3% of the total 1950 samples analyzed) as per its SOP [redacted] Section 2.3, i.e., *Approximately 10% of the first 1000 samples and 5% of the remaining number of samples, or 7 % of the total number of samples is selected for incurred sample reanalysis.* For each selected subject, within each period, two samples were selected. One was close to the Cmax, and the second sample was selected from the elimination phase. 141 out of 142 samples (99.3%) were found to be within ±20% bias. Thus, ISR were within acceptance criteria specified in its SOP [redacted] Section 2.3. Additionally, the applicant's ISR approach (# of samples chose, nature of samples chose, calculation approach for % difference, and acceptance criteria) is consistent with the FDA Guidance for Industry: Bioanalytical Method Validation (May 2018)[35]

[35] https://www.fda.gov/downloads/drugs/guidances/ucm070107.Pdf

Reviewer's Overall Comments on Bioanalytical Results:

The applicant's bioanalytical results for the fed study are adequate.

4.1.2.4 Pharmacokinetic Results

4.1.2.4.1 Arithmetic Mean Pharmacokinetic Parameters – Reviewer calculated

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
cmax	ng/mL	22.885	72.33	12.90	119.00	23.008	74.14	12.70	123.00	0.99
tmax	hr	3.000	.	1.00	10.00	3.000	.	1.50	10.00	1.00
AUCINF	ng hr/mL	274.342	124.30	133.79	2317.61	283.112	136.32	131.04	2531.55	0.97
KE	hr-1	0.162	27.24	0.05	0.24	0.162	22.22	0.07	0.23	1.00
THALF	hr	4.844	46.36	2.95	13.25	4.563	29.70	3.08	9.71	1.06
Auc0-4	ng hr/mL	51.437	57.64	22.08	202.85	52.113	76.67	23.44	284.03	0.99
Auc4-8	ng hr/mL	67.351	76.30	32.66	360.38	66.098	96.41	25.56	434.08	1.02
Auc8-12	ng hr/mL	59.412	109.64	29.13	445.30	60.440	109.99	23.59	447.30	0.98

4.1.2.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Methylphenidate (No of subjects completed=39) Dose (1 x 60 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (2017-4351)							
Parameter	Contrast	Test	N	RLD	N	Ratio	90% C.I.
AUC_{inf}	A vs B	226.302	39	229.235	37	98.72	95.79-101.75
C_{max}	A vs B	20.705	39	20.805	39	99.52	96.17-102.98
AUC_{0-4}	A vs B	46.510	39	46.500	39	100.02	92.35-108.33
AUC_{4-8}	A vs B	60.053	39	56.017	39	107.20	102.15-112.51
AUC_{8-12}	A vs B	50.042	39	49.855	39	100.37	96.21-104.72

Data source: Module 2.7.1, Clinical Summary, Table 3A

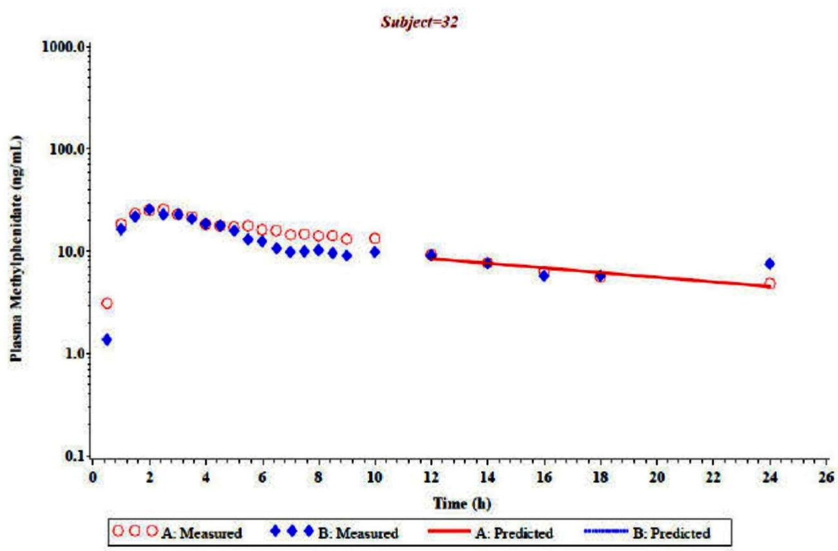
4.1.2.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

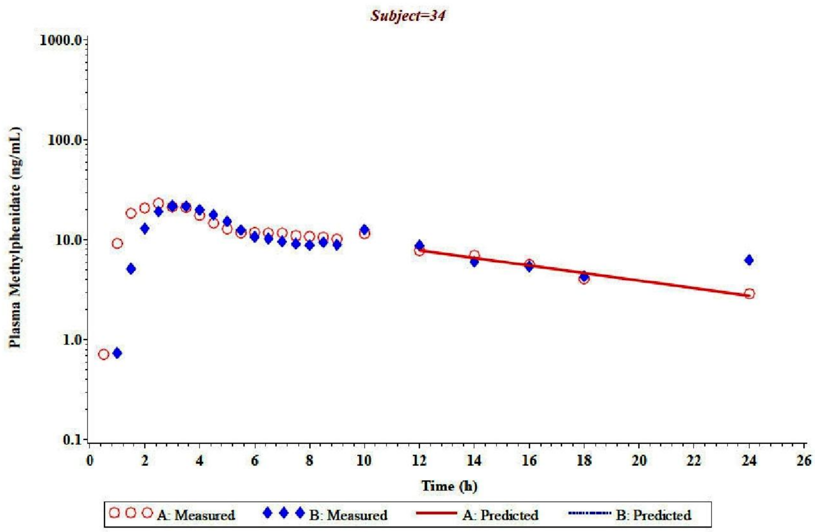
Methylphenidate (No of subjects completed = 39) Dose 60 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (2017-4351)							
Parameter	Unit	Test	N	RLD	N	Ratio	90% C.I.
AUC_{inf}	ng hr/mL	226.26	39	229.27	37	0.99	95.76-101.70
C_{max}	ng/mL	20.71	39	20.80	39	1.00	96.17-102.98
AUC_{0-4}	ng hr/mL	46.52	39	46.51	39	1.00	92.34-108.31
AUC_{4-8}	ng hr/mL	60.06	39	56.01	39	1.07	102.16-112.53
AUC_{8-12}	ng hr/mL	50.03	39	49.84	39	1.00	96.20-104.73

4.1.2.4.4 Additional Information for the Study

Root Mean Square Error	Not calculated in the output of DB SAS code of partial AUC analysis
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 ☒ 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

AUCt/AUCi ratios are not calculated because AUCt is not a recommended PK parameter per the PSG. Based on the individual PK profiles (Module 5.3.1.2, Appendix 16.2.6), the terminal phase of methylphenidate is well characterized in the fed study except two subjects (#32 and #34) whose AUCi were not calculated in the applicant and reviewer's analyses due to increasing concentration at the last time point (both were reference treatments [A=Test; B=Reference], as shown below).





Comments on PK results: adequate

Since this is an ER product, the reviewer conducted a confirmative SAS analysis using the partial AUC program (pAUC_macro) with the SAS datasets submitted by the applicant. The applicant used actual sampling time and the DB SAS program used nominal sampling time in the analysis. The results indicate that the geometric mean ratios and 90% CIs of Cmax calculated by the reviewer are the same as that by the applicant. There are small differences in the results of AUC0-4, AUC4-8, AUC8-12, and AUCi between the applicant and reviewer's analyses likely due to different sampling time used in the analysis (actual vs nominal) and different selection of data points for the determination of the terminal phase.

For both the applicant and reviewer's calculations, the 90% CIs for least squares geometric mean of LnCmax, LnAUC0-4, LnAUC4-8, LnAUC8-12, and LnAUCI in the fed study are within the BE acceptable range of 80.00-125.00%.

The median Tmax of methylphenidate in current study is 3 hours for both the Test (range: 1-10 hours) and Reference (range: 1.5-10 hours) treatments.

The double peak PK profiles are still observed in the fed study but the 2nd peak were less apparent compared to that in the fasting study. For some subjects there appeared to be only one peak. The observation is consistent with the RLD labeling, i.e., *When administered with a high fat breakfast to adults, Ritalin LA had a longer lag time until absorption began and variable delays in the time until the first peak concentration, the time until the interpeak minimum, and the time until the second peak. The first peak concentration and the extent of absorption were unchanged after food relative to the fasting state, although the second peak was approximately 25% lower*. The observation also explained that the median Tmax in the fed study (3h for both Test and Reference) was earlier than the fasting study (5.5h for Test and 5h for Reference), because for majority of subjects the Tmax was at the first peak in the fed study and was at the second peak in the fasting study. Similar difference in Tmax between fasting and fed conditions were also observed in other in-house ANDAs (please see next section regarding food effect)

4.1.2.4.5 Comments on Food Effect:

The RLD labeling states effect of food on the first and second peak of the PK profile, but does not have clear statement regarding food effect on Cmax and AUC. The reviewer summarized the arithmetic means for Cmax, Tmax and AUCi in the current and in-house ANDAs as shown in the below table:

ANDA	Parameter	Test			Reference		
		Fasting	**Fed**	**%diff***	**Fasting**	**Fed**	**%diff***
A211796 (Current ANDA)	AUCI	212.340	274.416	29.2	208.995	283.170	35.5
	CMAX	26.725	22.885	-14.4	26.442	23.008	-13.0
	TMAX	5.5	3	-2.5	5	3	-2.0
A078458 (RS)	AUCI	202.24	231.14	14.3	192.74	220.15	14.2
	CMAX	26.76	21.76	-18.7	24.96	21.19	-15.1
	TMAX	5.5	3	-2.5	5.5	3.07	-2.4
[redacted] (b) (4)							

* For AUC and Cmax, %difference is calculated as (fed-fasting)/fasting ×100%; For Tmax, %difference is calculated as fed-fasting (hours). Please note partial AUC is not compared because PSG recommends different pAUCs for fasting (AUC0-3, AUC3-7, and AUC7-12) and fed (AUC0-4, AUC4-8, and AUC8-12) studies.

In current ANDA, Cmax reduced by approximately 13~14%, AUCi increased by approximately 29-35%, and Tmax was approximately 2-2.5 hrs earlier in the fed conditions compared to fasting conditions. The food effect was similar for the Test and Reference products.

Similar food effect, i.e., decreased Cmax, increased AUCi and earlier Tmax, was observed in approved A078458 (RS). [redacted] (b) (4)

Analysis of Individual T/R Ratios

The reviewer evaluated the distribution of individual Test/Reference (T/R) ratios for the PK parameters as given below. The results are presented for information only and will not be communicated to the applicant (please see discussion in Section 3.3)

Subject#	T/R Cmax	T/R TMAX	T/R AUCi	T/R AUC0-4	T/R AUC4-8	TR AUC8-12
(b) (6) [redacted]	1.35	0.71	1.10	1.44	1.01	0.97
	1.00	1.00	0.95	0.94	0.92	0.81
	1.02	1.17	1.04	0.91	1.20	1.15
	0.96	1.25	1.03	0.87	1.08	0.98
	0.90	1.07	0.93	0.88	0.84	0.99
	0.91	1.50	1.01	0.82	1.21	0.96
	1.19	0.40	0.90	1.97	0.80	0.87
	0.99	1.43	0.93	0.63	1.18	1.04
	1.08	0.86	1.34	1.22	1.06	1.18
	0.79	1.20	0.97	0.82	1.07	0.94

Subject#	T/R Cmax	T/R TMAX	T/R AUCi	T/R AUC0-4	T/R AUC4-8	TR AUC8-12
(b) (6) [redacted]	1.01	1.00	1.12	1.41	1.02	1.24
	1.04	0.63	0.82	1.32	1.04	0.86
	1.24	0.25	1.09	1.41	1.10	0.77
	1.03	0.88	1.16	1.07	1.08	1.33
	0.94	1.67	1.07	0.86	1.21	1.20
	1.05	0.60	0.90	1.12	0.84	0.93
	0.95	1.20	0.90	0.85	1.13	1.29
	0.97	2.00	1.24	0.80	1.37	1.12
	0.77	1.50	0.85	0.54	1.20	0.99
	0.94	1.00	0.88	0.94	0.98	0.86
	1.00	1.00	0.93	1.16	1.01	0.90
	1.12	0.33	1.06	1.37	1.37	0.92
	0.69	0.50	0.84	0.81	0.71	0.97
	1.11	1.17	1.04	0.64	1.16	1.17
	0.86	1.18	0.99	0.68	1.10	0.98
	0.96	0.67	0.92	1.18	0.88	0.77
	0.97	1.25	0.92	0.71	0.83	1.00
	1.03	1.20	1.01	0.88	1.76	1.47
	0.99	1.20	1.04	0.76	1.36	1.06
	1.23	2.67	0.99	0.91	1.33	1.13
	0.99	1.25	.	1.06	1.25	1.31
	0.89	0.83	0.93	0.95	1.11	1.00
	1.06	0.83	.	1.35	1.00	0.99
	0.96	1.20	0.94	0.93	1.08	1.04
	1.01	0.93	0.91	1.00	0.95	0.94
	1.12	0.50	0.98	2.07	1.35	0.73
	0.95	0.35	0.89	1.05	0.88	0.85
	1.04	1.00	1.00	1.24	1.06	1.01
	0.98	1.00	1.12	1.16	0.92	0.98
Not within range	4	16	1	14	7	7
Total # of subjects (n =)	39	39	39	39	39	39
% not within range	10.26	41.03	2.56	35.90	17.95	17.95

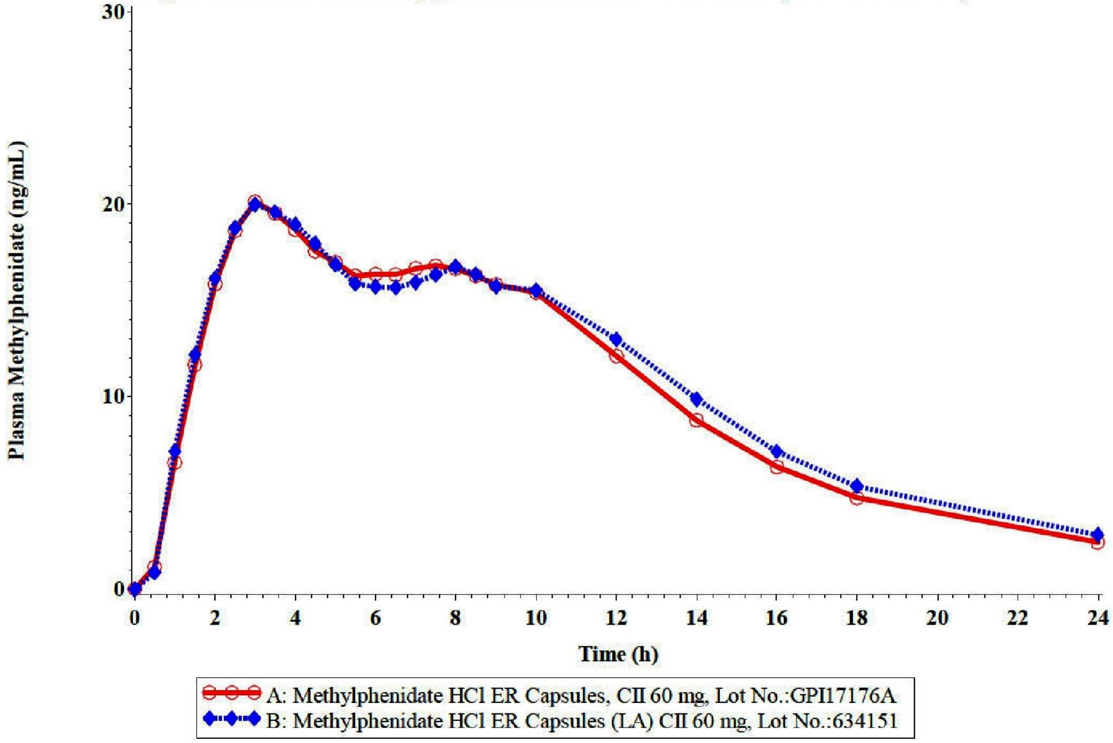
Note: The values of T/R ratio not within 0.8 – 1.25 are highlighted;
AUCi of two subjects [redacted] (b) (6), both reference treatment) were not calculated due to increasing concentration at the last time point

4.1.2.5 Overall Comment

Was the fed bioequivalence study acceptable? adequate

Mean Plasma Concentration Profile, Single-Dose Fed Bioequivalence Study (Firm generated)

Figure 11-1 Mean Plasma Methylphenidate Concentration-Time Profiles (A: n = 39 / B: n = 39)



4.1.3 Single-Dose Pivotal Fasting Sprinkle Bioequivalence Study

4.1.3.1 Study Design

4.1.3.1.1 Study Information

Study Number	2018-4455
Study Title	A Single-Dose, Bioequivalence Study of Two Formulations of Methylphenidate HCl 60 mg Extended-Release Capsules Sprinkled on Applesauce under Fasting Conditions
Study Type	☑In Vivo BE ☐In Vitro BE ☐Permeability ☐Other
Submission Location: **Study Report** **Validation Report** **Bioanalytical Report**	 Module 5.3.1.2, *2018-4455-study-report* Module 5.3.1.4, *2018-4455-validation-report* Module 5.3.1.4, *2018-4455-bioanalytical-report*
Clinical Site (Name, Address, Phone #, Fax#)	(b) (4) [redacted]
Principal Clinical Investigator (Name, Email)	
Dosing Dates	Period 1: January 31, 2018 Period 2: February 07, 2018
Analytical Site (Name, Address, Phone #, Fax #)	(b) (4) [redacted]
Principal Analytical Investigator (Name, Email)	
Analytical Dates	Feb 12, 2018 – Feb 16, 2018
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) Fifteen (15) days (January 31, 2018 – February 15, 2018) b) -35 to -15 °C
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	This period is covered by the established Long Term Stability of one hundred and twenty seven (127) days at -25 ± 10°C.
LTSS Data Location	2018-4455-validation-report.pdf, page 469 and page 472

Data source:
Module 2.7.1, Clinical Summary, Table 10d
Module 5.3.1.2, Fasting Sprinkle Study Report (Study #2018-4455)

4.1.3.1.2 Product Information

Same as the fasting study (Section **4.1.1.1.2**)

4.1.3.1.3 Study Design, Single-Dose Fed Bioequivalence Study

Number of Subjects	Enrolled: 26 Dosed: 26 Completed: 24* Samples Analyzed: 24 Statistically Analyzed: 24
No. of Sequences	2
No. of Periods	2
No. of Treatments	2
No. of Groups	1
Washout Period	7 days
Randomization	☒ Yes ☐ No Module 5.3.1.2, Appendix 16.1.7, Randomization Scheme
Blood Sampling Times	prior to dosing (0-hour), and at 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 5.5, 6, 6.5, 7, 7.5, 8, 8.5, 9, 10, 12, 14, 16, 18, and 24 hours after drug administration, total 25 samples in each period.
IRB Approval	☒ Yes Date: 24 Jan 2018 ☐ No
Informed Consent	☒ Yes Date: 24 Jan 2018 ☐ No
Length of Fasting	Subjects fasted from at least 10 hours prior to drug administration until at least 4 hours postdose.
Length of Confinement	Subjects were confined in-house from at least 10 hours prior to drug administration until at least 24 hours post-dose in each period.
Was the drug product administered per labeling for specialized dosage forms e.g. ODT)?	☐ Yes ☐ No ☒ N/A
Safety Monitoring	☒ Yes ☐ No

* Two subjects dropped out. Please see Section 4.1.3.2.2
Data Source: Module 5.3.1.2, Fasting Sprinkle Study Report (Study #2018-4455)

Comments on Study Design: Adequate

The PK sampling times in the current study are sufficient to capture the Cmax.

Per the RLD label, an average half-life of Ritalin LA is about 3.5 hours. The mean half-life in current study is 4.5 hours for Test treatment and 4.4 hours for Reference treatment, respectively. The sampling duration of 24 hours (> 3-fold half-lives) and washout period of 7 days (> 5-fold half-lives) in the current study are sufficient to characterize the half-life and complete elimination.

The fasting sprinkle study design is acceptable.

4.1.3.2 Clinical Results

4.1.3.2.1 Demographic Profile of Subjects

Study No. 2018-4455			
		Treatment Groups	
		Trt A N = 26	**Trt B** N = 24
Age (years)	**Mean ± SD**	41 ± 11	41 ± 10
	Range	23 - 59	23 - 59
Age Group	**<18**	0 (0%)	0 (0%)
	18 - 40	14 (53.8%)	13 (54.2%)
	41 - 64	12 (46.2%)	11 (45.8%)
	65 - 75	0 (0%)	0 (0%)
	>75	0 (0%)	0 (0%)
Sex	**Female**	15 (57.7%)	13 (54.2%)
	Male	11 (42.3%)	11 (45.8%)
Race	**White**	6 (23.1%)	6 (25.0%)
	Black or African American	18 (69.2%)	16 (66.7%)
	Asian	0 (0%)	0 (0%)
	Other	2 (7.7%)	2 (8.3%)
Ethnicity	**Not Hispanic or Latino**	26 (100%)	24 (100%)
BMI	**Mean ± SD**	28.1 ± 3.0	28.4 ± 2.8
	Range	21.0 - 32.0	21.0 - 32.0
Other Factors		N/A	N/A

Data source: Module 2.7.1, Clinical Summary, Table 7d

Is the demographics profile of subjects completing the bioequivalence study in agreement with the current drug product recommendation?	☒ Yes ☐ No

4.1.3.2.2 Dropout Information

Study No. 2018-4455				
Subject No.	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
[redacted]	**Reason:** Adverse event (vaginal abscess) **Time Dropped-out:** 08:40 **Date Dropped-out:** [redacted] **Treatment:** Test	1	No	N/A
	Reason: Withdrawal by subject (personal) **Time Dropped-out:** 16:23 **Date Dropped-out:** [redacted]	1	No	N/A

	Treatment: Test			

Data source: Module 2.7.1, Clinical Summary, Table 12d

Table 10-2 Discontinued Subjects

Subject	Reason for Discontinuation	Details	Period	Last Treatment Received	Time From Last Dosing[a] (h)
[redacted] (b) (6)	ADVERSE EVENT	Subject withdrew prior to period 2 check-in due to health complaint (adverse event vaginal abscess).	1	A	144.65
	WITHDRAWAL BY SUBJECT	Subject withdrew prior to period 2 check-in due to personal reasons.	1	A	152.27

[a]Time elapsed from when the subject started consuming the applesauce-drug mixture of the last received treatment until the time of discontinuation.

Data source: Module 5.3.1.2, Fasting Sprinkle Study Report Table 10.2;

Are dropouts appropriate? If no, please comment.	☒ Yes ☐ No ☐ N/A

Two subjects, Subjects [redacted] (b) (6), withdrew during the study prior to Period II check-in due to AE and personal reason, respectively.

The fasting sprinkle protocol Section 15.0 states that *Samples from subjects included in the PK dataset will be assayed.*

Per the fasting sprinkle protocol Section 14.2, *Data from the following subjects will be included in the PK dataset:*

- *Subjects from whom the estimation of Cmax and AUC (AUC0-3, AUC3-7, AUC7-12, and AUCinf) parameters will be **possible for both periods**; and*
- *Subjects who complied with all protocol requirements or encountered protocol deviations that do not impact the estimation of the PK parameters.*

Therefore, Period I PK samples of Subjects [redacted] (b) (6) were not assayed per the protocol. The applicant's handling of dropout subject is consistent with its protocol.

4.1.3.2.3 Study Adverse Events

Study No. 2018-4455			
System Organ Class Term Preferred Term	**Reported Incidence by Treatment Group** n (%) of Subjects		
	A N = 26	**B** N = 24	**Total** N = 26
Subjects with One or More TEAEs	**7 (26.9%)**	**8 (33.3%)**	**12 (46.2%)**
Subjects with No TEAEs	19 (73.1%)	16 (66.7%)	14 (53.8%)
Cardiac disorders	**1 (3.8%)**	**3 (12.5%)**	**4 (15.4%)**
Palpitations	0 (0%)	1 (4.2%)	1 (3.8%)

Study No. 2018-4455			
System Organ Class Term Preferred Term	**Reported Incidence by Treatment Group** n (%) of Subjects		
	A N = 26	**B** N = 24	**Total** N = 26
Tachycardia	1 (3.8%)	2 (8.3%)	3 (11.5%)
Eye disorders	**1 (3.8%)**	**0 (0%)**	**1 (3.8%)**
Vision blurred	1 (3.8%)	0 (0%)	1 (3.8%)
Gastrointestinal disorders	**6 (23.1%)**	**4 (16.7%)**	**8 (30.8%)**
Abdominal discomfort	1 (3.8%)	1 (4.2%)	2 (7.7%)
Dry mouth	1 (3.8%)	1 (4.2%)	2 (7.7%)
Flatulence	1 (3.8%)	0 (0%)	1 (3.8%)
Gastrooesophageal reflux disease	0 (0%)	1 (4.2%)	1 (3.8%)
Nausea	3 (11.5%)	1 (4.2%)	3 (11.5%)
General disorders and administration site conditions	**1 (3.8%)**	**2 (8.3%)**	**2 (7.7%)**
Feeling jittery	1 (3.8%)	1 (4.2%)	1 (3.8%)
Tenderness	1 (3.8%)	0 (0%)	1 (3.8%)
Vessel puncture site reaction	0 (0%)	1 (4.2%)	1 (3.8%)
Infections and infestations	**1 (3.8%)**	**0 (0%)**	**1 (3.8%)**
Vaginal abscess	1 (3.8%)	0 (0%)	1 (3.8%)
Investigations	**0 (0%)**	**1 (4.2%)**	**1 (3.8%)**
Neutrophil count decreased	0 (0%)	1 (4.2%)	1 (3.8%)
Nervous system disorders	**2 (7.7%)**	**1 (4.2%)**	**3 (11.5%)**
Dizziness	2 (7.7%)	1 (4.2%)	3 (11.5%)
Psychiatric disorders	**2 (7.7%)**	**0 (0%)**	**2 (7.7%)**
Depression	1 (3.8%)	0 (0%)	1 (3.8%)
Euphoric mood	1 (3.8%)	0 (0%)	1 (3.8%)
Hypervigilance	1 (3.8%)	0 (0%)	1 (3.8%)
Reproductive system and breast disorders	**0 (0%)**	**1 (4.2%)**	**1 (3.8%)**
Dysmenorrhoea	0 (0%)	1 (4.2%)	1 (3.8%)
Vascular disorders	**1 (3.8%)**	**0 (0%)**	**1 (3.8%)**
Hypertension	1 (3.8%)	0 (0%)	1 (3.8%)

Data source: Module 2.7.1, Clinical Summary, Table 8d

Subjects Experiencing Emesis (Include in eCTD)

N/A

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
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

Comments on Adverse Events: Adequate

Overall, there were 30 TEAEs affecting 12 subjects (46.2% of subjects dosed). Of these, 26 TEAEs in 10 subjects (38.5%) were deemed treatment-related (possible or probable relationship). All TEAEs were mild in severity and, apart from one, unlikely to be related TEAE, all resolved prior to the end of the study. No SAEs were reported during the conduct of the study as determined by the clinical investigator (per the fasting sprinkle study report Section 12).

The reviewer confirmed that majority of the TEAEs are common AEs of the RLD per the RLD labeling. The AE profile is comparable for the Test and Reference products. There is no safety concern of the test product from BE perspective.

4.1.3.2.4 Protocol Deviations

Study No. 2018-4455		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
Centrifugation of the subject's sample was completed 1 minute outside the protocol-specified 60 minute time frame due to a timing error.	[redacted]	(b) (6)
Centrifugation of the subject's sample was completed 3 minutes outside the protocol-specified 60 minute time frame due to a timing error.		
The subject's period 2, 6-hour blood pressure and pulse rate measurements were taken 1 minute earlier than the protocol-specified window due to staff oversight.		
The subject's period 2, 6-hour blood pressure and pulse rate measurements were taken 2 minutes earlier than the protocol-specified window due to staff oversight.		

Study No. 2018-4455		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
The subject's period 2, 6-hour blood pressure and pulse rate measurements were taken 5 minutes earlier than the protocol-specified window due to staff oversight.	[redacted] (b) (6)	

Data source: Module 2.7.1, Clinical Summary, Table 13d

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 Protocol Deviations: Adequate

The deviations in the timing of sample centrifugation, blood pressure, and pulse rate measurement are not considered to have impact on study outcome.

Comments on Concomitant medications: Adequate

Per the fasting sprinkle study report Section 12.2.1, no concomitant medications were given during the study except non-drug therapy, as shown below.

Table 12-2 Summary of Concomitant Nondrug Therapy

Subject	Period	Treatment	NDT	Adverse Event (PT)	Relationship to Study Drug
[redacted] (b) (6)	2	A	Gingerale (237mL)	Nausea	PROBABLE
	1	A	Other, Specify: Lanced and wound was packed	Vaginal abscess	UNLIKELY
	1	B	Hot Pack	Dysmenorrhoea	UNLIKELY
	2	B	Cold (Ice) Pack	Vessel puncture site reaction	UNRELATED
	2	B	Gingerale (237mL)	Gastrooesophageal reflux disease	POSSIBLE

NDT, non-drug therapy; PT, preferred term.

Data source: Module 5.3.1.2, Fasting Sprinkle Study Report Table 12-2

Per the CRF, Subject [redacted] (b) (6) received ginger ale at 21:06 on [redacted] (b) (6), i.e., 13 hours and 35 minutes after Period II dosing (7:31 on [redacted] (b) (6), test product); Subject [redacted] (b) (6) received ginger ale at 14:27 on [redacted] (b) (6), i.e., 6 hours and 9 minutes after Period II dosing (8:18 on [redacted] (b) (6), reference product).

Per protocol Section 10.4, *water will be restricted from 1 hour prior to drug administration until 1 hour postdose (except the water administered with the drug). Access to water will otherwise be freely available to subjects*. The reviewer does not consider that carbonated soft drink flavoured with ginger have an impact on the PK of the drug.

Reviewer's Overall Comments on Dropout/Adverse Events/Protocol Deviations:

- Handling of dropouts in the fasting sprinkle study was consistent with the protocol.
- AE profile is comparable between the test and reference treatments. There is no safety concern of the test product.
- Protocol deviation did not compromise the integrity of the study.
- There is no concomitant medications in the fasting sprinkle study.

The clinical results of the fasting sprinkle study are **adequate.**

4.1.3.3 Bioanalytical Results

4.1.3.3.1 SOPs dealing with Sample Analysis including Repeat Analysis

Same as that for the fasting study.

4.1.3.3.2 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. 2018-4455 Methylphenidate								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.100	0.200	0.500	1.50	4.00	9.00	18.0	30.0
Inter day Precision (%CV)	5.1	5.0	3.5	1.4	2.5	1.9	1.0	0.7
Inter day Accuracy (%Actual)	93.9	100.5	98.6	103.3	103.0	100.7	101.1	98.7
Linearity	0.9992 to 1.0000							
Linearity Range (ng/mL)	0.100 to 30.0							
Sensitivity/LOQ (ng/mL)	0.100							

Bioequivalence Study No. 2018-4455 Methylphenidate				
Parameter	**Quality Control Samples**			
Concentration (ng/mL)	0.300	7.5	15.0	24.0
Inter day Precision (%CV)	5.0	2.5	1.9	2.5
Inter day Accuracy (%Actual)	99.7	99.7	98.0	99.2

Data source: Module 2.7.1, Clinical Summary, Table 14b

Are the concentrations of standard curve and QC samples relevant to the concentration of the samples?	☒ Yes ☐ No Concentration data are provided in Module 5.3.1.2 as SAS dataset and in Appendix 16.2.5. Most subject samples are within 0.5 to 25 ng/mL (calibration rage: 0.100 ng/mL to 30 ng/mL) and QCs are well distributed (0.3, 7.5, 15, and 24 ng/mL)
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 Module 5.3.1.4, Bioanalytical Report, Appendix 6
Were chromatograms serially or randomly selected?	☒ serially ☐ randomly Subjects [redacted] (b) (6)
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 Module 5.3.1.4, Bioanalytical Report, Appendix 7

Data source: Module 2.7.1, Clinical Summary, Table 14

4.1.3.3.3 Reanalysis of Study Samples

Study No.: 2018-4455 Additional information, *2018-4455-bioanalytical-report*, pages 27-36 Analyte: Methylphenidate								
	Nr. of samples reanalyzed				**Nr. of recalculated values used after reanalysis**			
	Actual Nr.		**% of assays**		**Actual Nr.**		**% of assays**	
Reason why assay was repeated	**A**	**B**	**A**	**B**	**A**	**B**	**A**	**B**
Pharmacokinetic	0	0	0	0	0	0	0	0
AULOQ	30	27	5.00	4.50	30	27	5.00	4.50
CP	2	3	0.33	0.50	1	1	0.17	0.17
UISR	3	0	0.50	0	3	0	0.50	0
Total	**35**	**30**	**5.83**	**5.00**	**34**	**28**	**5.67**	**4.67**

Code	Definition
AULOQ	Above the Upper Limit of Quantitation ({0} {1}).
CP	Confirm presence of peak in pre-dose
UISR	Unacceptable Internal Standard Response.

Data source: Module 2.7.1, Clinical Summary, Table 9d

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 Although the reviewer agrees with the repeat assay, a confirmative PK analysis was conducted by the reviewer because the drug product is a modified release dosage form
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: adequate

A total of nine (9) batches were generated during study sample analysis and all were accepted (fasting sprinkle bioanalytical report Table 5)..

Above the Upper Limit of Quantitation (AULOQ)

Fifty-seven (57) samples were repeated due to Above the Upper Limit of Quantitation (code: AULOQ). The reviewer spot checked the numerical raw data and confirmed that these samples were correctly identified for repeat per the applicant's [redacted] (b) (4) ('Repeat Sample Analysis Procedure and Acceptance Criteria') Section 2.2.6, i.e., "*Samples that are AULOQ are repeated with an appropriate validated dilution factor using the appropriate blank matrix. A set of dilution QCs with the same dilution factor as the diluted samples are included*". For example as shown below from the 100% numerical raw data, [redacted] (b) (4), (b) (6).

[redacted] (b) (4), (b) (6)

Per SOP [redacted] (b) (4) Section 2.2.6.2, *in order to accept the results of the diluted samples, two-thirds (two out of three) of the dilution QCs should meet the acceptance criteria*. The reviewer checked the two repeated batch runs [redacted] (b) (6)) and confirmed that at least 2/3 of dilution QCs in the repeat batch runs met the acceptance criteria (±15% nominal value).

For all 57 samples repeated under code AULOQ, the repeated values were above the upper limit of quantitation after correction for dilution (fasting sprinkle bioanalytical report Table 3). In addition, the dilution integrity has been established in the pre-study method validation. The bioanalytical repeats for these samples are acceptable.

Confirm Presence of Peak in Pre-dose (CP)

From the total of 48 pre-dose samples, 5 were repeated for "confirm presence of peak in pre-dose (code: CP)".

Per SOP [redacted] Section 2.2.9, *Samples are identified for CP if one or more of the following apply:*

- *A peak that is present at the retention time of the analyte in the blank of the pre-dose is >20% of the analyte peak area of the STD A within the batch.*
- *The analyte/ISTD area ratio of a peak that is present at the retention time of the pre-dose with ISTD sample is >20% of the analyte/ISTD area ratio of the STD A within the batch.*

The reviewer spot checked the 100% numerical raw data and confirmed these samples were correctly identified for repeat per the applicant's SOP [redacted]. For example, as shown below, pre-dose sample [redacted]. In the repeated run [redacted], there was still peak at the retention time of analyte but [redacted]:

[redacted]

It should be noted that for all 5 samples coded as "CP", although there were peak at the retention time of the analyte in the original run, the concentrations were BLQ from both the original and repeated runs, as shown below:

Sample Name	% of LLOQ in the original run	% of LLOQ in the repeat run	Reported result (ng/mL)
[redacted] (b) (4)	48.5	8.6	BLQ
	20.1	0.0	BLQ
	44.5	0.0	BLQ
	30.1	30.8	BLQ
	22.5	9.6	BLQ

BLQ: Below the lower limit of quantitation (0.100 ng/mL)
LLOQ: Lower Limit of Quantitation
% of LLOQ = (Peak Area Ratio in the Sample/Peak Area Ratio in the LLOQ standard) × 100%
Data source: Fasting Sprinkle Bioanalytical Report, Section 16.2

The bioanalytical repeats for these samples are acceptable.

Unacceptable Internal Standard Response (UISR)

Three (3) samples were repeated due to "Unacceptable Internal Standard Response (code: UISR)". The reviewer checked the numerical raw data and confirmed that these samples were correctly identified for repeat per the applicant's SOP [redacted] (b) (4) Section 2.2.8. For example, the IS area of sample [redacted] (b) (4), (b) (6) [redacted]. Therefore, this sample was identified as "UISR" and repeated per SOP [redacted] (b) (4) Section 2.2.8, i.e., *Study samples with internal standard response outside ±40% of the average ISTD response within a batch are repeated as UISR.* The repeated values met the acceptance criteria and were used as final sample values. The bioanalytical repeats for these samples are acceptable.

Incurred Sample Reanalysis (ISR)

The applicant provided a report for its incurred sample reanalysis (ISR) in fasting sprinkle bioanalytical report Section 16.3 and Table 4.

The ISR was conducted using 89 subject samples for methylphenidate (7.4% of the total 1200 samples analyzed) as per its SOP [redacted] (b) (4) Section 2.3, i.e., *Approximately 10% of the first 1000 samples and 5% of the remaining number of samples, or 7 % of the total number of samples is selected for incurred sample reanalysis.* For each selected subject, within each period, two samples were selected. One was close to the Cmax, and the second sample was selected from the elimination phase.
87 out of 89 samples (97.8%) were found to be within ±20% bias. Thus, ISR were within acceptance criteria specified in its SOP [redacted] (b) (4) Section 2.3. Additionally, the applicant's ISR approach (# of samples chose, nature of samples chose, calculation approach for % difference, and acceptance criteria) is consistent with the FDA Guidance for Industry: Bioanalytical Method Validation (May 2018)[36].
The applicant's bioanalytical results for the fasting sprinkle study are adequate.

[36] https://www.fda.gov/downloads/drugs/guidances/ucm070107.Pdf

4.1.3.4 Pharmacokinetic Results

4.1.3.4.1 Arithmetic Mean Pharmacokinetic Parameters – Reviewer Calculated

		Test				Reference				Ratio
Parameter	Unit	Mean	CV%	Min	Max	Mean	CV%	Min	Max	(T/R)
cmax	ng/mL	26.729	75.02	13.50	117.00	26.946	83.66	14.40	130.00	0.99
tmax	Hr	5.500	.	1.50	7.00	5.000	.	1.00	6.50	1.10
AUCINF	ng hr/mL	261.686	135.14	111.59	1903.69	268.360	147.47	112.27	2111.33	0.98
KE	hr-1	0.164	20.73	0.07	0.22	0.167	20.19	0.07	0.23	0.98
THALF	hr	4.494	31.81	3.21	10.23	4.388	30.66	3.07	9.86	1.02
Auc0-3	ng hr/mL	43.307	71.39	21.86	178.18	43.867	70.93	21.44	178.68	0.99
Auc3-7	ng hr/mL	82.082	77.21	43.94	367.43	80.607	85.45	46.05	394.80	1.02
Auc7-12	ng hr/mL	67.228	125.34	28.64	457.30	67.108	134.93	22.21	485.55	1.00

4.1.3.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Methylphenidate (No of subjects completed=24) Dose (1 x 60 mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Sprinkle Bioequivalence Study (2018-4455)							
Parameter	Contrast	Test	N	RLD	N	Ratio	90% C.I.
AUC_{inf}	A vs B	204.042	24	203.302	24	100.36	97.19-103.64
C_{max}	A vs B	23.862	24	23.771	24	100.38	95.80-105.18
AUC_{0-3}	A vs B	38.342	24	38.743	24	98.96	94.00-104.19
AUC_{3-7}	A vs B	73.185	24	70.815	24	103.35	97.57-109.47
AUC_{7-12}	A vs B	53.393	24	51.781	24	103.11	96.98-109.64

Data source: Module 2.7.1, Clinical Summary, Table 3A

4.1.3.4.3 Geometric Means and 90% Confidence Intervals - Reviewer Calculated

Methylphenidate (No of subjects completed = 24) Dose 60 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fasting Sprinkle Bioequivalence Study (2018-4455)							
Parameter	Unit	Test	N	RLD	N	Ratio	90% C.I.
AUC_{inf}	ng hr/mL	204.09	24	203.42	24	1.00	97.18-103.58
C_{max}	ng/mL	23.86	24	23.77	24	1.00	95.80-105.18
AUC_{0-3}	ng hr/mL	38.39	24	38.92	24	0.99	93.69-103.85
AUC_{3-7}	ng hr/mL	73.21	24	70.83	24	1.03	97.57-109.50
AUC_{7-12}	ng hr/mL	53.37	24	51.77	24	1.03	96.96-109.64

4.1.3.4.4 Additional Information for the Study

Root Mean Square Error	Not calculated in the output of DB SAS code of partial AUC analysis
Is there a Tmax difference between Test and Reference?	☒ Yes ☐ No

If yes, please provide brief explanation (or detailed explanation, including Tmax analysis, for substantial difference).	Minor difference in median Tmax (Test 5.5h vs Reference 5.0h) is acceptable. See comments below
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

AUCt/AUCi ratios are not calculated because AUCt is not a recommended PK parameter per the PSG. Based on the individual PK profiles (Module 5.3.1.2, Appendix 16.2.6), the terminal phase of methylphenidate is well characterized in the fasting sprinkle study.

Comments on PK results: adequate
Since this is an ER product, the reviewer conducted a confirmative SAS analysis using the partial AUC program (pAUC_macro) with the SAS datasets submitted by the applicant. The applicant used actual sampling time and the DB SAS program used nominal sampling time in the analysis. The results indicate that the geometric mean ratios and 90% CIs of Cmax calculated by the reviewer are the same as that by the applicant. There are small differences in the results of AUC0-3, AUC3-7, AUC7-12, and AUCi between the applicant and reviewer's analyses likely due to different sampling time used in the analysis (actual vs nominal) and different selection of data points for the determination of the terminal phase.

For both the applicant and reviewer's calculations, the 90% CIs for least squares geometric mean of LnCmax, LnAUC0-3, LnAUC3-7, LnAUC7-12, and LnAUCI in the fasting sprinkle study are within the BE acceptable range of 80.00-125.00%.

The median Tmax of methylphenidate in current study is 5.5 hours for Test (range: 1.5-7.0 hours) and 5.0 hours for Reference (range: 1.0-6.5 hours) treatments. The minor difference is acceptable for the indication, i.e., treatment of Attention Deficit Hyperactivity Disorder (ADHD), of the drug product.

Per the RLD labeling, Ritalin LA PK profile has 2 distinct peaks approximately 4 hours apart. The reviewer confirmed that double peak profiles were observed in all individual subjects and consistent between the Test and Reference treatment (Module 5.3.1.2, Appendix 16.2.6, Individual PK Data). For majority of subjects, the Tmax occurred at the 2^{nd} peak.

Analysis of Individual T/R Ratios

The reviewer evaluated the distribution of individual Test/Reference (T/R) ratios for the PK parameters as given below. The results are presented for information only and will not be communicated to the applicant (please see discussion in Section 3.3)

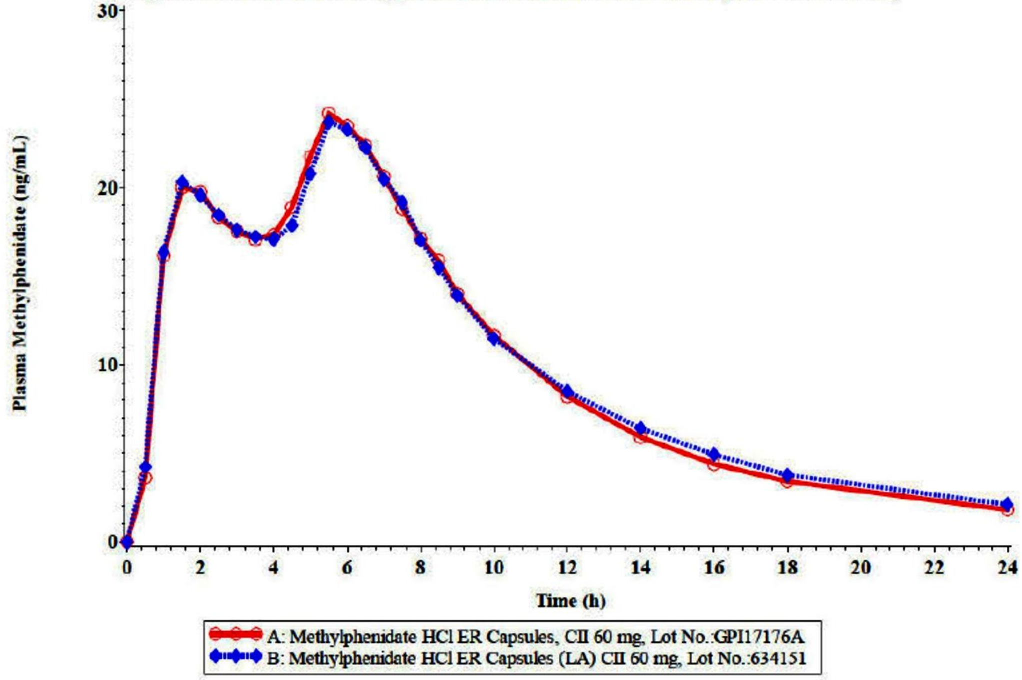
Subject#	T/R Cmax	T/R TMAX	T/R AUCi	T/R AUC0-3	T/R AUC3-7	T/R AUC7-12
(b) (6) [redacted]	1.13	3.00	0.93	1.09	1.18	0.92
	1.16	0.88	1.13	1.16	1.17	1.06
	0.78	1.33	0.99	0.96	0.85	1.29
	0.89	1.00	0.91	0.79	0.98	0.94
	1.02	5.50	1.05	0.85	0.98	1.29
	1.08	1.00	1.07	1.03	1.12	1.03
	0.87	1.13	1.12	1.14	1.00	1.20
	0.99	2.67	0.82	0.88	0.93	0.70
	1.05	0.83	1.11	1.19	1.24	0.96
	1.02	1.00	0.96	1.01	0.94	0.98
	0.99	1.09	0.94	0.84	0.98	0.99
	0.90	1.08	0.90	1.00	0.93	0.94
	1.02	1.00	1.00	1.06	0.95	1.02
	0.98	0.30	1.11	1.08	0.73	1.19
	0.81	1.75	0.97	0.71	0.74	1.56
	1.21	0.92	1.12	1.26	1.21	0.90
	1.04	4.33	0.95	0.85	1.17	1.16
	0.99	1.00	1.11	1.16	1.07	1.16
	0.78	0.27	0.97	1.04	0.96	0.89
	1.08	0.67	1.11	0.94	1.04	1.09
	1.19	2.67	1.00	0.97	1.33	0.78
	1.34	0.85	1.06	1.14	1.33	1.01
	0.99	4.33	0.88	0.86	1.26	1.13
	1.06	0.92	0.97	0.94	1.09	0.93
Not within range	3	11	0	3	5	5
Total # of subjects (n =)	24	24	24	24	24	24
% not within range	12.50	45.83	0.00	12.50	20.83	20.83

4.1.3.5 Overall Comment

Was the fasting sprinkle bioequivalence study acceptable? adequate

Mean Plasma Concentration Profile, Single-Dose Fed Bioequivalence Study (Firm generated)

Figure 11-1 Mean Plasma Methylphenidate Concentration-Time Profiles (A: n = 24 / B: n = 24)



4.1.4 Single-Dose Pilot Fed Bioequivalence Study

The firm submitted summary tables of a pilot fed (Study #2017-4358) in Module 2.7.1 Clinical Summary. The pilot study was designed as open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study comparing the oral bioavailability of the test product, Granules Pharmaceuticals Inc.'s Methylphenidate Hydrochloride ER Capsules, 60 mg, to the RS product, Mayne Pharma LLC's Methylphenidate Hydrochloride ER Capsules, 60 mg, in healthy adult male and female subjects under fed conditions.

Per Module 2.7.1 Clinical Summary Table 2a, the test product lot (Lot #GPI17176A) used in the pilot fed study was the same lot used in the pivotal fasting (Study #2018-4413), pivotal fed (Study #2017-4351), and pivotal fasting sprinkle (Study #2018-4455) studies, i.e., same drug product formulation. Therefore, per the Guidance for Industry, Submission of Summary Bioequivalence Data for ANDAs (effective May 2011)[37], the applicant submitted all necessary bioequivalence summary tables as presented below.

4.1.4.1 Study Design

4.1.4.1.1 Study Information

Study Number	2017-4358

[37] Guidance for Industry, Submission of Summary Bioequivalence Data for ANDAs, May 2011: https://www.fda.gov/downloads/Drugs/.../Guidances/UCM134846.pdf

Study Title	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Methylphenidate HCl 60 mg Extended-Release Capsules under Fed Conditions			
Study Type	☑In Vivo BE	☐In Vitro BE	☐Permeability	☐Other
Submission Location: **Study Report** **Validation Report** **Bioanalytical Report**	Not included Not included Not included			
Clinical Site **(Name, Address, Phone #, Fax#)**	(b) (4) [redacted]			
Principal Clinical Investigator **(Name, Email)**	[redacted]			
Analytical Site **(Name, Address, Phone #, Fax #)**	[redacted]			
Principal Analytical Investigator **(Name, Email)**	[redacted]			
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) Sixteen (16) days (September 26, 2017 - October 12, 2017) b) -35 to -15 °C			
Long-Term Storage Stability (LTSS) Coverage (no. days @ temp °C)	This period is covered by the established Long Term Stability of one hundred and twenty seven (127) days at -25 ± 10°C.			
LTSS Data Location	Not applicable			

Data source: Module 2.7.1, Clinical Summary, Table 10a

4.1.4.1.2 Product Information

Same test lot (#GPI17176A) and RS lot (#634151) were used in the pilot fed study as that in the pivotal fasting (Study #2018-4413), pivotal fed (Study #2017-4351), and pivotal fasting sprinkle (Study #2018-4455) studies.

4.1.4.2 Clinical Results

4.1.4.2.1 Demographic Profile of Subjects

Study No: 2017-4358			
		TRT A **N = 9**	**TRT B** **N = 10**
Age (years)	**Mean ± SD** **Range**	46 ± 13 29 - 59	44 ± 13 28 - 59
Age Group	**< 18** **18 - 40** **41 - 64** **65 - 75** **> 75**	0 (0.0%) 3 (33.3%) 6 (66.7%) 0 (0.0%) 0 (0.0%)	0 (0.0%) 4 (40.0%) 6 (60.0%) 0 (0.0%) 0 (0.0%)
Sex	**Male** **Female**	4 (44.4%) 5 (55.6%)	4 (40.0%) 6 (60.0%)
Race	**Asian** **Black** **White** **Other**	0 (0.0%) 3 (33.3%) 6 (66.7%) 0 (0.0%)	0 (0.0%) 4 (40.0%) 6 (60.0%) 0 (0.0%)
Ethnicity	**Hispanic/Latino**	1 (11.1%)	1 (10.0%)
BMI (kg/m²)	**Mean ± SD** **Range**	25.2 ± 3.9 19.9 - 33.0	24.9 ± 3.7 19.9 - 33.0
Other Factors		N/A	N/A

Data source: Module 2.7.1, Clinical Summary, Table 7a

4.1.4.2.2 Dropout Information

Study No. 2017-4358				
Subject No	**Reason for dropout/replacement**	**Period**	**Replaced?**	**Replaced with**
(b) (6) [redacted]	**Reason:** Non-Compliance with Protocol Restrictions - Dismissed **Time Dropped-out:** 18:20 **Date Dropped-out:** [redacted] (b) (6) **Treatment:** Reference	1	No	N/A

Data source: Module 2.7.1, Clinical Summary, Table 12a

4.1.4.2.3 Study Adverse Events

System Organ Class Term Preferred Term	Reported Incidence by Treatment Groups	
	Fed Bioequivalence Study **Study No: 2017-4358**	
	TRT A N = 9	**TRT B** N = 10
Cardiac disorders		

System Organ Class Term Preferred Term	**Reported Incidence by Treatment Groups** **Fed Bioequivalence Study** **Study No: 2017-4358**	
	TRT A N = 9	**TRT B** N = 10
Bradycardia	0 (0.0%)	1 (10.0%)
Gastrointestinal disorders		
Abdominal discomfort	1 (11.1%)	0 (0.0%)
Diarrhoea	1 (11.1%)	0 (0.0%)
Dry mouth	1 (11.1%)	0 (0.0%)
General disorders and administration site conditions		
Feeling hot	1 (11.1%)	0 (0.0%)
Feeling jittery	2 (22.2%)	0 (0.0%)
Injury, poisoning and procedural complications		
Contusion	1 (11.1%)	0 (0.0%)
Nervous system disorders		
Slow speech	1 (11.1%)	0 (0.0%)
Psychiatric disorders		
Paranoia	1 (11.1%)	0 (0.0%)
Vascular disorders		
Hypertension	1 (11.1%)	0 (0.0%)
Total	**3 (33.3%)**	**1 (10.0%)**

Data source: Module 2.7.1, Clinical Summary, Table 8a

4.1.4.2.4 Protocol Deviations

Study No. 2017-4358		
Type	**Subject #s (Test)**	**Subject #s (Ref.)**
10.12 Sample Processing and Storage – The time at which Period 1, time point 14, draw 22 samples were placed in the freezer was not recorded.	(b) (6) [redacted]	

Data source: Module 2.7.1, Clinical Summary, Table 13a

4.1.4.3 Bioanalytical Results

4.1.4.3.1 Sample Analysis Calibration and Quality Control

Bioequivalence Study No. 2017-4358 **Methylphenidate**								
Parameter	**Standard Curve Samples**							
Concentration (ng/mL)	0.100	0.200	0.500	1.50	4.00	9.00	18.0	30.0
Inter day Precision (%CV)	0.4	1.9	1.7	1.1	3.7	1.4	3.4	1.3
Inter day Accuracy (%Actual)	98.8	99.0	99.6	102.7	102.5	97.0	100.0	100.3
Linearity	0.9988 to 0.9996							

Linearity Range (ng /mL)	0.100 to 30.0
Sensitivity/LOQ (ng /mL)	0.100

Bioequivalence Study No. 2017-4358 Methylphenidate			
Parameter	Quality Control Samples		
Concentration (ng /mL)	0.300	15.0	24.0
Inter day Precision (%CV)	2.7	1.4	1.5
Inter day Accuracy (%Actual)	98.3	100.0	98.8

Data source: Module 2.7.1, Clinical Summary, Table 14a

4.1.4.3.2 Reanalysis of Study Samples

Study No.: 2017-4358 Additional information, 16.5 Analytical Report, Page(s): N/A Analyte: Methylphenidate								
	Nr. of samples reanalyzed				Nr. of recalculated values used after reanalysis			
	Actual Nr.		% of assays		Actual Nr.		% of assays	
Reason why assay was repeated	A	B	A	B	A	B	A	B
Pharmacokinetic	0	0	0	0	0	0	0	0

Data source: Module 2.7.1, Clinical Summary, Table 9a

4.1.4.4 Pharmacokinetic Results

4.1.4.4.1 Arithmetic Mean Pharmacokinetic Parameters – Firm Calculated

Methylphenidate (No of subjects completed = 9)											
					Mean Parameters (CV%)						
Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Product ID, Dosage Form, Route)	Subjects (No. M/F) Age: mean(range)	Cmax (ng/mL)	Tmax (h)	AUC0-t (ng.h/mL)	AUC0-∞ (ngh/mL)	t½ (h)	Kel (1/h)	Study Report Location
2017-4358	A Single-Dose, Comparative Bioavailability Study of Two Formulations of Methylphenidate HCl 60 mg Extended-Release Capsules under Fed Conditions	Open-label, single-dose, randomized, 2-periods, 2-treatments, 2-sequences, crossover	Dose: 60 mg A: Methylphenidate hydrochloride Extended-Release Capsules, CII 60 mg, Lot No.: GPI17176A (Granules Pharmaceuticals, Inc., USA) p.o.	9 healthy subjects (4 M/5 F) 46 years (29-59)	17.388 (30)	Median 3.00 (2.00-3.50)	179.404 (32)	197.207 (29)	6.33 (64)	0.1380 (41)	Not applicable

Methylphenidate (No of subjects completed = 9)											
					Mean Parameters (CV%)						
Study Ref. No.	Study Objective	Study Design	Treatments (Dose, Product ID, Dosage Form, Route)	Subjects (No. M/F) Age: mean(range)	Cmax (ng/mL)	Tmax (h)	AUC0-t (ng.h/mL)	AUC0-∞ (ngh/mL)	t½ (h)	Kel (1/h)	Study Report Location
			Dose: 60 mg B: Methylphenidate Hydrochloride Extended-Release Capsules (LA) CII 60 mg, Lot No.: 634151 (Mayne Pharma, USA) p.o.		16.448 (27)	Median 3.00 (2.00-8.00)	178.724 (32)	196.244 (31)	5.10 (19)	0.1402 (19)	

Data source: Module 2.7.1, Clinical Summary, Table 2a

4.1.4.4.2 Geometric Means and 90% Confidence Intervals - Firm Calculated

Methylphenidate (No of subjects completed=9) Dose (60 x mg) Least Squares Geometric Means, Ratio of Means, and 90% Confidence Intervals							
Fed Bioequivalence Study (2017-4358)							
Parameter	Contrast	Test	N	RLD	N	Ratio	90% C.I.
AUC_{inf}	A vs B	190.623	9	189.345	8	100.68	92.79-109.23
C_{max}	A vs B	16.960	9	16.092	9	105.39	97.21-114.26
AUC_{0-4}	A vs B	43.431	9	38.160	9	113.81	98.30-131.78
AUC_{4-8}	A vs B	42.913	9	41.911	9	102.39	98.06-106.92
AUC_{8-12}	A vs B	37.526	9	36.711	9	102.22	96.44-108.34

Data source: Module 2.7.1, Clinical Summary, Table 3a

4.1.4.5 Overall Comments on Pilot Fed Study

- The firm submitted summary tables of a pilot fed (Study #2017-4358). The test product used in the pilot fed study is the same lot, i.e., bio-exhibit Batch #GPI17176A used in the pivotal fasting, fed and fasting sprinkle studies.

- The pilot fed study was designed as open-label, single-dose, randomized, two-period, two-treatment, two-sequence, crossover study comparing the oral bioavailability of the test product, Granules Pharmaceuticals Inc.'s Methylphenidate Hydrochloride ER Capsules, 60 mg, to the RS product, Mayne Pharma LLC's Methylphenidate Hydrochloride ER Capsules, 60 mg, in healthy adult male and female subjects under fed conditions. A total of 9 subjects (4 male/5 female) completed the pilot study.

- The 90% CIs of T/R ratios for Cmax (97.21-114.26%), AUCinf (92.79-109.23%), AUC4-8 (98.06-106.92%) and AUC8-12 (96.44-108.34%) were within the BE acceptance range. The upper limit of 90% CI for AUC0-4 (98.30-131.78%) was out of the BE acceptance range.

- The applicant stated that "*Based on the results it was concluded to proceed with higher number of subjects for pivotal bioequivalence studies*", indicating that the reason of the test formulation not meeting BE criteria (parameter AUC0-4 only) may be inadequate study power (N=9). The pivotal fed study was conducted in 39 subjects.

- Three subjects experienced AE following administration of test product and one subject experienced AE following administration of reference product. There was no safety concern. In addition, the AE profile was similar between Test and Reference treatments in the pivotal BE studies.

The pilot fed BE study (#2017-4358) is acceptable.

4.2 Formulation Data

4.2.1 Test Formulation

Ingredient	Function	10 mg		20 mg		30 mg		40 mg		60 mg	
		%w/w	Amount (mg)/Capsule	%w/w	Amount (mg)/Capsule	%w/w	Amount (mg)/Capsule	%w/w	Amount (mg)/Capsule	%w/w	Amount (mg)/Capsule
Methylphenidate Hydrochloride, USP	Active ingredient	[redacted] (b) (4)	[redacted]	[redacted] (b) (4)	[redacted]	[redacted] (b) (4)	[redacted]	[redacted] (b) (4)	[redacted]	[redacted] (b) (4)	[redacted] (b) (4)
Polyethylene glycol, NF [redacted] (b) (4)	[redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (4)
Cellaburate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Hypromellose Acetate Succinate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Acetyltributyl Citrate, NF [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Talc, USP [redacted] (b) (4)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted] (4)
Fill weight of Capsule	[redacted]	[redacted]	100.3	[redacted]	200.6	[redacted]	301.0	[redacted]	401.4	[redacted]	602.0

(b) (4) [redacted]

[redacted]

(b) (4)

(b) (4)

Component	[redacted]	Amount per Unit (mg/Capsule)	% w/w per Total capsule weight of 161.3 mg	Function
[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Titanium Dioxide	[redacted]	[redacted]	[redacted]	[redacted]
FD&C Yellow #5	[redacted]	[redacted]	[redacted]	Colorant
FD&C Yellow #6	[redacted]	[redacted]	[redacted]	Colorant

(b) (4)

(b) (4)

[redacted]

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[redacted] (b) (4)

The reviewer verified that the composition of RLD formulations above are current[41,42]. Ritalin® [redacted] (b) (4) [redacted]. [43]

[redacted] (b) (4)

[41] GDRP; CC # 12770541, C12770541DB_CC01242017, dated 03/13/2017: http://panorama.fda.gov/document/view?ID=58c1b896019d2c43e2879e58e1234f0d

[42] [redacted] (b) (4)

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[redacted] (b) (4)

The formulation design and drug release mechanism are similar between test and reference products, thus the formulation differences are not expected to contribute significantly to any changes in PK or safety profiles when comparing test vs. RLD.

4.2.3 Inactive Ingredients (IIG Table)

Component	10 mg Amount (mg)/Capsule	20 mg Amount (mg)/Capsule	30 mg Amount (mg)/Capsule	40 mg Amount (mg)/Capsule	60 mg Amount (mg)/Capsule	Maximum daily intake (mg) based on MDD[a]	IIG limit (mg)[b,c]	Ref. of Approved Drug[d]
Polyethylene glycol (b) (4) [redacted]	[redacted] (b) (4)							
[redacted]								
Cellaburate								
Hypromellose Acetate Succinate								
Acetyltributyl Citrate								
Talc								
[redacted]								
Titanium Dioxide								
FD&C Yellow #5								
FD&C Yellow #6								
[redacted]								

(b) (4) [redacted]

[redacted]

Evaluation of Elemental Iron

Per Module 3.2.P.4 Control of Excipient, elemental iron is contained in excipient Talc [redacted] The reviewer calculated elemental iron consumption based on MDD, as summarized below:

Excipient	Maximum daily intake of excipient based on	Amount of elemental iron in excipient (%w/w)[a]	Amount of Elemental Iron in excipient (mg)	Maximum daily intake of Elemental Iron Based on MDD (mg)	Elemental iron content above/below than 5mg
Talc	[redacted]				

[redacted]

Thus, the drug product complies with 21 CFR73.1200(c), which limits the amount of elemental iron to not more than 5 mg per day.

Are all strengths of the test product proportionally similar per the BA/BE guidance criteria?	☒ Yes ☐ No ☐ N/A
Are the amounts of all inactive ingredients, based on Maximum Daily Dose (MDD), within IIG (per unit) limits?	☒ Yes ☐ No
If no, are they all within IIG (per day) limits?	☐ Yes ☐ No ☒ N/A
If no, are additional data or Pharm/Tox consult necessary?	☐ Yes ☐ No ☒ N/A
Are all color additives and elemental iron within limits specified by CFR (if applicable) or less than 0.1% of the total unit weight (w/w)?	☒ Yes ☐ No ☐ N/A
Are all strengths of the test formulation acceptable?	☒ Yes ☐ No

Comments on Formulation:

[redacted]

- All inactive ingredients utilized in the test formulation are within or below the listed IIG levels for orally administered products.

- MDI of elemental iron is within the acceptance limit of not more than 5 mg.

- The 10 mg, 20 mg, 30 mg and 40 mg strengths of the test product formulations are proportionally similar to that of the 60 mg strength which underwent in vivo BE studies.

The test product formulations are **adequate**.

4.3 Dissolution Testing

4.3.1 Dissolution Data

4.3.1.1 QC Dissolution Data

60 mg

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.01 N HCl [redacted] (b) (4) and pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	% Dissolved in Acid Stage: 0.5 Hour – [redacted] (b) (4) % Dissolved (cumulative) in Buffer Stage: [redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 0.5 Hr	1 Hr	2 Hrs	4 Hrs	6 Hrs	10 Hrs	Study Report Location
MIS-018-030918	09/08/17	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17176 Mfg. Date: 06/09/2017	**60 mg Capsule**	12	Mean	50	50	50	97	99	99	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	1.2	1.6	1.4	2.1	1.6	1.4	
MIS-018-030918	09/08/17	Reference Product Methylphenidate Hydrochloride Extended-Release Capsules (LA) Lot # 634151 Exp. Date: 08/2018	**60 mg Capsule**	12	Mean	49	49	49	98	99	98	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	3.3	2.2	1.0	1.2	1.2	1.2	

Data source: Module 2.7.1, Clinical Summary, Table 5.1a

10 mg

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.01 N HCl ([redacted] (b) (4) and pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	% Dissolved in Acid Stage: 0.5 Hour – [redacted] (b) (4) % Dissolved (cumulative) in Buffer Stage: [redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**						**Study Report Location**
						0.5 Hr	**1 Hr**	**2 Hrs**	**4 Hrs**	**6 Hrs**	**10 Hrs**	
MIS-018-030918	09/14/17	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17179 Mfg. Date: 06/09/2017	**10 mg Capsule**	12	Mean	51	50	50	100	102	101	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	2.2	2.1	1.7	1.5	1.8	1.6	
MIS-018-030918	02/12/18	Reference Product Ritalin LA Capsules Lot # F0080 Exp. Date: 04/2020	**10 mg Capsule**	12	Mean	52	52	52	88	103	102	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	2.9	3.0	3.0	6.0	2.5	2.4	

Data source: Module 2.7.1, Clinical Summary, Table 5.1b

20 mg

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.01 N HCl [redacted] (b) (4) and pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	% Dissolved in Acid Stage: 0.5 Hour – [redacted] (b) (4) % Dissolved (cumulative) in Buffer Stage: [redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**						**Study Report Location**
						0.5 Hr	**1 Hr**	**2 Hrs**	**4 Hrs**	**6 Hrs**	**10 Hrs**	
MIS-018-030918	09/16/17	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17182 Mfg. Date: 06/09/2017	**20 mg Capsule**	12	Mean	48	48	48	96	97	96	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	2.6	1.8	1.9	1.8	1.1	3.0	
MIS-018-030918	02/12/18	Reference Product Ritalin LA Capsules Lot # F4211 Exp. Date: 04/2020	**20 mg Capsule**	12	Mean	52	52	52	88	104	104	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	1.7	1.7	1.7	1.5	1.3	1.3	

Data source: Module 2.7.1, Clinical Summary, Table 5.1c

30 mg

Dissolution Conditions	**Apparatus:**	1 (Basket)	
	Speed of Rotation:	100 RPM	
	Medium:	0.01 N HCl [redacted] (b) (4) and pH 6.8 Phosphate buffer [redacted] (b) (4))	
	Volume:	500 mL	
	Temperature:	37°C±0.5°C	
Firm's Proposed Specifications	% Dissolved in Acid Stage: 0.5 Hour – [redacted] (b) (4) % Dissolved (cumulative) in Buffer Stage: [redacted] (b) (4)		
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151		

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**						**Study Report Location**
						0.5 Hr	**1 Hr**	**2 Hrs**	**4 Hrs**	**6 Hrs**	**10 Hrs**	
MIS-018-030918	09/16/17	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17183 Mfg. Date: 06/09/2017	**30 mg Capsule**	12	Mean	49	49	50	95	99	98	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	1.6	1.5	1.6	1.1	1.1	1.2	
MIS-018-030918	02/13/18	Reference Product Ritalin LA Capsules Lot # APCA074 Exp. Date: 04/2020	**30 mg Capsule**	12	Mean	52	52	52	99	102	102	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	2.0	1.9	2.0	1.1	1.3	1.3	

Data source: Module 2.7.1, Clinical Summary, Table 5.1d

40 mg

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.01 N HCl [redacted] (b) (4) and pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	% Dissolved in Acid Stage: 0.5 Hour – [redacted] (b) (4) % Dissolved (cumulative) in Buffer Stage: 10 Hours [redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times						Study Report Location
						0.5 Hr	1 Hr	2 Hrs	4 Hrs	6 Hrs	10 Hrs	
MIS-018-030918	09/18/17	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17184 Mfg. Date: 06/09/2017	**40 mg Capsule**	12	Mean	50	50	50	97	100	100	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	0.9	0.7	0.9	0.7	0.5	0.5	
MIS-018-030918	02/13/18	Reference Product Ritalin LA Capsules Lot # APC34 Exp. Date: 05/2020	**40 mg Capsule**	12	Mean	50	51	51	98	103	102	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)						
					% CV	3.3	2.4	2.3	1.7	1.7	1.7	

Data source: Module 2.7.1, Clinical Summary, Table 5.1e

4.3.1.2 Multi-media Dissolution Data

60 mg – pH 1.2 (0.1N HCl)

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	**8 Hrs**	**12 Hrs**	**16 Hrs**	**24 Hrs**	
MIS-018-030918	03/02/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17176A Mfg. Date: 06/09/2017	**60 mg Capsule**	12	Mean	50	50	53	70	80	86	92	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted]						(b) (4)	
					% CV	2.9	3.1	2.9	8.3	7.2	5.9	3.9	
MIS-018-030918	03/01/18	Reference Product Methylphenidate Hydrochloride Extended-Release Capsules (LA) Lot # 634151 Exp. Date: 08/2018	**60 mg Capsule**	12	Mean	52	52	52	69	81	87	94	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted]						(b) (4)	
					% CV	1.9	2.1	1.9	1.6	1.6	1.6	1.5	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.1a

10 mg – pH 1.2 (0.1N HCl)

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times							Study Report Location
						1 Hr	2 Hrs	4 Hrs	8 Hrs	12 Hrs	16 Hrs	24 Hrs	
MIS-018-030918	02/16/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17179A Mfg. Date: 06/09/2017	**10 mg Capsule**	12	Mean	49	49	53	75	87	93	98	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)							
					% CV	2.2	2.2	2.2	2.1	2.3	2.7	3.6	
MIS-018-030918	02/14/18	Reference Product Ritalin LA Capsules Lot # F0080 Exp. Date: 04/2020	**10 mg Capsule**	12	Mean	52	51	52	56	96	102	103	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)							
					% CV	3.1	3.1	3.1	3.4	2.1	2.4	3.0	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.1b

20 mg – pH 1.2 (0.1N HCl)

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	**8 Hrs**	**12 Hrs**	**16 Hrs**	**24 Hrs**	
MIS-018-030918	02/21/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17182A Mfg. Date: 06/09/2017	**20 mg Capsule**	12	Mean	48	48	52	73	85	91	95	**Module 2.7.1.2- comparative *in-vitro* dissolution data**
					Range	(b) (4) [redacted]							
					% CV	1.4	1.3	1.2	1.2	1.1	1.2	1.4	
MIS-018-030918	02/26/18	Reference Product Ritalin LA Capsules Lot # F4211 Exp. Date: 04/2020	**20 mg Capsule**	12	Mean	51	51	51	55	95	100	101	**Module 2.7.1.2- comparative *in-vitro* dissolution data**
					Range	(b) (4) [redacted]							
					% CV	2.1	2.1	2.0	1.6	1.7	1.4	1.5	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.1c

30 mg – pH 1.2 (0.1N HCl)

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	**8 Hrs**	**12 Hrs**	**16 Hrs**	**24 Hrs**	
MIS-018-030918	02/22/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17183A Mfg. Date: 06/09/2017	**30 mg Capsule**	12	Mean	49	49	52	74	85	91	97	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted]						(b) (4)	
					% CV	2.2	2.0	1.8	1.5	1.7	1.9	2.6	
MIS-018-030918	02/22/18	Reference Product Ritalin LA Capsules Lot # APCA074 Exp. Date: 04/2020	**30 mg Capsule**	12	Mean	52	53	53	61	101	105	105	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted]						(b) (4)	
					% CV	1.6	1.6	2.1	2.1	1.9	1.4	1.3	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.1d

40 mg – pH 1.2 (0.1N HCl)

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	**8 Hrs**	**12 Hrs**	**16 Hrs**	**24 Hrs**	
MIS-018-030918	02/27/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17184A Mfg. Date: 06/09/2017	**40 mg Capsule**	12	Mean	48	49	53	74	86	92	97	**Module 2.7.1.2- comparative *in-vitro* dissolution data**
					Range	[redacted]						(b) (4)	
					% CV	5.5	0.6	1.0	2.2	2.0	2.4	3.3	
MIS-018-030918	03/02/18	Reference Product Ritalin LA Capsules Lot # APC34 Exp. Date: 05/2020	**40 mg Capsule**	12	Mean	51	51	51	58	99	99	99	**Module 2.7.1.2- comparative *in-vitro* dissolution data**
					Range	[redacted]						(b) (4)	
					% CV	2.0	2.2	2.1	2.4	2.4	2.6	2.8	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.1e

60 mg – pH 4.5

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 4.5 Acetate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times							Study Report Location
						1 Hr	2 Hrs	4 Hrs	8 Hrs	12 Hrs	16 Hrs	20 Hrs	
MIS-018-030918	03/01/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17176A Mfg. Date: 06/09/2017	60 mg Capsule	12	Mean	51	51	56	79	90	95	97	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)							
					% CV	2.4	2.6	2.1	1.2	0.8	1.0	1.0	
MIS-018-030918	02/28/18	Reference Product Methylphenidate Hydrochloride Extended-Release Capsules (LA) Lot # 634151 Exp. Date: 08/2018	60 mg Capsule	12	Mean	50	50	51	71	82	89	92	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)							
					% CV	2.6	2.4	2.5	2.5	2.4	2.5	2.6	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.2a

10 mg – pH 4.5

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 4.5 Acetate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times							Study Report Location
						1 Hr	2 Hrs	4 Hrs	8 Hrs	12 Hrs	16 Hrs	20 Hrs	
MIS-018-030918	02/21/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17179A Mfg. Date: 06/09/2017	**10 mg Capsule**	12	Mean	50	50	55	79	90	95	97	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)							
					% CV	1.8	1.2	1.2	1.0	1.0	1.1	1.4	
MIS-018-030918	02/20/18	Reference Product Ritalin LA Capsules Lot # F0080 Exp. Date: 04/2020	**10 mg Capsule**	12	Mean	50	53	53	54	90	101	103	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)							
					% CV	5.1	1.5	1.5	1.4	3.0	2.4	3.1	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.2b

20 mg – pH 4.5

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 4.5 Acetate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	**8 Hrs**	**12 Hrs**	**16 Hrs**	**20 Hrs**	
MIS-018-030918	02/24/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17182A Mfg. Date: 06/09/2017	**20 mg Capsule**	12	Mean	49	49	54	77	88	94	96	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)							
					% CV	2.0	2.1	1.7	1.1	1.3	1.4	1.7	
MIS-018-030918	02/24/18	Reference Product Ritalin LA Capsules Lot # F4211 Exp. Date: 04/2020	**20 mg Capsule**	12	Mean	51	51	51	52	87	96	98	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)							
					% CV	2.8	2.8	2.7	2.5	1.7	1.9	2.3	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.2c

30 mg – pH 4.5

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 4.5 Acetate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	**8 Hrs**	**12 Hrs**	**16 Hrs**	**20 Hrs**	
MIS-018-030918	02/25/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17183A Mfg. Date: 06/09/2017	**30 mg Capsule**	12	Mean	49	50	55	78	89	94	97	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted]						(b) (4)	
					% CV	1.8	1.8	1.8	1.6	1.8	2.1	2.5	
MIS-018-030918	02/26/18	Reference Product Ritalin LA Capsules Lot # APCA074 Exp. Date: 04/2020	**30 mg Capsule**	12	Mean	50	50	50	54	90	95	97	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted]						(b) (4)	
					% CV	1.4	1.3	1.3	1.7	1.6	1.9	1.9	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.2d

40 mg – pH 4.5

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 4.5 Acetate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**							**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	**8 Hrs**	**12 Hrs**	**16 Hrs**	**20 Hrs**	
MIS-018-030918	02/28/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17184A Mfg. Date: 06/09/2017	**40 mg Capsule**	12	Mean	48	49	54	77	87	92	94	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]							
					% CV	1.0	0.8	0.6	0.5	0.7	0.7	0.8	
MIS-018-030918	02/27/18	Reference Product Ritalin LA Capsules Lot # APC34 Exp. Date: 05/2020	**40 mg Capsule**	12	Mean	50	51	50	54	89	95	97	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]							
					% CV	1.5	1.4	1.5	2.4	2.5	2.4	2.3	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.2e

60 mg – pH 6.8

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 6.8 Phosphate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times			Study Report Location
						1 Hr	2 Hrs	4 Hrs	
MIS-018-030918	02/26/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17176A Mfg. Date: 06/09/2017	**60 mg Capsule**	12	Mean	51	80	102	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]		(b) (4)	
					% CV	2.1	1.7	0.8	
MIS-018-030918	03/01/18	Reference Product Methylphenidate Hydrochloride Extended-Release Capsules (LA) Lot # 634151 Exp. Date: 08/2018	**60 mg Capsule**	12	Mean	50	96	99	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]		(b) (4)	
					% CV	1.5	1.1	0.9	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.3a

10 mg – pH 6.8

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 6.8 Phosphate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**			**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	
MIS-018-030918	02/14/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17179A Mfg. Date: 06/09/2017	**10 mg Capsule**	12	Mean	49	85	101	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted]		(b) (4)	
					% CV	2.6	3.5	1.6	
MIS-018-030918	02/14/18	Reference Product Ritalin LA Capsules Lot # F0080 Exp. Date: 04/2020	**10 mg Capsule**	12	Mean	52	65	101	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted]		(b) (4)	
					% CV	2.8	4.0	2.0	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.3b

20 mg – pH 6.8

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 6.8 Phosphate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times			Study Report Location
						1 Hr	2 Hrs	4 Hrs	
MIS-018-030918	02/15/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17182A Mfg. Date: 06/09/2017	**20 mg Capsule**	12	Mean	48	82	99	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)			
					% CV	1.9	2.0	1.2	
MIS-018-030918	02/15/18	Reference Product Ritalin LA Capsules Lot # F4211 Exp. Date: 04/2020	**20 mg Capsule**	12	Mean	51	70	101	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)			
					% CV	4.2	5.8	3.5	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.3c

30 mg – pH 6.8

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 6.8 Phosphate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**			**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	
MIS-018-030918	02/16/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17183A Mfg. Date: 06/09/2017	**30 mg Capsule**	12	Mean	50	85	99	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]		(b) (4)	
					% CV	1.2	1.9	0.9	
MIS-018-030918	02/16/18	Reference Product Ritalin LA Capsules Lot # APCA074 Exp. Date: 04/2020	**30 mg Capsule**	12	Mean	51	73	100	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]		(b) (4)	
					% CV	2.7	7.0	1.8	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.3d

40 mg – pH 6.8

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	pH 6.8 Phosphate buffer
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**			**Study Report Location**
						1 Hr	**2 Hrs**	**4 Hrs**	
MIS-018-030918	02/25/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17184A Mfg. Date: 06/09/2017	**40 mg Capsule**	12	Mean	51	81	102	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]			
					% CV	2.1	2.6	0.9	
MIS-018-030918	02/23/18	Reference Product Ritalin LA Capsules Lot # APC34 Exp. Date: 05/2020	**40 mg Capsule**	12	Mean	50	65	100	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]			
					% CV	2.6	2.2	1.3	

Data source: Module 2.7.1, Clinical Summary, Table 5.2.3e

4.3.1.3 Alcohol Dose-Dumping Data

60 mg (0.1N HCl + 0% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	Study Report Location
MIS-019-031318R	01/30/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17176A Mfg. Date: 06/09/2017	60 mg Capsule	12	Mean	50	50	50	50	50	50	50	51	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	2.1	2.6	2.8	2.8	2.7	2.7	2.8	2.9	
MIS-019-031318R	02/20/18	Reference Product Methylphenidate Hydrochloride Extended-Release Capsules (LA) Lot # 634151 Exp. Date: 08/2018	60 mg Capsule	12	Mean	49	49	49	49	49	49	49	49	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	1.5	1.2	1.4	1.3	1.3	1.3	1.3	1.3	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.1a

10 mg (0.1N HCl + 0% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	01/26/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17179A Mfg. Date: 06/09/2017	**10 mg Capsule**	12	Mean	51	50	50	50	50	50	50	50	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]								
					% CV	5.4	2.4	2.3	1.6	1.8	1.5	1.8	1.6	
MIS-019-031318R	02/17/18	Reference Product Ritalin LA Capsules Lot # F0080 Exp. Date: 04/2020	**10 mg Capsule**	12	Mean	51	51	51	51	51	51	51	52	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]								
					% CV	3.8	3.8	3.8	3.9	3.9	3.9	3.9	3.8	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.1b

20 mg (0.1N HCl + 0% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
MIS-019-031318R	01/29/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17182A Mfg. Date: 06/09/2017	**20 mg Capsule**	12	Mean	49	50	50	50	50	50	50	50	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]								
					% CV	2.9	2.9	2.9	2.7	3.0	3.1	2.9	3.0	
MIS-019-031318R	02/17/18	Reference Product Ritalin LA Capsules Lot # F4211 Exp. Date: 04/2020	**20 mg Capsule**	12	Mean	50	50	50	50	50	50	50	50	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]								
					% CV	2.6	2.6	2.6	2.6	2.7	2.8	2.8	2.7	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.1c

30 mg (0.1N HCl + 0% Alcohol)

Dissolution Conditions	Apparatus:	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	Study Report Location
MIS-019-031318R	01/29/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17183A Mfg. Date: 06/09/2017	30 mg Capsule	12	Mean	51	51	51	51	51	51	51	51	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	5.3	4.5	5.2	5.1	5.2	5.0	5.0	5.2	
MIS-019-031318R	02/19/18	Reference Product Ritalin LA Capsules Lot # APCA074 Exp. Date: 04/2020	30 mg Capsule	12	Mean	50	50	50	50	50	50	50	50	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.1d

40 mg (0.1N HCl + 0% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	01/30/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17184A Mfg. Date: 06/09/2017	**40 mg Capsule**	12	Mean	53	53	54	54	54	54	54	54	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	7.4	4.6	6.0	6.3	6.5	6.6	6.4	6.5	
MIS-019-031318R	02/20/18	Reference Product Ritalin LA Capsules Lot # APC34 Exp. Date: 05/2020	**40 mg Capsule**	12	Mean	51	51	51	51	51	51	51	51	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	1.4	1.5	1.6	1.5	1.6	1.5	1.5	1.6	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.1e

60 mg (0.1N HCl + 5% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	5% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	Study Report Location
MIS-019-031318R	02/12/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17176A Mfg. Date: 06/09/2017	**60 mg Capsule**	12	Mean	51	51	51	51	52	51	51	51	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	2.3	2.4	2.4	2.4	2.4	2.4	2.4	2.4	
MIS-019-031318R	02/26/18	Reference Product Methylphenidate Hydrochloride Extended-Release Capsules (LA) Lot # 634151 Exp. Date: 08/2018	**60 mg Capsule**	12	Mean	49	50	50	50	50	50	50	50	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	3.1	3.0	3.0	2.9	3.0	3.0	2.9	3.0	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.2a

10 mg (0.1N HCl + 5% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	5% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	02/08/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17179A Mfg. Date: 06/09/2017	**10 mg Capsule**	12	Mean	50	50	50	50	50	50	50	50	**Module 2.7.1.2- comparative *in-vitro* dissolution data**
					Range	[redacted] (b) (4)								
					% CV	1.5	1.5	1.5	1.6	1.4	1.3	1.5	1.5	
MIS-019-031318R	02/23/18	Reference Product Ritalin LA Capsules Lot # F0080 Exp. Date: 04/2020	**10 mg Capsule**	12	Mean	50	50	50	50	50	50	50	51	**Module 2.7.1.2- comparative in-vitro dissolution data**
					Range	[redacted] (b) (4)								
					% CV	4.7	4.7	4.8	4.6	4.7	4.7	4.6	4.7	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.2b

20 mg (0.1N HCl + 5% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	5% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	02/08/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17182A Mfg. Date: 06/09/2017	**20 mg Capsule**	12	Mean	49	49	49	50	50	50	50	50	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	1.6	1.6	1.7	1.7	1.7	1.8	1.8	1.8	
MIS-019-031318R	02/24/18	Reference Product Ritalin LA Capsules Lot # F4211 Exp. Date: 04/2020	**20 mg Capsule**	12	Mean	51	51	51	51	51	51	51	51	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	2.8	2.8	2.8	2.8	2.8	2.8	2.8	2.8	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.2c

30 mg (0.1N HCl + 5% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	5% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	02/09/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17183A Mfg. Date: 06/09/2017	**30 mg Capsule**	12	Mean	49	49	49	49	49	49	50	50	**Module 2.7.1.2- comparative *in-vitro* dissolution data**
					Range	[redacted]							(b) (4)	
					% CV	2.1	2.5	2.2	2.2	2.1	2.1	2.2	2.2	
MIS-019-031318R	02/24/18	Reference Product Ritalin LA Capsules Lot # APCA074 Exp. Date: 04/2020	**30 mg Capsule**	12	Mean	50	51	51	51	51	51	51	51	**Module 2.7.1.2- comparative *in-vitro* dissolution data**
					Range	[redacted]							(b) (4)	
					% CV	1.5	1.5	1.5	1.4	1.4	1.5	1.4	1.3	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.2d

40 mg (0.1N HCl + 5% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	5% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	Study Report Location
MIS-019-031318R	02/12/18	Test Product Methylphenidate Hydrochloride Extended- Release Capsules Lot # GPI17184A Mfg. Date: 06/09/2017	**40 mg Capsule**	12	Mean	51	51	51	51	51	51	51	51	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	1.0	1.0	1.0	1.1	1.0	1.0	1.0	1.0	
MIS-019-031318R	02/26/18	Reference Product Ritalin LA Capsules Lot # APC34 Exp. Date: 05/2020	**40 mg Capsule**	12	Mean	50	50	50	50	50	50	50	50	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	2.1	2.1	2.0	2.1	2.0	2.2	2.1	2.1	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.2e

60 mg (0.1N HCl + 20% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	20% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	Study Report Location
MIS-019-031318R	02/07/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17176A Mfg. Date: 06/09/2017	**60 mg Capsule**	12	Mean	52	52	53	53	53	53	53	53	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	(b) (4)								
					% CV	3.0	3.1	3.1	3.1	3.0	3.1	3.1	3.1	
MIS-019-031318R	02/23/18	Reference Product Methylphenidate Hydrochloride Extended-Release Capsules (LA) Lot # 634151 Exp. Date: 08/2018	**60 mg Capsule**	12	Mean	50	51	51	51	51	51	51	51	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	(b) (4)								
					% CV	3.0	3.2	3.2	3.4	3.2	3.3	3.4	3.4	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.3a

10 mg (0.1N HCl + 20% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	20% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	02/03/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17179A Mfg. Date: 06/09/2017	**10 mg Capsule**	12	Mean	50	51	51	51	51	51	51	51	(b) (4) Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]								
					% CV	2.2	2.0	1.9	1.9	1.9	1.8	1.8	1.8	
MIS-019-031318R	02/21/18	Reference Product Ritalin LA Capsules Lot # F0080 Exp. Date: 04/2020	**10 mg Capsule**	12	Mean	53	53	53	54	54	54	54	55	(b) (4) Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]								
					% CV	5.5	5.4	5.3	5.3	5.3	5.3	5.3	5.3	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.3b

20 mg (0.1N HCl + 20% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	20% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	02/15/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17182A Mfg. Date: 06/09/2017	**20 mg Capsule**	12	Mean	49	49	49	49	49	49	49	49	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	1.9	1.9	1.9	1.9	2.0	1.9	1.9	1.9	
MIS-019-031318R	02/21/18	Reference Product Ritalin LA Capsules Lot # F4211 Exp. Date: 04/2020	**20 mg Capsule**	12	Mean	51	51	51	51	51	51	52	52	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	2.1	2.1	2.1	2.0	2.0	2.0	2.0	1.9	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.3c

30 mg (0.1N HCl + 20% Alcohol)

Dissolution Conditions	Apparatus:	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	20% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times								Study Report Location
						15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	
MIS-019-031318R	02/06/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17183A Mfg. Date: 06/09/2017	30 mg Capsule	12	Mean	51	52	52	51	51	51	52	52	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	3.5	3.7	3.7	3.6	3.6	3.7	3.8	3.7	
MIS-019-031318R	02/21/18	Reference Product Ritalin LA Capsules Lot # APCA074 Exp. Date: 04/2020	30 mg Capsule	12	Mean	50	51	51	51	51	52	52	53	Module 2.7.1.2- comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	1.7	1.8	1.8	1.7	1.7	2.0	2.0	2.0	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.3d

40 mg (0.1N HCl + 20% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	20% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	02/06/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17184A Mfg. Date: 06/09/2017	**40 mg Capsule**	12	Mean	51	51	52	52	52	52	52	51	(b) (4) Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]								
					% CV	1.0	0.9	0.9	0.8	0.8	0.8	0.9	1.0	
MIS-019-031318R	02/22/18	Reference Product Ritalin LA Capsules Lot # APC34 Exp. Date: 05/2020	**40 mg Capsule**	12	Mean	50	50	50	50	50	50	50	51	(b) (4) Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]								
					% CV	2.5	2.5	2.6	2.6	2.6	2.6	2.5	2.5	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.3e

60 mg (0.1N HCl + 40% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	40% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	02/02/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17176A Mfg. Date: 06/09/2017	**60 mg Capsule**	12	Mean	50	53	62	75	85	92	97	99	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	2.7	2.9	2.7	2.4	1.8	2.0	1.4	1.1	
MIS-019-031318R	02/16/18	Reference Product Methylphenidate Hydrochloride Extended-Release Capsules (LA) Lot # 634151 Exp. Date: 08/2018	**60 mg Capsule**	12	Mean	52	56	64	79	90	97	100	101	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	3.0	2.6	2.8	2.6	2.2	2.0	1.9	2.0	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.4a

10 mg (0.1N HCl + 40% Alcohol)

Dissolution Conditions			**Apparatus:**		USP Apparatus 1 (Basket)									
			Speed of Rotation:		100 RPM									
			Medium:		40% (v/v) Alcohol in 0.1 N HCl									
			Volume:		900 mL									
			Temperature:		37°C±0.5°C									
Firm's Proposed Specifications			N/A											
Dissolution Testing Site (Name, Address)			Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151											
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	01/31/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17179A Mfg. Date: 06/09/2017	**10 mg Capsule**	12	Mean	50	54	65	78	88	94	97	99	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	1.6	1.8	3.7	3.2	2.5	1.8	1.8	1.8	
MIS-019-031318R	02/13/18	Reference Product Ritalin LA Capsules Lot # F0080 Exp. Date: 04/2020	**10 mg Capsule**	12	Mean	59	77	91	98	102	103	104	104	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted] (b) (4)								
					% CV	5.4	3.4	2.8	2.7	2.7	2.7	2.7	2.8	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.4b

20 mg (0.1N HCl + 40% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	40% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	Study Report Location
MIS-019-031318R	02/01/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17182A Mfg. Date: 06/09/2017	20 mg Capsule	12	Mean	50	55	71	85	94	98	99	100	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]								
					% CV	2.6	2.7	3.0	2.8	2.5	2.3	2.4	2.4	
MIS-019-031318R	02/14/18	Reference Product Ritalin LA Capsules Lot # F4211 Exp. Date: 04/2020	20 mg Capsule	12	Mean	57	74	87	94	97	100	101	102	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	(b) (4) [redacted]								
					% CV		4.2	9.6	11.6	11.3 9.5	7.6	6.1	5.0	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.4c

30 mg (0.1N HCl + 40% Alcohol)

Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	40% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	02/01/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17183A Mfg. Date: 06/09/2017	**30 mg Capsule**	12	Mean	49	52	62	75	85	91	95	97	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	1.9	2.0	2.4	2.3	2.0	1.6	1.6	1.3	
MIS-019-031318R	02/15/18	Reference Product Ritalin LA Capsules Lot # APCA074 Exp. Date: 04/2020	**30 mg Capsule**	12	Mean	53	64	74	80	85	89	92	94	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	6.2	16.9	22.0	22.3	19.7	15.5	12.1	9.8	

Data source: Module 2.7.1, Clinical Summary, Table 5.3.4d

40 mg (0.1N HCl + 40% Alcohol)

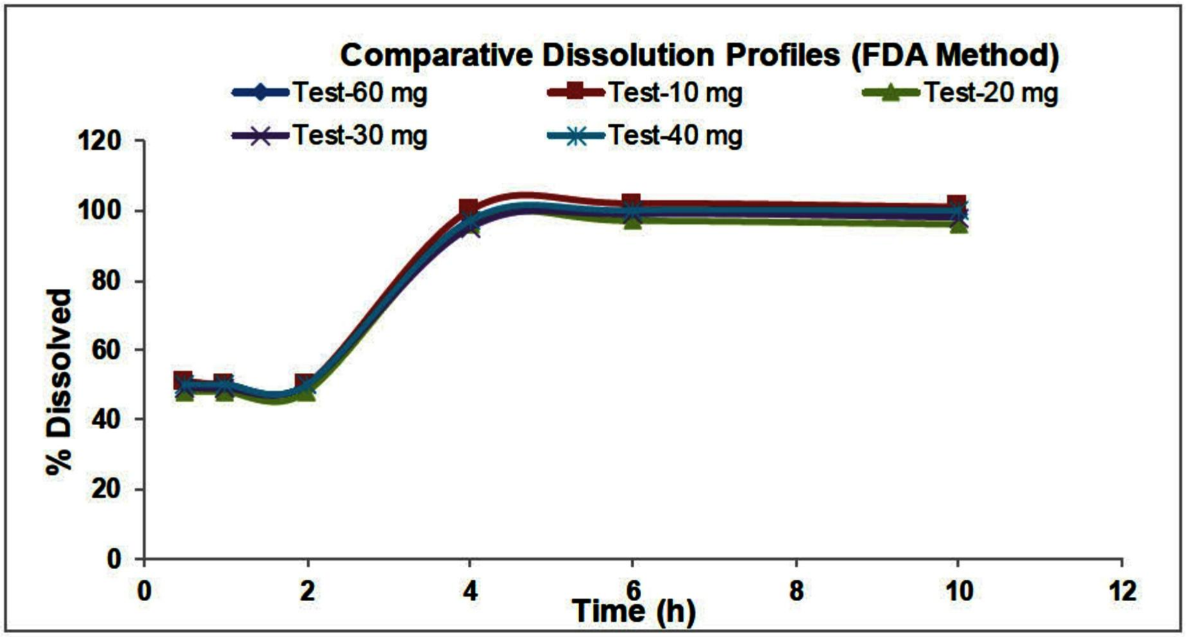
Dissolution Conditions	**Apparatus:**	USP Apparatus 1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	40% (v/v) Alcohol in 0.1 N HCl
	Volume:	900 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	N/A	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

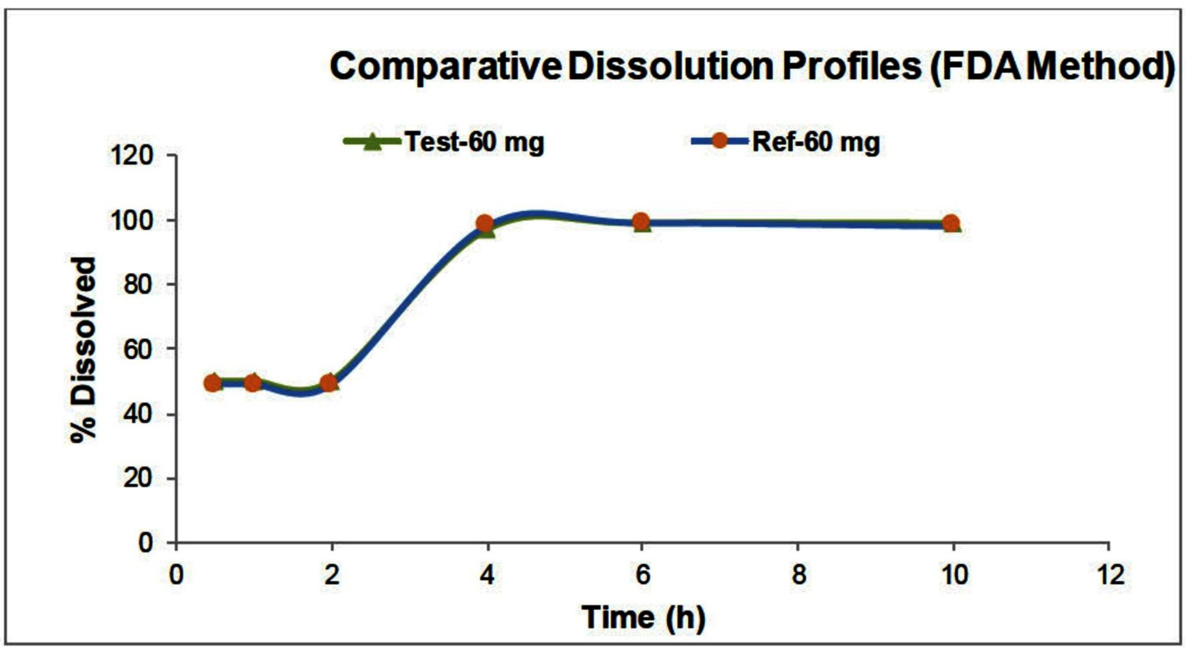
Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date) (Reference – Expiration Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times**								**Study Report Location**
						15 min	**30 min**	**45 min**	**60 min**	**75 min**	**90 min**	**105 min**	**120 min**	
MIS-019-031318R	02/02/18	Test Product Methylphenidate Hydrochloride Extended-Release Capsules Lot # GPI17184A Mfg. Date: 06/09/2017	**40 mg Capsule**	12	Mean	50	53	63	77	87	93	96	98	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	1.4	1.2	2.0	1.7	1.8	1.6	1.3	1.0	
MIS-019-031318R	02/15/18	Reference Product Ritalin LA Capsules Lot # APC34 Exp. Date: 05/2020	**40 mg Capsule**	12	Mean	53	71	84	91	95	96	98	98	Module 2.7.1.2-comparative *in-vitro* dissolution data
					Range	[redacted]							(b) (4)	
					% CV	2.7	2.7	2.3	2.0	1.9	1.8	1.7	1.6	

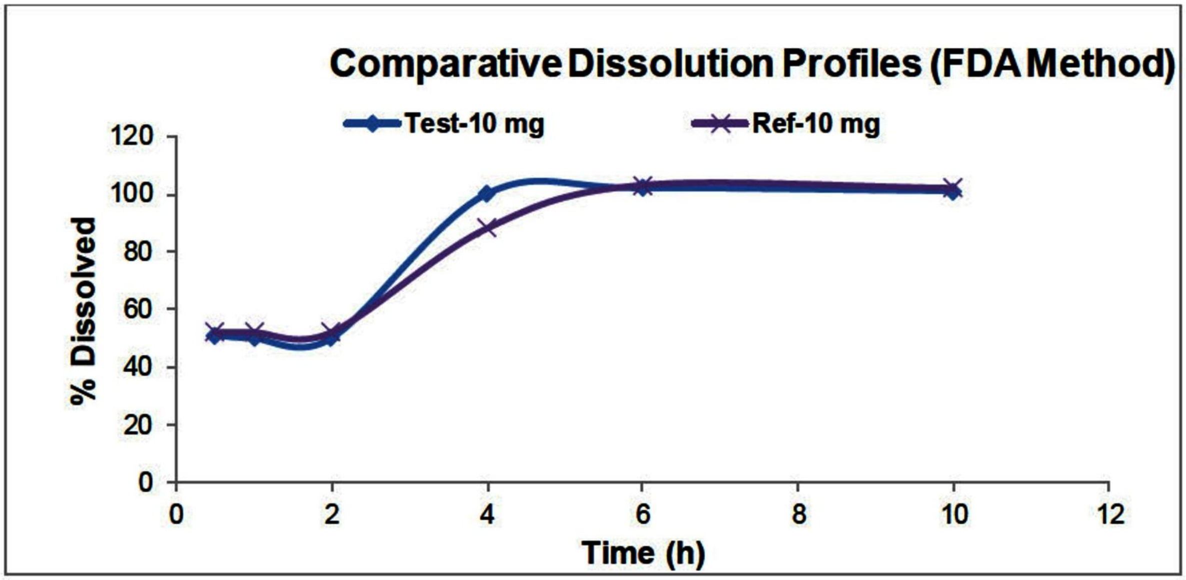
Data source: Module 2.7.1, Clinical Summary, Table 5.3.4e

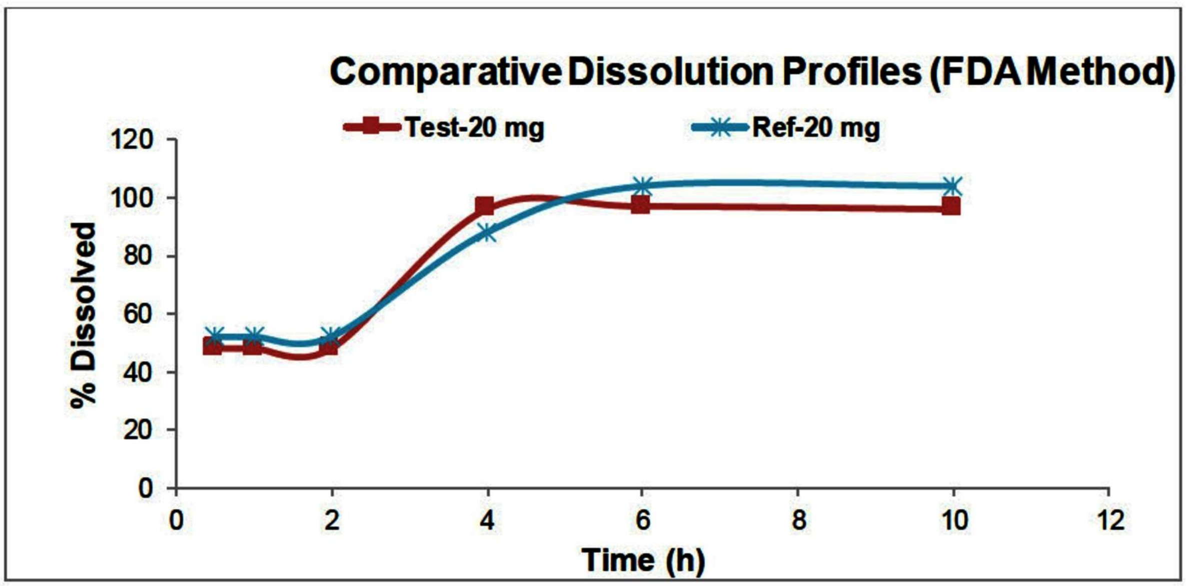
4.3.2 Dissolution Profiles

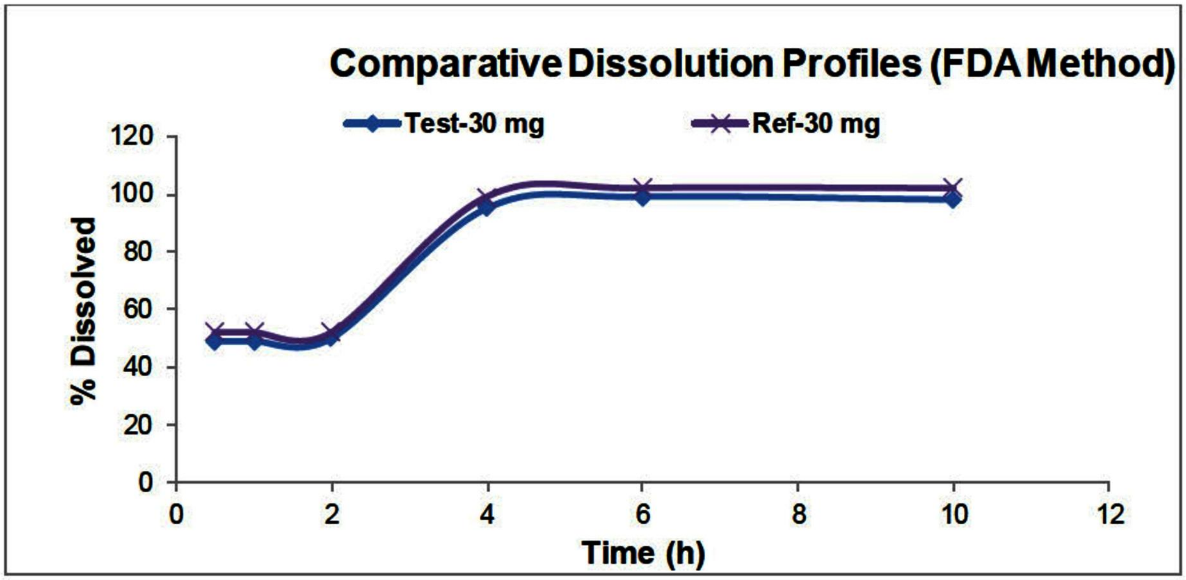
4.3.2.1 QC Dissolution Profiles (reviewer generated)

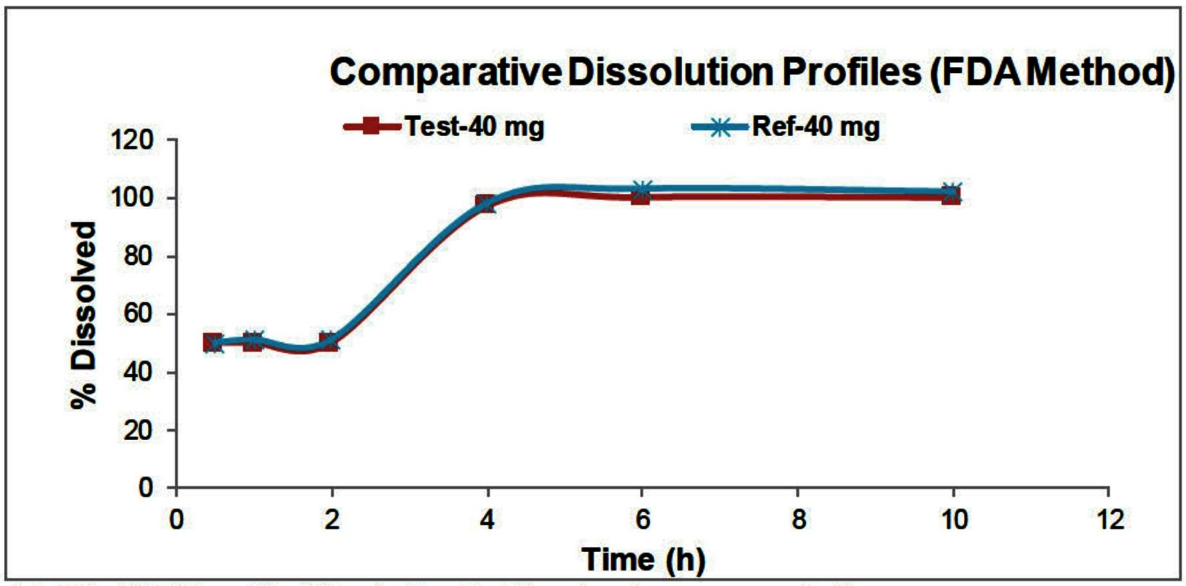





Comparative Dissolution Profiles (FDA Method)
Test-10 mg
Ref-10 mg
% Dissolved
Time (h)
0
20
40
60
80
100
120
0
2
4
6
8
10
12

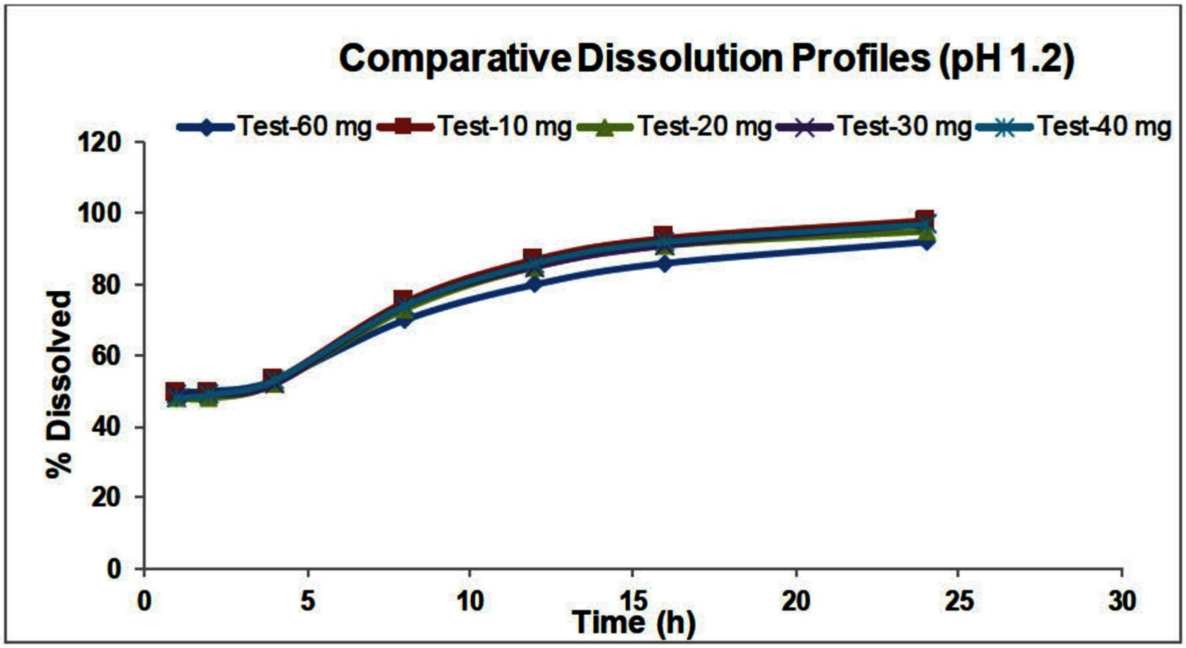

Comparative Dissolution Profiles (FDA Method)
Test-20 mg
Ref-20 mg
% Dissolved
Time (h)
0
20
40
60
80
100
120
0
2
4
6
8
10
12

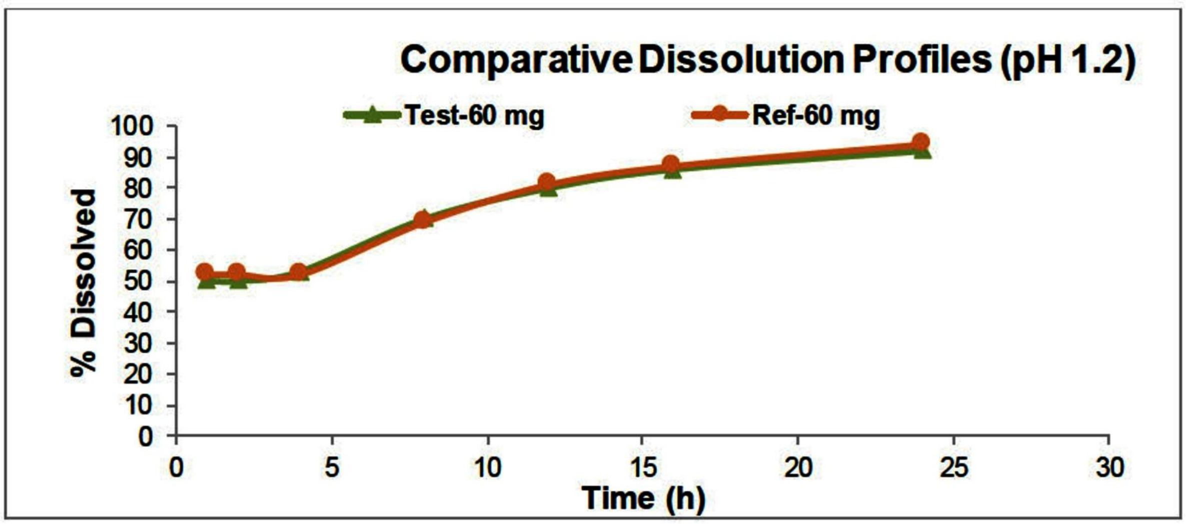


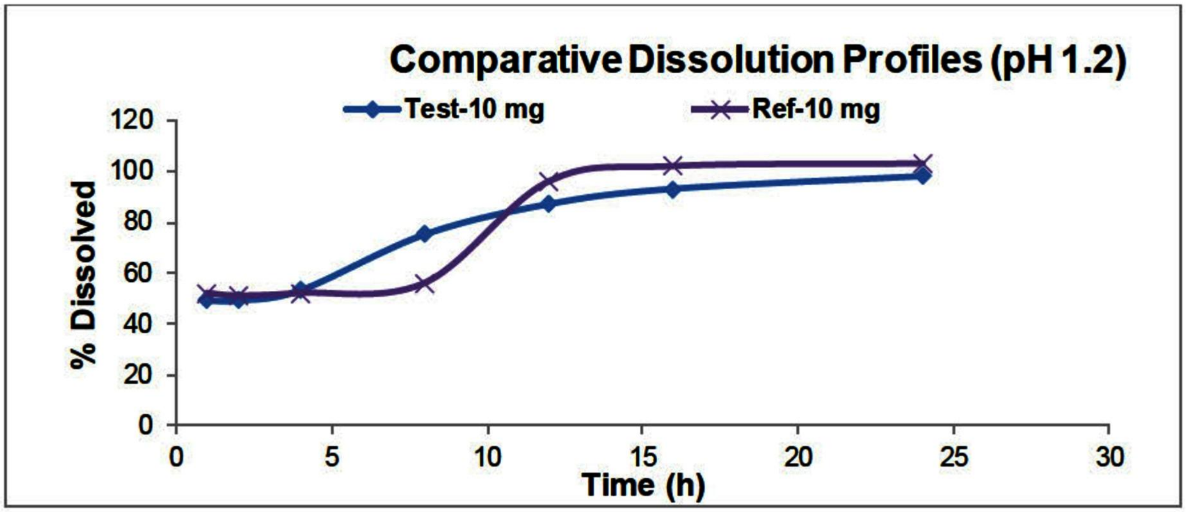


4.3.2.2 Multi-media Dissolution Profiles (reviewer generated)

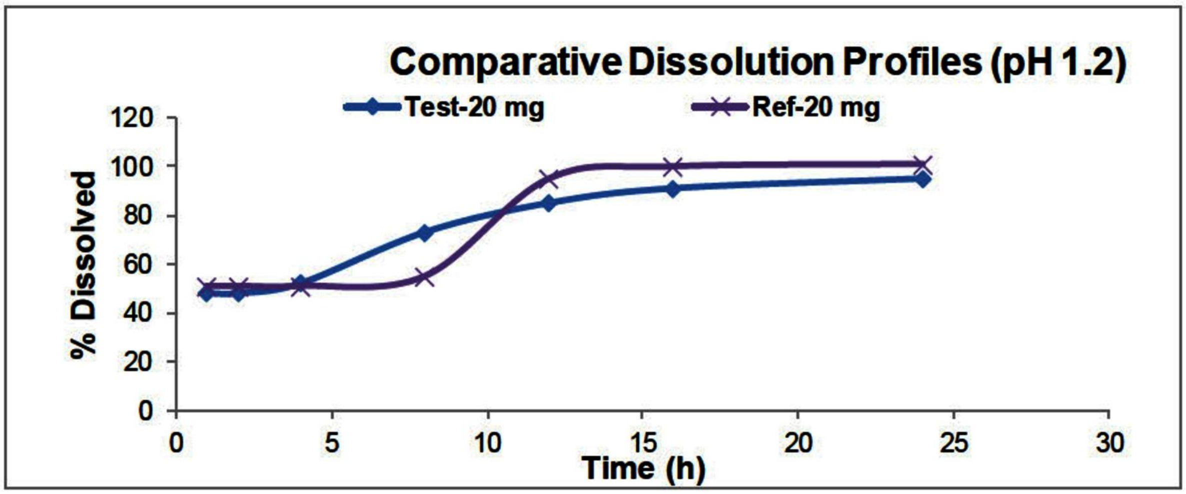
<u>pH 1.2</u>


Comparative Dissolution Profiles (pH 1.2)
Test-60 mg
Test-10 mg
Test-20 mg
Test-30 mg
Test-40 mg
% Dissolved
Time (h)
0
20
40
60
80
100
120
0
5
10
15
20
25
30

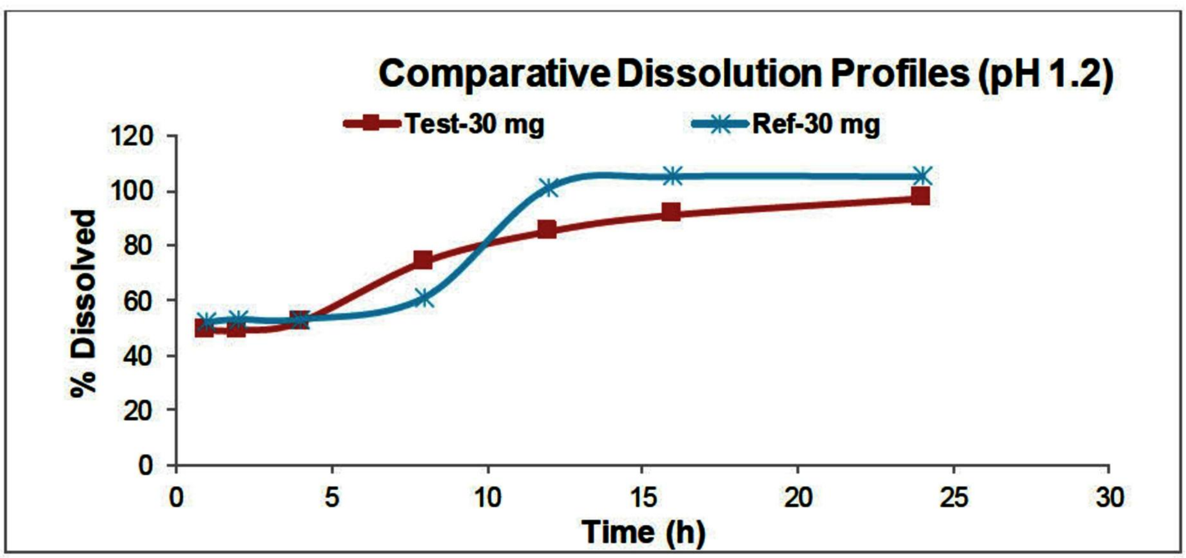

Comparative Dissolution Profiles (pH 1.2)
Test-60 mg
Ref-60 mg
% Dissolved
Time (h)
0
10
20
30
40
50
60
70
80
90
100
0
5
10
15
20
25
30



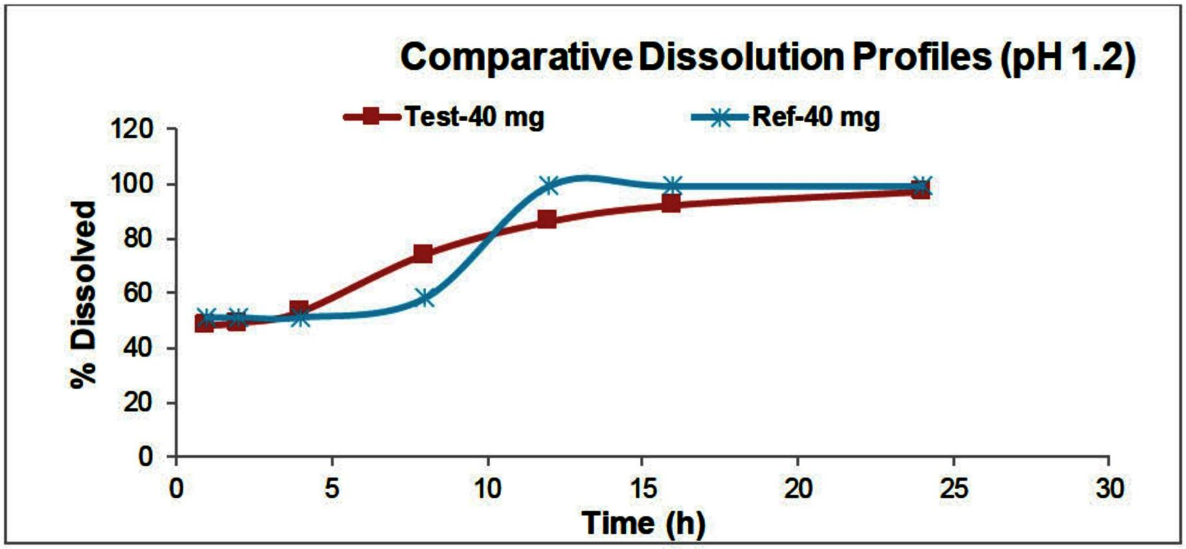
Comparative Dissolution Profiles (pH 1.2)
Test-10 mg
Ref-10 mg
% Dissolved
Time (h)



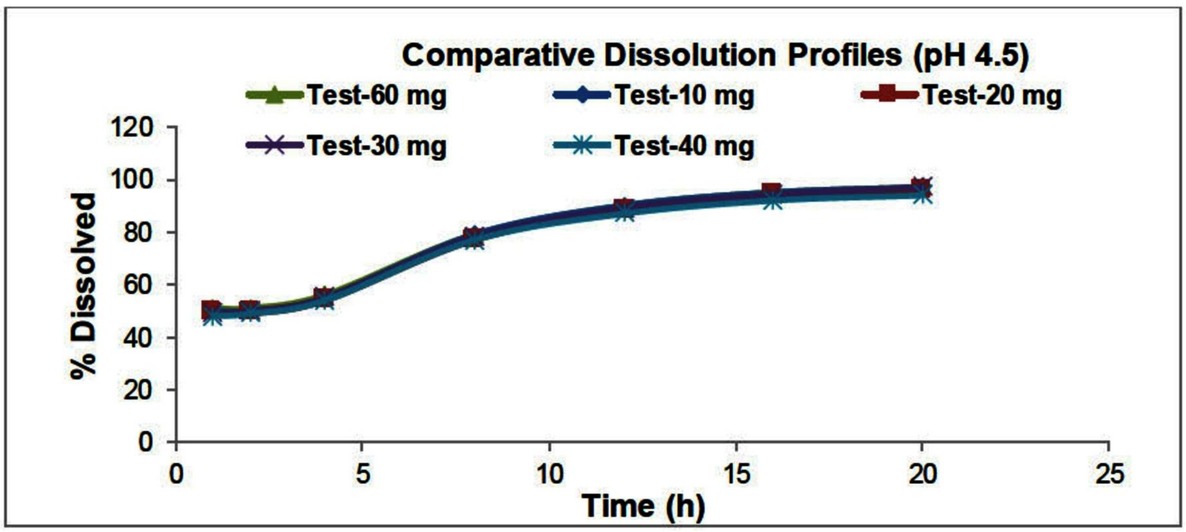
Comparative Dissolution Profiles (pH 1.2)
Test-20 mg
Ref-20 mg
% Dissolved
Time (h)

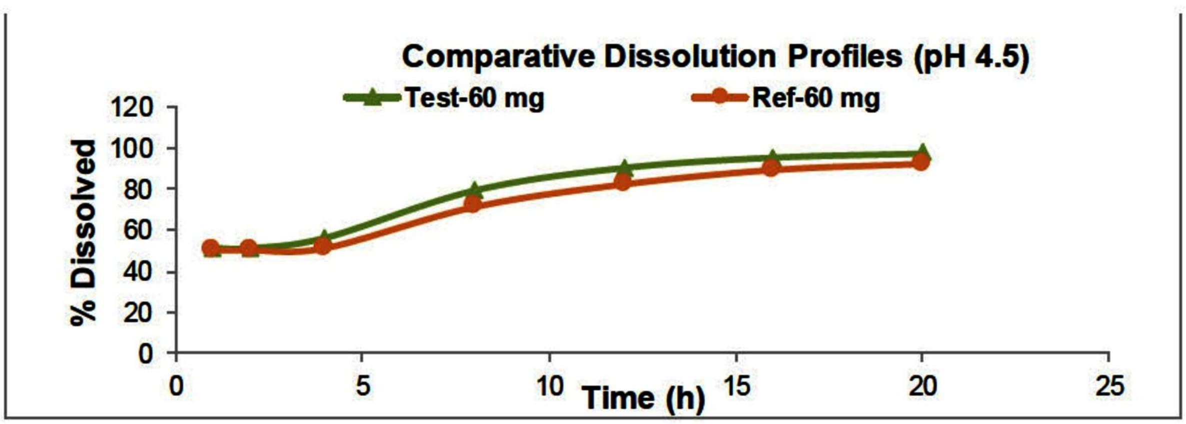


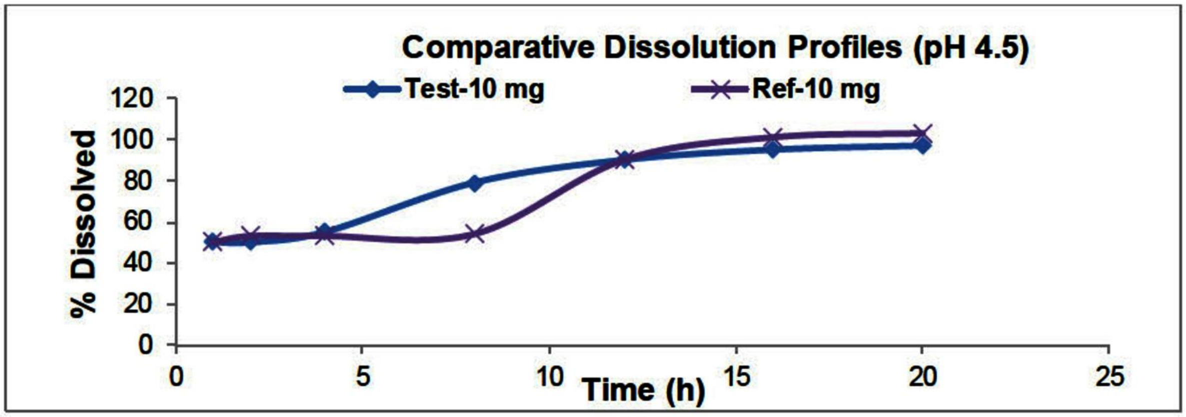
Comparative Dissolution Profiles (pH 1.2)
Test-30 mg
Ref-30 mg
% Dissolved
Time (h)

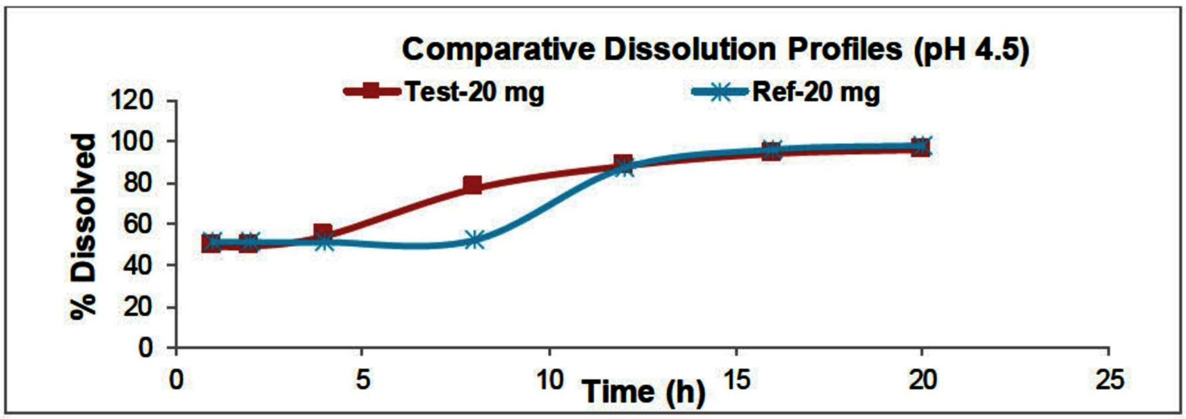

Comparative Dissolution Profiles (pH 1.2)
Test-40 mg
Ref-40 mg
% Dissolved
120
100
80
60
40
20
0
0
5
10
15
20
25
30
Time (h)

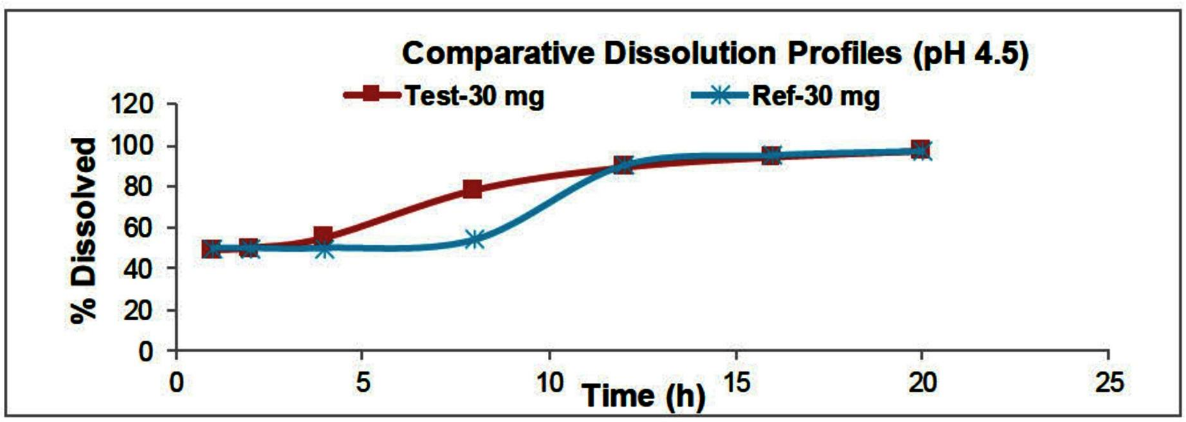
pH 4.5

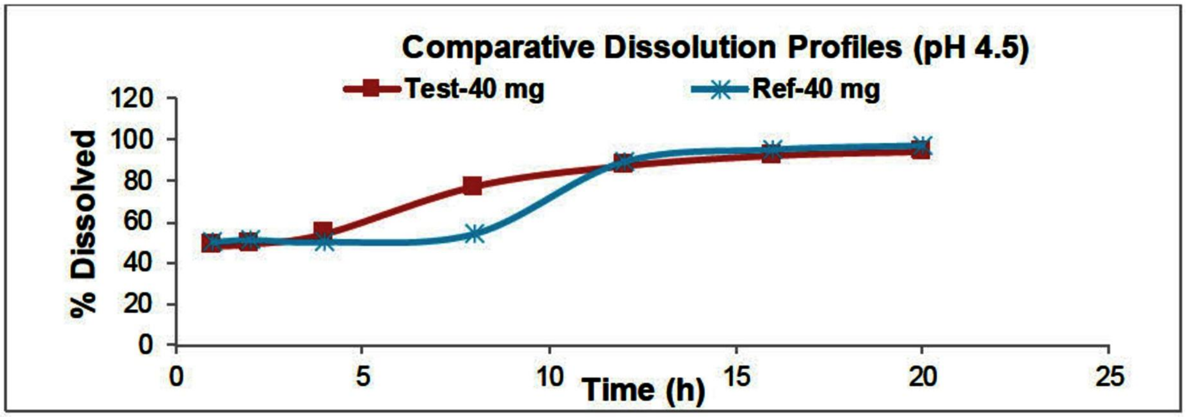

Comparative Dissolution Profiles (pH 4.5)
Test-60 mg
Test-10 mg
Test-20 mg
Test-30 mg
Test-40 mg
% Dissolved
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)


Comparative Dissolution Profiles (pH 4.5)
Test-60 mg
Ref-60 mg
% Dissolved
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)

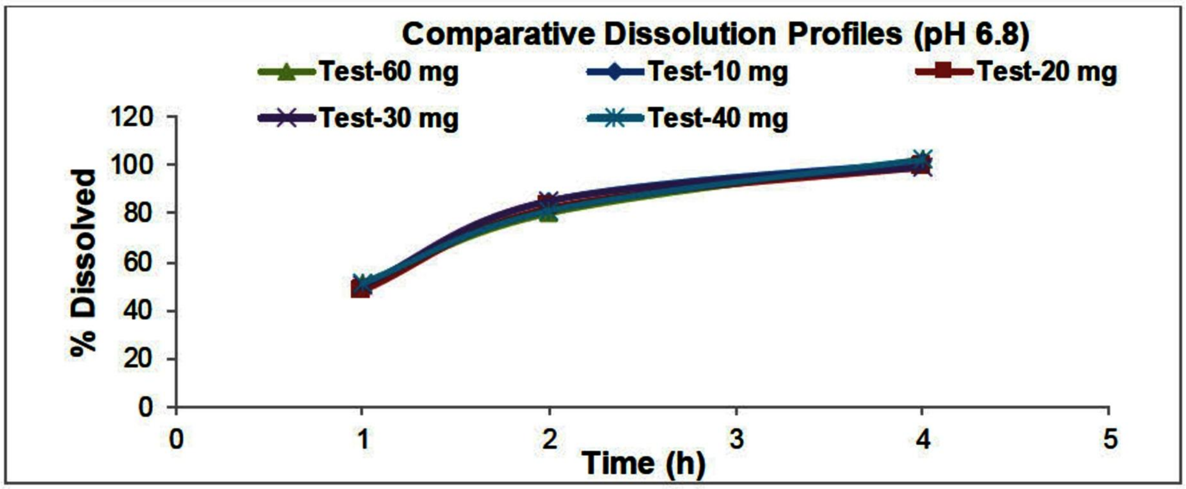

Comparative Dissolution Profiles (pH 4.5)
Test-10 mg
Ref-10 mg
% Dissolved
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)

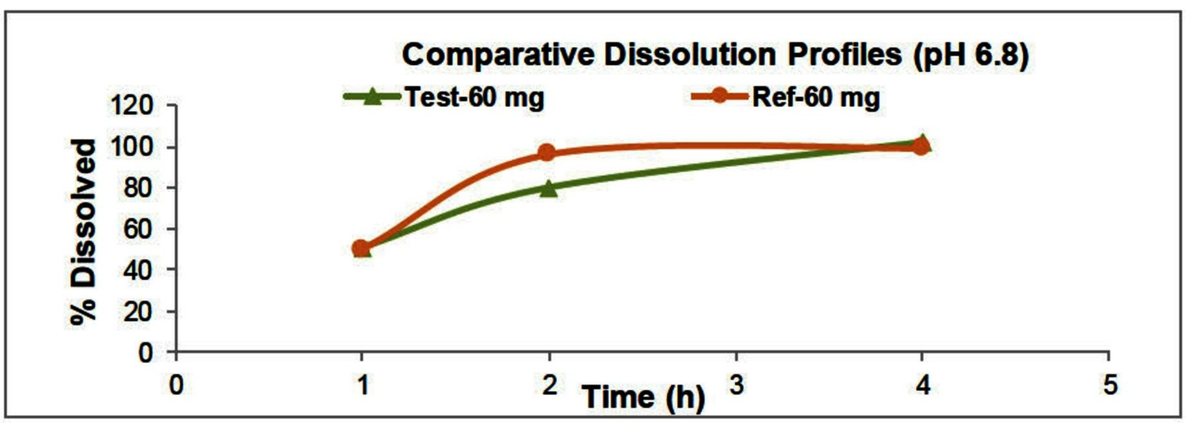

Comparative Dissolution Profiles (pH 4.5)
Test-20 mg
Ref-20 mg
% Dissolved
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)

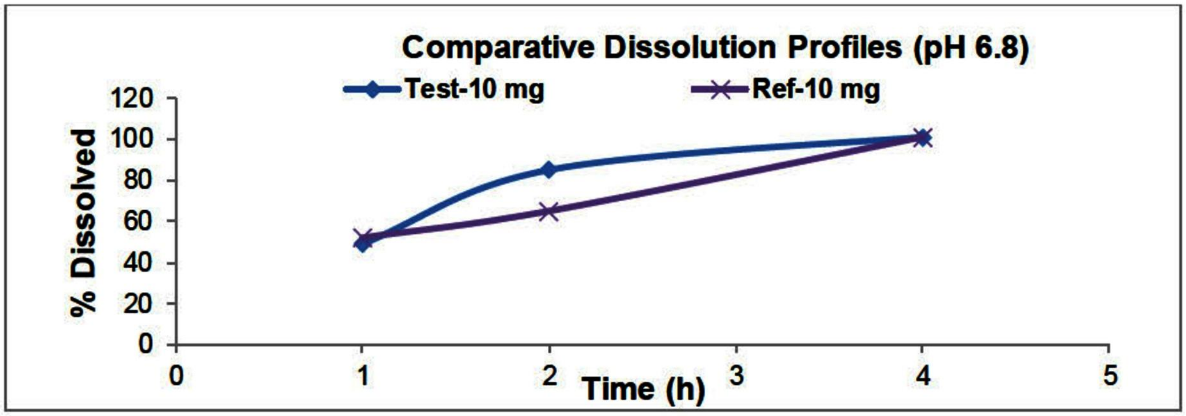

Comparative Dissolution Profiles (pH 4.5)
Test-30 mg
Ref-30 mg
% Dissolved
120
100
80
60
40
20
0
0
5
10
15
20
25
Time (h)

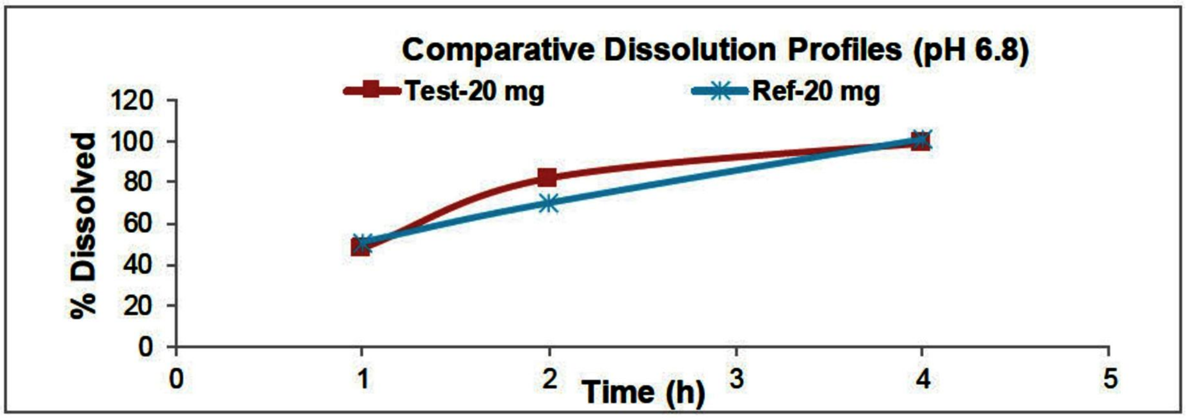

Comparative Dissolution Profiles (pH 4.5)
Test-40 mg
Ref-40 mg
% Dissolved
Time (h)
0
20
40
60
80
100
120
0
5
10
15
20
25

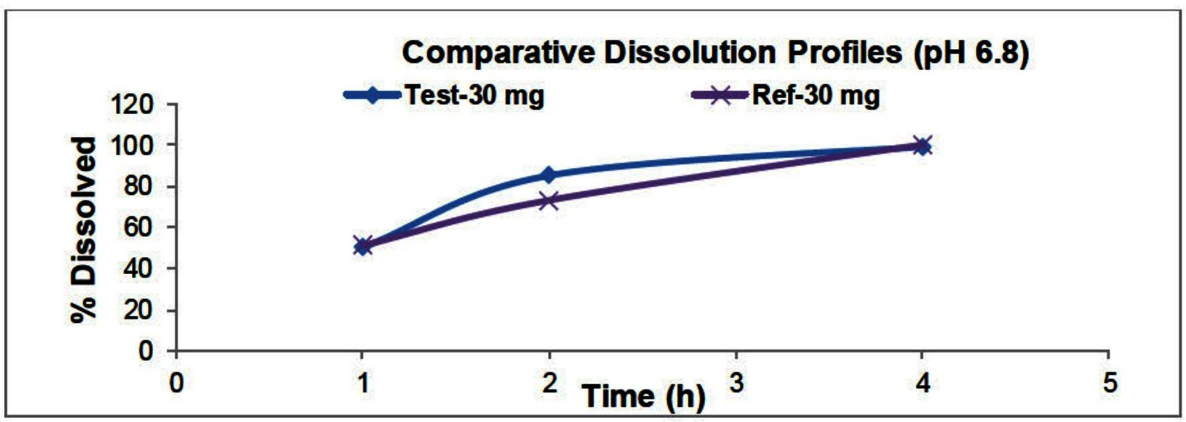
<u>**pH 6.8**</u>

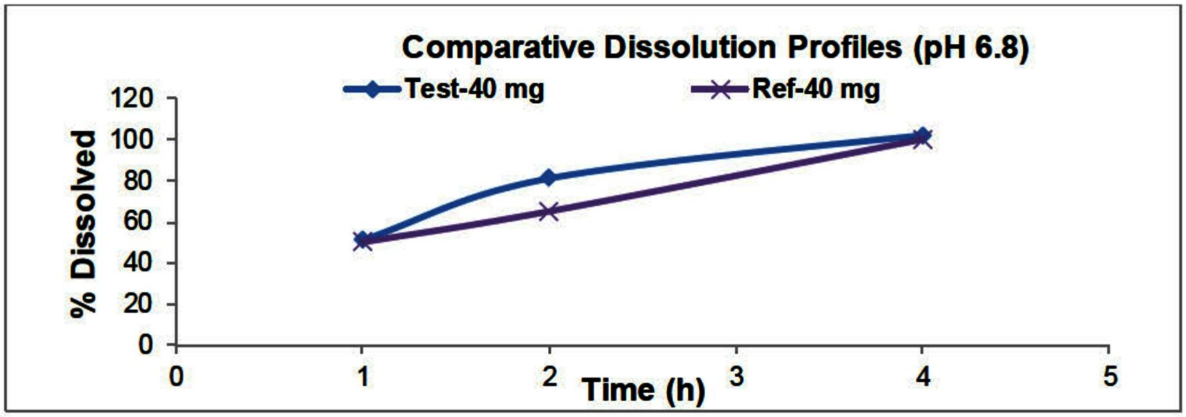

Comparative Dissolution Profiles (pH 6.8)
Test-60 mg
Test-10 mg
Test-20 mg
Test-30 mg
Test-40 mg
% Dissolved
Time (h)
0
20
40
60
80
100
120
0
1
2
3
4
5


Comparative Dissolution Profiles (pH 6.8)
Test-60 mg
Ref-60 mg
% Dissolved
Time (h)
0
20
40
60
80
100
120
0
1
2
3
4
5


Comparative Dissolution Profiles (pH 6.8)
Test-10 mg
Ref-10 mg
% Dissolved
Time (h)


Comparative Dissolution Profiles (pH 6.8)
Test-20 mg
Ref-20 mg
% Dissolved
Time (h)


Comparative Dissolution Profiles (pH 6.8)
Test-30 mg
Ref-30 mg
% Dissolved
Time (h)



4.3.3 F2 Metric

F2 metric calculated?	☒ Yes ☐ No
If no, reason why F2 not calculated	N/A

F2 metric Bio-strength vs Lower Strengths of Test Product

Test Bio-Strength (Batch #)	Test Lower Strength (Batch #)	QC media	pH 1.2	pH 4.5	pH 6.8
Test 60 mg (#GPI17176 [Bio-strength])	Test 10 mg (#GPI17179)	86.40	66.52	94.90	73.97
	Test 20 mg (#GPI17182)	84.29	72.72	82.53	76.98
	Test 30 mg (#GPI17183)	90.05	72.58	89.63	72.43
	Test 40 mg (#GPI17184)	100.00	69.56	78.87	96.88

F2 metric Test vs Reference

Test Strength (Batch #)	Reference Strength (Batch #)	QC media	pH 1.2	pH 4.5	pH 6.8
Test 60 mg (#GPI17176 [Bio-strength])	Ref 60 mg (#634151)	92.47	88.07	62.09	51.18
Test 10 mg (#GPI17179)	Ref 10 mg (#F0080)	60.15	50.88	47.27	46.56
Test 20 mg (#GPI17182)	Ref 20 mg (#F4211)	63.44	51.19	47.18	56.83
Test 30 mg (#GPI17183)	Ref 30 mg (#APCA074)	74.47	51.00	47.88	57.60

Test 40 mg (#GPI17184)	Ref 40 mg (#APC34)	93.92	51.22	48.73	51.39

4.3.4 Alcohol (Ethanol) Dose Dumping

Summary results of in vitro alcohol dose-dumping studies prepared by reviewer

% Methylphenidate Dissolved in 0% Ethanol at 2 Hours					
	10 mg	20 mg	30 mg	40 mg	60 mg
Test	[redacted]				
Reference					
% Methylphenidate Dissolved in 5% Ethanol at 2 Hours					
Test	[redacted]				
Reference					
% Methylphenidate Dissolved in 20% Ethanol at 2 Hours					
Test	[redacted]				
Reference					
% Methylphenidate Dissolved in 40% Ethanol at 2 Hours					
Test	[redacted]				
Reference					

Comments on alcohol dose dumping

For all 5 strengths of Granules Pharmaceuticals Inc.'s the test product, Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg, there is an alcohol dose-dumping effect as the mean % drug dissolved are not comparable in 0.1N HCl with no alcohol versus 0.1N HCl with 40% alcohol [redacted] However, for all 5 strengths, the drug release at 2 hours in 40% alcohol medium of the test product versus reference product are comparable [redacted] At each of the alcohol medium (5%, 20% and 40%) versus the 0% alcohol medium, the test product did not show increased % release compared to the reference product. Therefore, the risk of dose-dumping from each strength of the test product is not higher compared to the corresponding strength of the reference product. [47]

The 20 mg and 30 mg strengths of the Reference product showed some [redacted] variability at time points 30, 45, 60 and 75 minutes in 0.1N HCl + 40% alcohol. The individual unit and summary data are presented below:

[47] DARRTS: ANDA 076640, Submit/Final Date 05/16/2007, Author: B. Davit, Ph.D., J.D.

4.4.2 Methylphenidate HCl ER Capsules, 20 mg Vs. Ritalin LA Capsules, 20 mg in 40% Alcohol in 0.1N HCl

Unit #	% Drug released - in 40% (v/v) Alcohol in 0.1N HCl															
	Methylphenidate HCl ER Capsules, 20 mg								Ritalin LA Capsules, 20 mg							
	Lot # GPI17182A								Lot # F4211							
Time point	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	[redacted]															(b) (4)
2																
3																
4																
5																
6																
7																
8																
9																
10																
11																
12																
Mean																
Min																
Max																
%RSD	2.6	2.7	3.0	2.8	2.5	2.3	2.4	2.4	4.2	9.6	11.6	11.3	9.5	7.6	6.1	5.0
Reference: QC-0199-088, QC-0217-047																

4.4.3 Methylphenidate HCl ER Capsules, 30 mg Vs. Ritalin LA Capsules, 30 mg in 40% Alcohol in 0.1N HCl

Unit #	% Drug released - in 40% Alcohol in 0.1N HCl															
	Methylphenidate HCl ER Capsules, 30 mg								Ritalin LA Capsules, 30 mg							
	Lot # GPI17183A								Lot # APCA074							
Time point	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min	15 min	30 min	45 min	60 min	75 min	90 min	105 min	120 min
1	[redacted]															(b) (4)
2																
3																
4																
5																
6																
7																
8																
9																
10																
11																
12																
Mean																
Min																
Max																
%RSD	1.9	2.0	2.4	2.3	2.0	1.6	1.6	1.3	6.2	16.9	22.0	22.3	19.7	15.5	12.1	9.8
Reference: QC-0199-088, QC-0217-056																

Data source: Module 2.7.1, Dose Dumping Dissolution Report, Section 4

The reviewer considers that the variability is acceptable because 1) the variability is observed only from reference product, and 2) Per DB practice, the determination of dose dumping effect is based on the data at 2-hour time point.

4.3.5 Overall Comments on Dissolution Testing

At the time of current bioequivalence (BE) review, the dissolution-only review by the biopharmaceutical reviewer is still pending[48]. The applicant's dissolution data are

[48] GDRP, ANDA-211796-ORIG-1, Biopharmaceutics Quality Review is pending as of 09/05/2018

evaluated by the current BE reviewer from a waiver perspective only, i.e., for the waiver of the lower strengths of the test product, Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, and 40 mg. Thus, the following comments are not for determining a regulatory (quality control [QC]) dissolution method and dissolution specifications.

(b) (4) [redacted]

- The applicant conducted dissolution studies using unexpired batches for each strength of the test and reference products. For the 60 mg strength, the dissolution studies were conducted on the test (Batch # GPI17176) and reference (Batch #634151) bio-batches which underwent pivotal in vivo BE studies.

- The dissolution profiles for the bio-strength (60 mg) of the test product are comparable to those of the lower strengths, 10 mg, 20 mg, 30 mg, and 40 mg, as indicated by the f2 metrics (b) (4) [redacted]%).

- The firm conducted additional multi-media dissolution testing in various pH (0.1N HCl [pH1.2], pH 4.5 Acetate buffer, and pH 6.8 phosphate buffer) using USP Apparatus I (basket) at 100 rpm. The dissolution profiles for the bio-strength (60 mg) of the test product are similar to those of the lower strengths, 10 mg, 20 mg, 30 mg, and 40 mg in all pH media. The multi-media dissolution testing is acceptable.

- The risk of dose-dumping from each strength of the test product is not (b) (4) [redacted] compared to the corresponding strength of the reference product.

- Based on the f2 metrics, there is some small difference in the dissolution profiles between the test and reference product under pH 4.5 (10 mg, 20 mg, 30 mg and 40 mg strengths) and under pH 6.8 (10 mg strength only). The difference is considered acceptable because: (1) The 60 mg strengths of test and reference products which underwent in vivo BE studies showed comparable dissolution profiles; and (2) The f2 values of test vs. reference for the lower strengths are only marginally below 50.

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[49] FDA External Dissolution Database, accessed on 09/04/2018

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However due to the deficiencies in the pivotal BE studies, the DBI does not deem the 10 mg, 20 mg, 30 mg and 40 mg strengths of the test product to be bioequivalent to the corresponding strengths of the reference product based on criteria set forth in under 21 CFR § 320.24 (b) (6).

4.4 Attachments

4.4.1 Additional Studies (If applicable)

4.4.1.1 Pilot Fed Bioequivalence Study

Are there any additional studies? (e.g. pilot, failed) **If yes, please provide the location of report (complete/summary).**	☒ Yes ☐ No Pilot fed study #2017-4358
Number of Subjects	11
Are the test formulations in the pilot/failed studies and pivotal studies similar[50]?	Yes
What was the objective of pilot/failed study?	Please refer to Section **4.1.4**
Please comment on reason(s) of failure.	Please refer to Section **4.1.4**
Any serious adverse events or deaths reported?	Please refer to Section **4.1.4**

4.4.2 SAS Output

Provide hyperlink or location for the study data and study output.
(Click insert tab and go to object and select create from file then choose display as icon. Then browse the file you want to add and insert and OK.)

Study	**SAS Data**	**SAS Code**	**SAS Output/Table**
Pivotal Fasting #2018-4413	Fasting 2018-4413.xlsx	A211796 Fasting partial_AUC_for Methy	211796Fast-ANALYSIS .rtf
Pivotal Fed #2017-4351	Fed 2017-4351.xlsx	A211796 fed-pan partial_AUC_for Methy	211796ANALYSIS.doc
Pivotal Fasting Sprinkle #2018-4455	Sprinkle 2018-4455.xlsx	A211796 Sprinkle Fasting partial_AUC_fc	211796Fast-ANALYSIS .doc

[50] Submission of Summary Bioequivalence Data for Abbreviated New Drug Applications

BIOEQUIVALENCE DEFICIENCY TO BE PROVIDED TO THE APPLICANT

ANDA:	211796
APPLICANT:	Granules Pharmaceuticals Inc.
DRUG PRODUCT:	Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

The Division of Bioequivalence I (DBI) has completed its review and has identified the following deficiency:

Per your bioanalytical report for the pivotal fasting study #2018-4413, the original run [redacted] (b) (6) was "incomplete" due to "Sample processing error." This batch was re-extracted and analyzed in run [redacted] (b) (6). However, you did not provide real-time documentation providing details of the "sample processing error." In this regard, SOP [redacted] (b) (4) ('Repeat Sample Analysis Procedure and Acceptance Criteria') does not specify criteria for "sample processing error." Please provide a detailed explanation of the reason for re-extraction of the original run [redacted] (b) (6) in the pivotal fasting BE study with supporting real-time documentation. Please also provide the analytical raw data for said run and the resulting methylphenidate concentration values in SAS Transport format as applicable (.xpt).

The bioequivalence comments provided in this communication are comprehensive as of issuance. However, these comments are subject to revision if chemistry, manufacturing and controls, microbiology, labeling, or other scientific, regulatory or inspectional issues or concerns 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,

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

5 COMPLETED ASSIGNMENT FOR 211796 ID: 36370

Reviewer:	Cui, Dapeng		**Date Completed:**
Verifier:	,		**Date Verified:**
Division:	Division of Bioequivalence		
Description:	Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg		

Items:

ID	*Letter Date*	*Productivity Category*	*Sub Category*	*Score*	*Subtotal*
36370	9/20/2018	BIO	ANDA Original [1]	1	1
36370	9/20/2018	Parallel	Fasting Study (Full template) [1]	1	1
36370	9/20/2018	Parallel	Fed Study (Full Template) [1]	1	1
36370	9/20/2018	Parallel	Sprinkle Study (Full Template) [1]	1	1
36370	9/20/2018	Parallel	Pilot and Failed Full Extra Study for the Same Formulation as the Proposed Formulation [0.25]	0.25	0.25
36370	9/20/2018	Parallel	Dissolution-Based Waiver (MR) (For all waiver strengths) [0.5]	0.5	0.5
36370	9/20/2018	Parallel	In-Vitro Dose-Dumping in Alcohol (For all strengths) [0.5]	0.5	0.5
				Total:	5.25

DIVISION OF BIOEQUIVALENCE AMENDMENT REVIEW

ANDA No.	211796			
Drug Product Name	Methylphenidate Hydrochloride Extended-Release Capsules			
Strength(s)	10 mg, 20 mg, 30 mg, 40 mg, and 60 mg			
Applicant Name	Granules Pharmaceuticals Inc.			
Applicant Address	3701 Concorde Parkway Chantilly, Virginia 20151			
Applicant's Contact Name and Mailing Address	Vamsi Nama, Director Regulatory Affairs			
Applicant's Contact Telephone Number	[redacted] (b) (6)			
Applicant's Contact Fax Number	703-378-1578			
Applicant's Contact Email Address	vamsi.nama@granulesindia.com			
Original Submission Date(s)	04/02/2018, Sequence 0001 (1), original submission 05/18/2018, Sequence 0002 (2), applicant's response to Filing Information Request (IR) with re-submitted bioequivalence (BE) summary tables			
Submission Date(s) of Amendment(s) Under Review	10/04/2018, Sequence 0005 (5), applicant's response to Discipline Review Letter (DRL)-Bioequivalence (BE) 10/22/2018, Sequence 0006 (6), applicant's response to DRL-Drug Substance, Drug Product, Process, and Biopharmaceutics			
Primary Reviewer	Dapeng Cui, Ph.D.			
Secondary Reviewer	Tao Bai, Ph.D.			
Tertiary Reviewer	Utpal Munshi, Ph.D.			
Study Number(s)	2018-4413	2017-4351	2018-4455	2017-4358
Study Type(s)	Pivotal Fasting	Pivotal Fed	Pivotal Fasting Sprinkle	Pilot Fed
Strength(s)	1 × 60 mg	1 × 60 mg	1 × 60 mg	1 × 60 mg
Clinical Site	[redacted] (b) (4)			
Clinical Site Address				
Analytical Site				
Analytical Site Address				
Office of Study Integrity and Surveillance (OSIS) status	**<u>Backlog, Year 1 and Year 2 ANDAs</u>** ☐ **Pending** ☐ **Complete**		**<u>Post October 1, 2014 ANDAs</u>** ☐ **To Be Determined by OSIS** ☐ **Pending For Cause Inspection**	

	☐ N/A (Waiver/Deem Bioequivalent)		☒ Complete ☐ N/A (Waiver/Deem Bioequivalent)
Waiver/Deem Bioequivalent	☒ 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/IR ☒ N/A (Review is Adequate)		
Major Deficiency Theme	N/A		
Justification for Major Designation	N/A		
Overall Review Result	☒ Adequate ☐ Inadequate		
Product Specific Guidance (PSG) Referenced in Review	***Reminder: Check PSG in development spreadsheet on V:drive (if PSG is under development, wait for PSG to post to finalize the review)*** ☒ Recommended/Latest Revision Date: Mar 2015 RLD Number: NDA 021284 https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM281454.pdf ☐ N/A (no PSG available at time of review)		
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, 5	Pivotal Fasting	60 mg	☒ Adequate ☐ Inadequate
1, 2, 5	Pivotal Fed	60 mg	☒ Adequate ☐ Inadequate
1, 2, 5	Pivotal Fasting Sprinkle	60 mg	☒ Adequate ☐ Inadequate
1, 2	Pilot Fed	60 mg	☐ Adequate ☐ Inadequate ☒ N/A (For information)
1, 2, 5, 6	Waivers	10, 20, 30, 40 mg	☒ Adequate ☐ Inadequate
1, 2	Alcohol Dose Dumping	10, 20, 30, 40 and 60 mg	☒ Adequate ☐ Inadequate

* Per latest Biopharmaceutics review dated 01/04/2019, applicant's proposed QC dissolution method is acceptable; however, Biopharmaceutics review is still inadequate pending applicant's acceptance of FDA-recommended dissolution specification acceptance criteria and clarification of the buffer pH value in the modified FDA method (See discussion in Executive Summary and Section 4.3).

Review of A Discipline Review Letter (DRL) Response

1. EXECUTIVE SUMMARY

This is a review of response to Discipline Review Letter (DRL) submitted by the applicant on 10/04/2018.

Per the original bioequivalence (BE) review dated 09/17/2018,[1] the pivotal fasting BE study (#2018-4413) was found **inadequate** due to a deficiency in the bioanalytical repeat analysis. The BE deficiency was provided to the applicant in a DRL dated 09/17/2018.[2] In the current submission dated 10/04/2018, the applicant has satisfactorily addressed the BE deficiency (see **Section 3**). Said study is therefore **adequate.**

The test product formulation is adequate per the original BE review dated 09/17/2018.

The Biopharmaceutics review of the applicant's Quality Control (QC) dissolution testing method was not available at the time of original BE review dated 09/17/2018. The applicant's dissolution data were evaluated by DBI from a waiver perspective only and were deemed adequate to support the waiver requests. Per the Biopharmaceutics review dated 09/18/2018[3], the applicant dissolution testing method was deemed inadequate due to lack of data demonstrating discriminating ability. In a DRL dated 09/25/2018 issued by the Office of Pharmaceutical Quality (OPQ)[4], the applicant was recommended to: 1) demonstrate the discriminating ability of the dissolution method, and 2) submit dissolution testing data using both applicant-proposed method and the FDA recommended method with additional early timepoints. The applicant responded to the above Biopharmaceutics deficiencies in its submission 10/22/2018 with new dissolution data. Per the current BE reviewer's evaluation, for both methods, the dissolution profiles are comparable between the bio-strength (60 mg) of the test product and those of the lower strengths, 10 mg, 20 mg, 30 mg, and 40 mg (please refer to Section **4.3**). Per the latest Biopharmaceutics review (archived 01/04/2019)[5], the applicant's originally-proposed dissolution method (Acid Stage: 500 mL of 0.01 N HCl [redacted] (b) (4) for 2 hours; Buffer Stage: 500 mL of pH 6.8 Phosphate buffer [redacted] (b) (4) using USP Apparatus 1 [basket] at 100 rpm) is acceptable; however, the Biopharmaceutics review outcome is still inadequate pending 1) clarification of buffer pH value in the modified FDA method; and 2) acceptance of the Agency-recommended dissolution specifications. While the Biopharmaceutics review outcome is inadequate, the deficiencies issued do not affect the acceptability of the submitted dissolution data with respect to evaluating the firm's waiver request. However, the Division of Biopharmaceutics has been contacted by email that should the QC dissolution method change in response to the Biopharmaceutics

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[1] GDRP ANDA-211796-ORIG-1, Bioequivalence Review, A211796DB000N-Review01-04022018, 09/17/2018

[2] GDRP ANDA-211796-ORIG-1, Documents, A211796N000DB-DisciplineReviewLetter01-PM-04022018, 09/17/2018

[3] GDRP ANDA-211796-ORIG-1, Biopharmaceutics Review, ANDA 211796 Biopharm_Dissolution 08242018_Draft_1st_IR, 09/18/2018

[4] GDRP ANDA-211796-ORIG-1, Documents, ANDA 211796 DRL Deficiencies, 09/25/2018

[5] GDRP ANDA-211796-ORIG-1, Biopharmaceutics Review, ANDA 211796_Methylphenidate ER Capsules_Dissolution_Biopharmaceutics_FINAL, 01/04/2018

deficiencies, that they contact the Division of Bioequivalence I (DBI) [6]. DBI will reassess the firm's waiver request for the non-biostudy strengths accordingly.

The applicant's multi-media dissolution testing and alcohol dose-dumping studies were deemed adequate per the original BE review dated 09/17/2018.

Based on (i) acceptable BE studies on the 60 mg strength, (ii) acceptable in vitro dissolution testing of all strengths using the QC method and in multi-media and (iii) proportional similarity of the formulations across all strengths, DBI deems that the 10 mg, 20 mg, 30 mg and 40 mg strengths of the test product are bioequivalent to the corresponding strengths of the RLD product based on criteria set forth in under 21 CFR § 320.24 (b) (6).

Per the original BE review dated 09/17/2018, the OSIS status for the clinical and analytical sites is complete and adequate.

The application is **adequate**.

[6] V:\DIVISION\BIO\BIO1\Email Reference\ANDA 211796 Methylphenidate Hydrochloride ER Capsules\RE A211796 (Methylphenidate Hydrochloride ER Capsules).pdf

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3. REVIEW OF SUBMISSION

Deficiency #1:

Per your bioanalytical report for the pivotal fasting study #2018-4413, the original run [redacted] was "incomplete" due to "Sample processing error." This batch was re-extracted and analyzed in run [redacted]. However, you did not provide real-time documentation providing details of the "sample processing error." In this regard, SOP [redacted] ('Repeat Sample Analysis Procedure and Acceptance Criteria') does not specify criteria for "sample processing error." Please provide a detailed explanation of the reason for re-extraction of the original run [redacted] in the pivotal fasting BE study with supporting real-time documentation. Please also provide the analytical raw data for said run and the resulting methylphenidate concentration values in SAS Transport format as applicable (.xpt).

Applicant's Response to Deficiency #1:

As confirmed by the CRO, [redacted]., the samples from batch [redacted] were extracted and submitted for analysis on [redacted]. On [redacted], the Technician that extracted this batch reported that the extraction buffer was not added to batch samples.

[redacted] *Upon realizing this mistake, the error was immediately reported to the Production Manager on* [redacted].

Since the validated sample processing procedure was not respected for the samples extracted in batch [redacted], and due to the uncertainty of the impact of the omitted processing step on the data generated for this batch, the acquisition of this analytical run was aborted. Please refer to the corresponding batch sequence cover sheet (Copy# 2018-4413-20) provided in Module 1.2.

As an additional observation, the internal standard response from the calibration standards and QC samples were notably different in comparison to the batch study samples (potential source of bias in the quantitation of incurred samples). This discrepancy can be related to the omitted extraction buffer. The batch internal standard response graph from the original partially acquired batch [redacted] and the re-extracted batch "[redacted] are provided in Module 1.2 (ISTD-response graph CR01 and CR01RE).

In this batch, a total of 236 samples were included in this analytical run (includes the calibration standards and QC samples). Once the processing error was discovered, the batch acquisition was aborted; hence, only 142 of the 236 samples were injected (only 60% of the batch samples were acquired). Although, 6 out of 8 calibration standards *were acquired in batch* [redacted]*, only 4 out of the 12 QC samples were injected (one QC A, one QC B and two QC C samples). This is an insufficient number of QCs to accept the data from this batch. 100% of the study analytical raw data was presented in Appendix 7 of the Originally submitted Bio-Analytical report (including this partially acquired run, pages 634-644). For reference study analytical raw data for batch* [redacted] *is also provided in Module 1.2.*

The samples were re-extracted on [redacted] *under batch ID* [redacted] *according to the validated sample processing procedure. This batch was successfully acquired, and the data was reported.*

As described above, the data from batch [redacted] *is not valid due to sample processing error (omission of the extraction buffer) and the batch was only partially acquired with an insufficient number of QC samples at each concentration level. Therefore, resulting data in SAS transport format (.xpt) is not provided.*

Reviewer's comments on applicant's response to deficiency #1 - adequate

In the original submission, the applicant did not provide details of the "sample processing error" of the rejected original batch Run [redacted] (for Subjects [redacted] In its response to DRL, the applicant explained that for the original run extraction buffer was not added to the batch samples due to technician's mistake. The applicant also provided a real-time documentation, i.e., batch sequence cover sheet [redacted])[7], which described the incidence, i.e., "*On* [redacted] *was running, the analyst reported that buffer was not added to the extracted samples during the extraction. The batch was aborted from acquisition after sample* [redacted] *by the operator with the permission of PM. CR01 will be re-extracted.*" The applicant stated in its DRL response that *upon realizing this mistake, the error was immediately reported to the PM on* [redacted]. The document was signed by the technician on [redacted], and was approved on [redacted]. Per the 100% raw data shown below, the acquisition date/time of the first sample was [redacted] 02:48:21AM, and the acquisition date/time of the last sample (before this batch run was stopped) was [redacted], 09:43:10AM, suggesting that the extraction was conducted late on [redacted] and the decision was made in the morning of [redacted] to abort the batch run.

[redacted]

[redacted]

[redacted] (b) (4), (b) (6)

Per the pre-study Method Validation Report (#BVP-PMRI-1640-16, Version 1.1) page #709, the pre-established extraction procedure is as below: [redacted] (b) (4)

Per the applicant's explanation, the technician omitted the step of adding buffer, i.e., none of the samples had buffer added when the batch was transferred to LC-MS/MS. As buffer was not added during sample extraction, the original run was aborted after injection and acquisition of 142 samples (119 subject samples and 23 Blank/Standard/QC samples) out of the total planned 236 samples. The 119 subject samples from the original run included all samples from Subjects [redacted] (b) (6)

As the pre-established sample processing procedure was not followed, the reviewer agrees with the applicant's decision of whole batch repeat for the original run [redacted] (b) (6) Additionally, all injected 142 samples in the original batch meet the repeat analysis criterion in SOP [redacted] (b) (4) ('Repeat Sample Analysis Procedure and Acceptance Criteria') Section 2.2.4, "*A study sample is repeated due to one or more of the following reasons: ...f) Extraction Error*".

The applicant stated in its response that "*only 4 out of the 12 QC samples were injected (one QC A, one QC B and two QC C samples). This is an insufficient number of QCs to accept the data from this batch.*" This is consistent with its pre-established SOP [redacted] (b) (4) "*The total number of QC samples to be included in an analytical batch is at least 5% of the total number of unknown samples, or a minimum of twelve (12) QC samples, whichever is greater.*" Therefore, the number of QC samples injected (4) was less than the number of required QC samples (12) per its SOP. Additionally, the applicant's approach is consistent with the FDA Guidance for Industry: Bioanalytical

Method Validation (May2018)[8], Section C "*Total QCs should number at least five percent of the total samples analyzed, or be at least six in number (low-, mid-, and high-QCs, in duplicate), whichever is greater*".

The applicant also observed that in the original run, the internal standard (IS) response from the calibration curve (CC) standards and QC samples were notably different compared to the study samples (subject samples showed higher IS response compared to CC/QC samples); whereas the IS response were generally consistent in all samples in the repeated run (as shown in the submitted ISTD response graph from the original and repeated runs)[9]. The applicant stated that *"this discrepancy can be related to the omitted extraction buffer"*. [redacted] (b) (4)

In the response to DRL, the applicant did not submit methylphenidate concentration values of the original run in SAS Transport format. The applicant explained that only 142 of the 236 samples (60% of the batch) were acquired including 6 out of 8 CC standards, and 4 out of the 12 QC samples. This is an insufficient number of QCs to accept the data from the original batch.

The reviewer agrees that values from the original run are not valid for the formal statistical analysis due to the fact that the original run was aborted before its completion, i.e., number of QC samples not meeting the SOP as discussed above. For information purpose, the reviewer compared the original and repeated values of the 119 subject samples that were injected/acquired in the original run (as shown in **Appendix 4.1**). All 119 sample values were higher in the repeated run compared to the original run. The differences are generally small, i.e., less than 20% for most samples. As a conservative approach, the reviewer conducted a sensitivity statistical analysis using the original values of the 119 samples (as shown in **Appendix 4.2**). The analysis using original values did not change the statistical outcome, i.e., the 90% CIs for least squares geometric mean of LnCmax, LnAUC0-3, LnAUC3-7, LnAUC7-12, and LnAUCI are still within the BE acceptable range of 80.00-125.00%.

Based on the submitted information, there is no clear and direct evidence that there was indeed a sample processing error of "extraction buffer not added" for the original batch Run [redacted] (b) (6). However, per the above sensitivity statistical analysis, even using the original data from the failed run, the statistical analysis of the fasting study still passes the BE acceptable range of 80.00-125.00%; the 90%CIs of all five PK parameters were non-marginal using original or repeated values. The DBI does not suspect any fraud regarding the applicant's whole batch repeat of the original Run [redacted] (b) (6)

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[8] https://www.fda.gov/downloads/drugs/guidances/ucm070107.Pdf
[9] EDR, ANDA 211796, Submission 10/04/2018, Module 1.2, ISTD-response graph CR01 and CR01RE: \\cdsesub1\evsprod\anda211796\0005\m1\us\istd-response-graph-cr01-and-cr01re.pdf

[redacted] for the following reasons: 1) The number of rejected runs was relatively low (1, 2 and 0 in the fasting, fed and fasting sprinkle studies, respectively). The percentage of repeated samples was relatively low (<10%) in all three BE studies; 2) All other repeat analyses were deemed acceptable per the original BE review dated 09/17/2018; and 3) The OSIS recommended accepting the submitted data from the current application without on-site inspection because outcome of recent inspections was No Action Indicated (NAI) for both the analytical and clinical sites.

All samples were re-extracted and re-injected as a repeat batch run [redacted]. The repeated batch run met the batch acceptance criteria. The values from the repeated batch were used in the final statistical analysis as reported in the original BE review dated 09/17/2018.[10]

The applicant's response to Bioequivalence Deficiency #1 is **adequate**.

2 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

[10] GDRP ANDA-211796-ORIG-1, Bioequivalence Review, A211796DB000N-Review01-04022018, 09/17/2018

[redacted] (b) (4)

4.2 Sensitivity Statistical Analysis

Statistical analysis using values from original run [redacted] (b) (6)

Methylphenidate (No of subjects completed = 24), Dose 60 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (2018-4413)							
Parameter	**Unit**	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC_{inf}	ng hr/mL	200.67	24	195.41	24	1.03	98.91-106.62
C_{max}	ng/mL	25.46	24	25.31	24	1.01	94.01-107.67
AUC_{0-3}	ng hr/mL	36.70	24	37.33	24	0.98	90.10-107.27
AUC_{3-7}	ng hr/mL	75.05	24	73.72	24	1.02	95.15-108.94
AUC_{7-12}	ng hr/mL	54.43	24	51.69	24	1.05	96.84-114.52

Statistical analysis using values from repeated run [redacted] (b) (6)
(below table is from original BE review dated 09/17/2018)[11]

Methylphenidate (No of subjects completed = 24), Dose 60 mg LS Geometric Means, Ratio of Means, and 90% Confidence Intervals Fasted Bioequivalence Study (2018-4413)							
Parameter	**Unit**	**Test**	**N**	**RLD**	**N**	**Ratio**	**90% C.I.**
AUC_{inf}	ng hr/mL	203.82	24	197.83	24	1.03	99.59-106.58
C_{max}	ng/mL	25.87	24	25.61	24	1.01	94.67-107.79
AUC_{0-3}	ng hr/mL	37.37	24	37.83	24	0.99	90.72-107.55
AUC_{3-7}	ng hr/mL	76.26	24	74.58	24	1.02	95.80-109.16
AUC_{7-12}	ng hr/mL	55.27	24	52.33	24	1.06	97.19-114.77

[11] GDRP ANDA-211796-ORIG-1, Bioequivalence Review, A211796DB000N-Review01-04022018, 09/17/2018

SAS output of the sensitivity analysis

Study	SAS Data	SAS Code	SAS Output/Table
Pivotal Fasting #2018-4413	Fasting 2018-4413_sensitivity.:	Sensitivity A211796 Fasting partial_AUC_fc	211796Fast-ANALYSIS .doc

4.3 Dissolution Testing (Submission 10/22/2018)

4.3.1 Dissolution Data

10 mg - Applicant Proposed Method

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	[redacted] (b) (4) 0.01 N HCl [redacted] (b) (4) and [redacted] (b) (4) pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	[redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	Study Report Location
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17179A Mfg. 06/09/2017	10 mg Capsule	12	Mean Min Max	[redacted] (b) (4)													Module 2.7.1-dissolution report
					%CV	1.7	1.9	1.6	1.5	1.5	1.5	3.9	3	2	1.6	1.6	1.7	1.8	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17180A Mfg. 08/08/2017	10 mg Capsule	12	Mean Min Max	[redacted] (b) (4)													
					% CV	2.5	1.8	1.7	1.8	1.8	1.8	1.5	1.4	1.8	2.2	2.3	2.3	2.6	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17181A Mfg. 08/07/2017	10 mg Capsule	12	Mean Min Max	[redacted] (b) (4)													
					%CV	1.9	1.2	1.2	1.1	1.2	1.2	1.2	1.2	1.4	2.3	3.1	3.2	3.1	

Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

20 mg - Applicant Proposed Method

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	[redacted] (b) (4) 0.01 N HCl [redacted] (b) (4) and pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	[redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times 10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	Study Report Location
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17182A Mfg. 06/09/2017	20 mg Capsule	12	Mean	[redacted] (b) (4)													Module 2.7.1- dissolution report
					Min														
					Max														
					%CV	2.6	1.9	1.9	2	2	1.9	1.8	1.8	1.8	1.6	1.3	1.3	1.3	

Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

30 mg - Applicant Proposed Method

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	[redacted] (b) (4) 0.01 N HCl ([redacted] (b) (4)) and pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	[redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

	Testing		Dosage	No. of		Collection Times	Study

Study Ref No.	Date	Product ID \ Batch No. (Test – Mfg. Date)	Strength & Form	Dosage Units		10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	Report Location
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17183A Mfg. 06/09/2017	30 mg Capsule	12	Mean Min Max	[redacted] (b) (4)													Module 2.7.1-dissolution report
					%CV	2.2	1.9	1.8	1.8	1.6	1.8	2	2	1.8	1.2	1.1	0.9	0.9	

Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

40 mg - Applicant Proposed Method

Dissolution Conditions	Apparatus:	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	[redacted] (b) (4) 0.01 N HCl [redacted] (b) (4) and pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	[redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times													Study Report Location
						10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17184A Mfg. 06/09/2017	40 mg Capsule	12	Mean Min Max	[redacted] (b) (4)													Module 2.7.1-dissolution report
					%CV	1.3	0.6	0.6	0.6	0.6	0.6	0.9	0.9	0.7	0.8	0.5	0.5	0.5	

Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

60 mg - Applicant Proposed Method

Dissolution Conditions	Apparatus:	1 (Basket)

	Speed of Rotation:	100 RPM
	Medium:	[redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	[redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	**Testing Date**	**Product ID \ Batch No. (Test – Mfg. Date)**	**Dosage Strength & Form**	**No. of Dosage Units**		**Collection Times** 10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	**Study Report Location**
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17176A Mfg. 06/09/2017	60 mg Capsule	12	Mean	[redacted] (b) (4)													Module 2.7.1-dissolution report
					Min														
					Max														
					%CV	2.9	1.8	1.9	1.8	1.8	1.9	1.9	1.8	1.7	2.1	1.1	0.8	0.8	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17177A Mfg. 08/08/2017	60 mg Capsule	12	Mean	[redacted] (b) (4)													
					Min														
					Max														
					% CV	1.9	0.9	0.8	0.9	0.8	0.9	0.9	0.8	0.8	1.3	1.5	1.3	1	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17178A Mfg. 08/09/2017	60 mg Capsule	12	Mean	[redacted] (b) (4)													
					Min														
					Max														
					%CV	1.7	1.1	1.1	1.1	1.1	1.1	1.6	1.3	1.5	2.7	2.7	2.4	2.2	

Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

10 mg – FDA Recommended Method

Dissolution Conditions	**Apparatus:**	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	[redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C

Firm's Proposed Specifications	[redacted] (b) (4)																		
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151																		
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times													Study Report Location
						10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17179A Mfg. 06/09/2017	10 mg Capsule	12	Mean Min Max	[redacted] (b) (4)													Module 2.7.1-dissolution report
					%CV	1.8	1.3	1.5	1.6	1.5	1.5	1.6	1.6	1.7	1.6	1.5	1.2	1.2	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17180A Mfg. 08/08/2017	10 mg Capsule	12	Mean Min Max	[redacted] (b) (4)													
					% CV	1.4	1.3	1.5	1.5	1.4	1.5	1.5	1.5	1.5	1.5	1.4	1.1	0.8	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17181A Mfg. 08/07/2017	10 mg Capsule	12	Mean Min Max	[redacted] (b) (4)													
					%CV	1.4	1.4	1.7	1.6	1.6	1.4	1.3	1.3	1.3	1.3	1.2	1.2	2.6	

Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

20 mg - FDA Recommended Method

Dissolution Conditions	Apparatus:	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	[redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	[redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

	Testing		Dosage	No. of		Collection Times	Study

Study Ref No.	Date	Product ID \ Batch No. (Test – Mfg. Date)	Strength & Form	Dosage Units		10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	Report Location
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17182A Mfg. 06/09/2017	20 mg Capsule	12	Mean	[redacted]													Module 2.7.1-dissolution report
					Min														
					Max														
					%CV	2.6	1.9	2	1.8	1.7	1.8	1.9	1.9	1.8	1.7	1.6	1.1	0.9	

Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

30 mg - FDA Recommended Method

Dissolution Conditions		
Dissolution Conditions	Apparatus:	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	[redacted] 0.01 N HCl [redacted] and pH 6.8 Phosphate buffer [redacted]
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	[redacted]	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times													Study Report Location
						10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17183A Mfg. 06/09/2017	30 mg Capsule	12	Mean	[redacted]													Module 2.7.1-dissolution report
					Min														
					Max														
					%CV	2.1	1.3	1.3	1.5	1.4	1.3	1.4	1.4	1.3	1.2	1.1	1	0.9	

Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

40 mg - FDA Recommended Method

Dissolution Conditions		
Dissolution Conditions	Apparatus:	1 (Basket)

	Speed of Rotation:	100 RPM
	Medium:	[redacted] (b) (4) 0.01 N HCl [redacted] (b) (4) and pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	[redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times													Study Report Location
						10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17184A Mfg. 06/09/2017	40 mg Capsule	12	Mean	[redacted] (b) (4)													Module 2.7.1-dissolution report
					Min														
					Max														
					%CV	1.5	0.7	0.9	0.9	0.9	0.8	1.1	1	1	0.9	0.8	0.6	0.5	

Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

60 mg - FDA Recommended Method

Dissolution Conditions	Apparatus:	1 (Basket)
	Speed of Rotation:	100 RPM
	Medium:	[redacted] (b) (4) 0.01 N HCl [redacted] (b) (4) and pH 6.8 Phosphate buffer [redacted] (b) (4)
	Volume:	500 mL
	Temperature:	37°C±0.5°C
Firm's Proposed Specifications	[redacted] (b) (4)	
Dissolution Testing Site (Name, Address)	Granules Pharmaceuticals Inc. 3701 Concorde Pkwy, Chantilly, VA 20151	

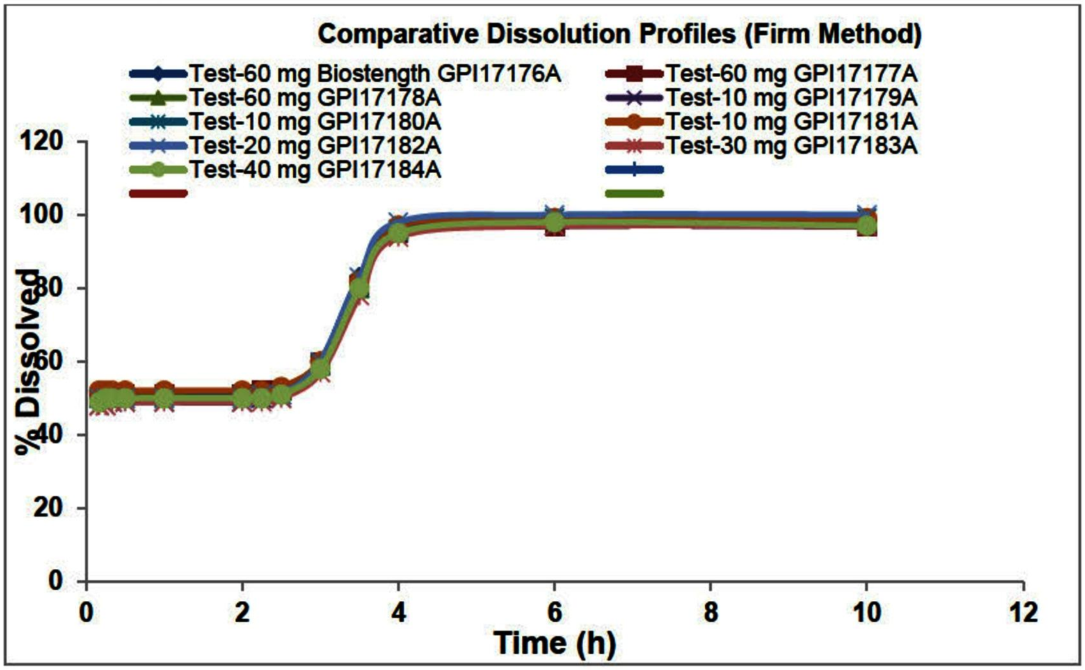
Study Ref No.	Testing Date	Product ID \ Batch No. (Test – Mfg. Date)	Dosage Strength & Form	No. of Dosage Units		Collection Times													Study Report Location
						10 min	15 min	20 min	30 min	1 Hrs	2 Hrs	2.25 Hrs	2.5 Hrs	3 Hrs	3.5 Hrs	4 Hrs	6 Hrs	10 Hrs	
	10/20/18	Test Product	60 mg Capsule	12	Mean	[redacted] (b) (4)													Module 2.7.1-
					Min														

MIS-042-101918		Methylphenidate Hydrochloride ER Capsules, Lot # GPI17176A Mfg. 06/09/2017			Max	[redacted]													dissolution report
					%CV	1.9	2	1.7	2	1.9	1.9	1.9	1.8	1.7	1.4	1.2	0.8	0.7	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17177A Mfg. 08/08/2017	**60 mg Capsule**	12	Mean	[redacted]													
					Min														
					Max														
					% CV	1	0.8	1	1	1	1	0.7	0.7	0.9	0.8	1	1	1	
MIS-042-101918	10/20/18	Test Product Methylphenidate Hydrochloride ER Capsules, Lot # GPI17178A Mfg. 08/09/2017	**60 mg Capsule**	12	Mean	[redacted]													
					Min														
					Max														
					%CV	1.1	0.8	0.7	0.8	0.9	0.7	0.7	0.7	0.7	0.7	0.8	0.7	0.6	

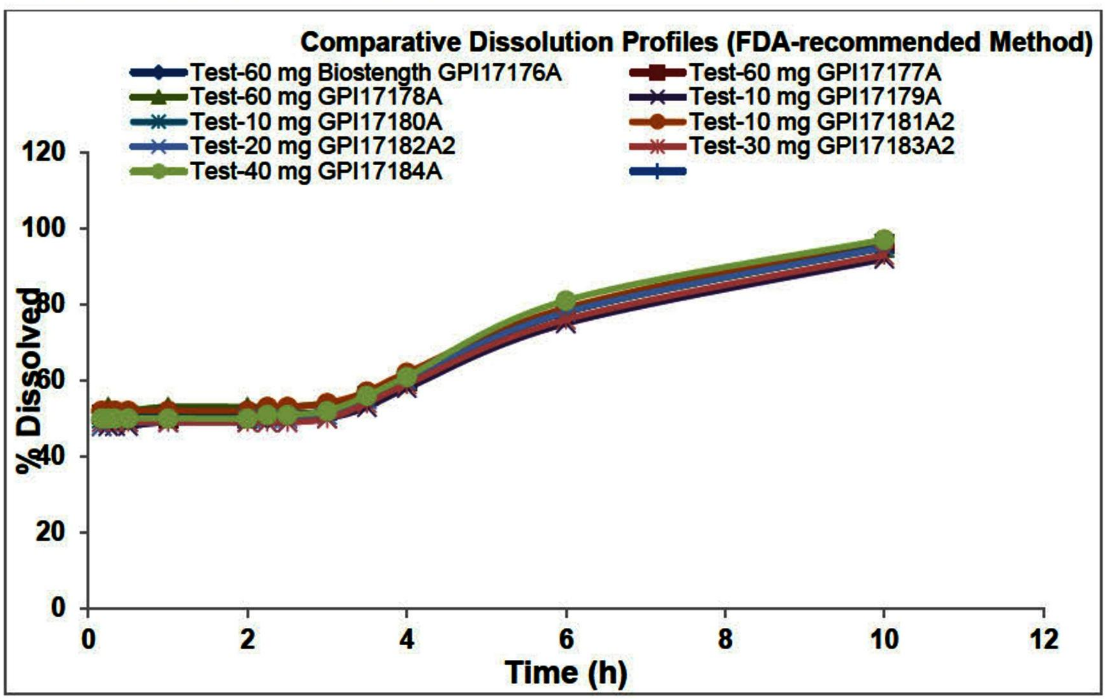
Data source: Module 2.7.1, Dissolution Report (MIS-042-101918)

4.3.2 Dissolution Profiles

Applicant Proposed Dissolution Method



FDA Recommended Dissolution Method



4.3.3 F2 Metric

F2 metric Bio-strength vs Other Strengths of Test Product

Test Bio-Strength (Batch #)	Test Other Strength (Batch #)	QC media Applicant-proposed Method	QC media FDA-recommended Method
Test 60 mg (#GPI17176, Bio-strength)	Test 10 mg (#GPI17179)	85.98	82.87
	Test 10 mg (#GPI17180)	91.99	94.29
	Test 10 mg (#GPI17181)	88.07	81.42
	Test 20 mg (#GPI17182)	94.65	95.32
	Test 30 mg (#GPI17183)	79.16	88.64
	Test 40 mg (#GPI17184)	89.11	90.92
	Test 60 mg (#GPI17177)	91.09	94.79
	Test 60 mg (#GPI17178)	91.53	80.83

(b) (4)

[redacted]

In the original submission, the applicant submitted Quality Control (QC) dissolution testing using a method [redacted] (b) (4)) which is the same compared to that in the FDA Dissolution Database [redacted] (b) (4) .

[12] FDA External Dissolution Database, accessed on 12/22/2018: http://www.accessdata.fda.gov/scripts/cder/dissolution

At the time of original BE review dated 09/17/2018[13], the Biopharmaceutics review of the applicant's Quality Control (QC) dissolution testing method was not available. The applicant's dissolution data were evaluated from a waiver perspective only and were deemed adequate to support the waiver request. The applicant's multi-media dissolution testing and alcohol dose-dumping studies were also deemed adequate per the original BE review.

Per the Biopharmaceutics review dated 09/18/2018[14], the applicant's QC dissolution method was deemed inadequate due to lack of data demonstrating discriminating ability. Briefly, the applicant was recommended to: 1) demonstrate the discriminating ability of the dissolution method, and 2) submit dissolution testing data using both applicant-proposed method and the method in the FDA External Dissolution Database; for both method, the Biopharmaceutics DRL recommended [redacted] (b) (4) The above Biopharmaceutics deficiencies were provided to the applicant in a DRL dated 09/25/2018[15],

In its submission 10/22/2018, the applicant discussed the list of critical material attributes (CMA) and critical process parameters (CPP) affecting dissolution profiles per Biopharmaceutics DRL deficiency #1. The applicant also submitted new dissolution data conducted on exhibit batches of all five strengths of the test product using the two methods with early timepoints per Biopharmaceutics DRL deficiency #2. However, per the submitted dissolution comparison report (Module 2.7.1, also shown below), [redacted] (b) (4)

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[13] GDRP ANDA-211796-ORIG-1, Bioequivalence Review, A211796DB000N-Review01-04022018, 09/17/2018
[14] GDRP ANDA-211796-ORIG-1, Biopharmaceutics Review, ANDA 211796 Biopharm_Dissolution 08242018_Draft_1st_IR, 09/18/2018
[15] GDRP ANDA-211796-ORIG-1, Documents, ANDA 211796 DRL Deficiencies, 09/25/2018

[redacted] (b) (4)

[redacted] (b) (4)

Based on dissolution data in submission 10/22/2018, for both the applicant-proposed method and the FDA-recommended method [redacted] (b) (4)), the dissolution profiles for the bio-strength (60 mg, Batch # GPI17176A) of the test product are comparable to those of the lower strengths, 10 mg, 20 mg, 30 mg, and 40 mg, as indicated by the f2 metrics (>50%) in Section **4.3.3**. RLD product dissolution data was not provided in current submission 10/22/2018. This is deemed acceptable from BE perspective, because: 1) The latest Biopharmaceutics review deemed that applicant's original QC dissolution method is acceptable (please see comments below); and 2) The applicant submitted dissolution testing data of all five RLD strengths (including Bio-lot #634151) using the original QC method in its original submission.

The applicant's multi-media dissolution testing and alcohol dose-dumping studies were deemed adequate per the original BE review dated 09/17/2018.

Per the latest Biopharmaceutics review (archived 01/04/2019)[17], the applicant originally proposed dissolution method [redacted] (b) (4) is acceptable. However, the Biopharmaceutics review outcome is still inadequate pending 1) clarification of pH value at buffer stage in its dissolution data using modified FDA Database method; and 2) acceptance of Biopharmaceutics reviewer-recommended dissolution specification acceptance criteria.

[17] GDRP ANDA-211796-ORIG-1, Biopharmaceutics Review, ANDA 211796_Methylphenidate ER Capsules_Dissolution_Biopharmaceutics_FINAL, 01/04/2018

5. RECOMMENDATIONS

- The Division of Bioequivalence I (DBI) finds the pivotal fasting BE study (#2018-4413) adequate. Granules Pharmaceuticals Inc. conducted the fasting study on its test product, Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg (Batch # GPI17176A), comparing it to Mayne Pharma LLC.'s Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg (Lot #634151).

- The DBI finds the pivotal fed BE study (#2017-4351) adequate. Granules Pharmaceuticals Inc. conducted the fed study on its test product, Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg (Batch # GPI17176A), comparing it to Mayne Pharma LLC.'s Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg (Lot #634151).

- The DBI finds the pivotal fasting sprinkle BE study (#2018-4455) adequate. Granules Pharmaceuticals Inc. conducted the fasting study on its test product, Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg (Batch # GPI17176A), comparing it to Mayne Pharma LLC.'s Methylphenidate Hydrochloride Extended-Release Capsules, 60 mg (Lot #634151).

- The formulations of the test product Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg are adequate. All inactive ingredients are below the acceptance levels for the FDA approved drug products of oral dosage forms. The 10 mg, 20 mg, 30 mg and 40 mg test product formulations are proportionally similar to that of the 60 mg strength which underwent in vivo BE studies.

- The in vitro dissolution testing conducted by the applicant are **adequate** from bioequivalence perspective. The dissolution profiles are similar between the bio-strength 60 mg of the test product are comparable to those of the lower strengths, 10 mg, 20 mg, 30 mg, and 40 mg.

- The DBI deems that the 10 mg, 20 mg, 30 mg, and 40 mg strength of the test product are bioequivalent to the corresponding strengths of the RLD product based on criteria set forth in 21 CFR § 320.24 (b) (6).

BIOEQUIVALENCE COMMENTS TO BE PROVIDED TO THE APPLICANT

ANDA:	211796
APPLICANT:	Granules Pharmaceuticals Inc.
DRUG PRODUCT:	Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg

The Division of Bioequivalence I (DBI) has completed its review 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}

Bing V. Li, Ph.D.
Director, Division of Bioequivalence I
Office of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

6. COMPLETED ASSIGNMENT FOR 211796 ID: 37509

Reviewer:	Cui, Dapeng	**Date Completed:**	
Verifier:	,	**Date Verified:**	
Division:	Division of Bioequivalence		
Description:	Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg		

Items:

ID	***Letter Date***	***Productivity Category***	***Sub Category***	***Score***	***Subtotal***
37509	1/18/2019	BIO	ANDA Amendment [1]	1	1
37509	1/18/2019	Parallel	Study Amendment [1]	1	1
				Total:	2

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

ANDA 211796

<u>ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS</u>

ANDA 211796

AMENDMENT ACKNOWLEDGEMENT
Standard
Minor

Granules Pharmaceuticals Inc.
3701 Concorde Parkway
Chantilly, VA 20151
Attention: Vamsi Nama
Director, Regulatory Affairs

Dear Madam:

This is in reference to your amendment received on February 26, 2019, submitted under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.

This amendment is subject to the provisions of the Generic Drug User Fee Amendments Reauthorization of 2017 (GDUFA II). FDA has made an initial determination that this is a standard minor amendment. The GDUFA goal date for review of this standard minor amendment is May 25, 2019.

If you have any questions, contact Megan Tychinski, Regulatory Project Manager, at (240) 402 - 2717.

Sincerely,

{See appended electronic signature page}

Megan Tychinski
Regulatory Project Manager
Office of Generic Drugs
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Megan
Tychinski

Digitally signed by Megan Tychinski
Date: 2/28/2019 07:57:05AM
GUID: 556dc3e3004eeaee540b388a26735dfb

[redacted]

ANDA 211796

COMPLETE RESPONSE

Granules Pharmaceuticals Inc.
3701 Concorde Parkway
Chantilly, VA 20151
Attention: Vamsi Nama
Director, Regulatory Affairs

Dear Madam:

This is in reference to your abbreviated new drug application (ANDA) received for review on April 2, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), for Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have completed our review of this ANDA, as amended, and have determined that we cannot approve this ANDA in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PHARMACEUTICAL QUALITY

Drug Product

1. [redacted] (b) (4) [redacted].

2. Please submit the following drug product samples.

   a. Your 60 mg capsules from the 3 exhibit batches

   b. Unexpired 60 mg RLD

   To
   Attn: Qinghua Ge PQRPM

   Office of Pharmaceutical Quality
   Center for Drug Evaluation and Research
   WO75 RM4621A
   10903 New Hampshire Avenue
   Silver Spring, MD 20993-0002

Biopharmaceutics

3. You mentioned the pH of the FDA recommended Dissolution Method as pH 6.8 (page #5 of the dissolution report comparison). Please clarify the pH of the phosphate buffer in the FDA dissolution method used for dissolution testing of your proposed drug product.

4. Based on the dissolution data available, we determined that your proposed dissolution acceptance criteria for the proposed product are [redacted]. Therefore, implement the following dissolution method and acceptance criteria for each strength of your proposed product, Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.

   Method: <u>Acid Stage</u>: 500 mL of 0.01 N HCl [redacted] for 2 hours; <u>Buffer Stage</u>: 500 mL of pH 6.8 Phosphate buffer [redacted] using USP Apparatus 1 (basket) at 100 rpm

   Acceptance Criteria:

Time (hrs)	Percent (%) Release
Acid Stage	
0.5 hr	NLT [redacted]%
2.0 hrs	NMT [redacted]%
Buffer Stage (after 2 hours in Acid Stage)	
3.0 hrs*	[redacted]%
6.0 hrs*	NLT [redacted]%

*include two hours in Acid Stage

   Update your drug product release and stability specifications accordingly. In addition, please be advised that all proposed exhibit batches are expected to meet these revised dissolution specifications in your stability program through your proposed expiry period. If dissolution failures are observed on stability, these should be described. Discuss any corrective actions to avert such dissolution failures and provide a new batch to demonstrate correction of the issue, if needed.

<u>**DRUG SUBSTANCE / PROCESS / FACILITY INSPECTION / BIOEQUIVALENCE / LABELING**</u>

There are no further questions for the above listed disciplines at this time. The comments provided in this communication are comprehensive as of the date the discipline review was completed. However, these comments are subject to revision if any scientific or regulatory division identifies additional concerns, as well as any concerns due to inspection results that may arise in the future. Additionally, the compliance status of each facility named in the application may be reevaluated upon resubmission.

FDA publishes new and revised product-specific guidances describing the Agency's current recommendations on demonstrating bioequivalence and certain other approval requirements. To ensure you are using the most accurate, sensitive, and reproducible methodology to demonstrate bioequivalence, as required by FDA regulations (21 CFR320.24(a)), please continue to monitor for the availability of new and revised product specific guidances in the

Federal Register and on the FDA Web site at the following address: https://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.

We remind you that it is your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling. It is also your responsibility to ensure that your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the Electronic Orange Book are addressed and updated in your application. Also, ensure that your labeling aligns with your patent and exclusivity statements.

OTHER

The resubmission to this CR letter will be considered to represent a **MINOR** AMENDMENT, given that the deficiencies have been classified as **MINOR**.

Provided that the amendment contains no additional information that requires a substantial expenditure of resources to review, prominently identify the submission with the following wording in bold, capital letters at the top of the first page of the submission:

> **RESUBMISSION**
> **MINOR**
> **COMPLETE RESPONSE AMENDMENT**
> **DRUG PRODUCT / BIOPHARMACEUTICS**

Upon review of your amendment, FDA may identify information in the amendment that may require a change in classification and an adjustment to the goal date.

Within one year after the date of this letter, you are required to respond by taking one of the actions available under 21 CFR 314.110(b). If you do not take one of these actions, we may consider your lack of response a request to withdraw the ANDA under 21 CFR 314.110(c)(1). You may also request an extension of time in which to resubmit the application. A resubmission must fully address all the deficiencies listed. Additionally, a partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

The drug product may not be marketed without final Agency approval under section 505(j) of the FD&C Act.

ANNUAL FACILITY FEES

The Generic Drug User Fee Amendments of 2012 (GDUFA) (Public Law 112-144, Title III) established certain provisions[1] 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

[1] Some of these provisions were amended by the Generic Drug User Fee Amendments of 2017 (GDUFA II) (Public Law 115-52, Title III).

occur by June 1 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.

In addition, we note that GDUFA requires that certain non-manufacturing sites and organizations listed in generic drug submissions comply with the self-identification requirement. The failure of any facility, site, or organization to comply with its obligation to self-identify and/or to pay fees when due may raise significant concerns about that site or organization and is a factor that may increase the likelihood of a site inspection prior to approval. FDA does not expect to give priority to completion of inspections that are required simply because facilities, sites, or organizations fail to comply with the law requiring self-identification or fee payment.

Additionally, we note that the failure of any facility referenced in the application to self-identify and pay applicable fees means that FDA will not consider the GDUFA application review goal dates to apply to that application.

If you have any questions, call Megan Tychinski, Regulatory Project Manager, Division of Project Management, at (240) 402 - 2717.

Sincerely yours,

{See appended electronic signature page}

Denise P. Toyer McKan, PharmD
Director, Division of Project Management
Office of Regulatory Operations
Office of Generic Drugs

Denise Toyer McKan

Digitally signed by Denise Toyer McKan
Date: 1/29/2019 12:05:38PM
GUID: 5277df670008860f7e1231f730a8684c

[redacted]

ANDA 211796

PROCESS INFORMATION REQUEST

Granules Pharmaceuticals Inc.
Attention: Praveenkumar Devakadaksham
Director QA
3701 Concorde Parkway
Chantilly, VA 20151

Dear Praveenkumar Devakadaksham:

Please refer to your Abbreviated New Drug Application (ANDA) dated April 02, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Methylphenidate Hydrochloride Extended-Release Capsules 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.

We also refer to your June 27, 2018, October 22, 2018 and November 05, 2018 submission, containing quality information.

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 7 days, in order to continue our evaluation of your ANDA.

Comments and information requests:

A. <u>Process</u>

1. [redacted] (b) (4)

2. [redacted] (b) (4) [redacted].

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:

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

INFORMATION REQUEST
QUALITY

If you have any questions, please contact Qinghua Ge, Regulatory Business Process Manager, at 240-402-7623.

Sincerely,

{See appended electronic signature page}

Qinghua Ge
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Qinghua
Ge

Digitally signed by Qinghua Ge
Date: 11/30/2018 11:59:05AM
GUID: 5a204ebd0016c8f54124c662a855562b

[redacted]

ANDA 211796

DISCIPLINE REVIEW LETTER

Granules Pharmaceuticals Inc.
3701 Concorde Parkway
Chantilly, VA 20151

Attention: Vamsi Nama
Director Regulatory Affairs

Dear Vamsi Nama:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on 04/02/2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Methylphenidate Hydrochloride Extended-Release Capsules 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.

Reference is also made to any amendments submitted prior to the issuance of this letter.

We have concluded the quality review of this ANDA and have identified the following initial deficiencies:

LIST DEFICIENCIES

A. <u>Drug substance</u>

1. [redacted] (b) (4)

2. [redacted] (b) (4)

B. <u>Drug Product</u>

1. [redacted] (b) (4)

2. [redacted] (b) (4)

3. [redacted] (b) (4)

a. [redacted] (b) (4)

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

3 Pages have been withheld in full as b4 (CCI/TS) immediately following this page

13. [redacted] (b) (4):

a. [redacted] (b) (4)

b. [redacted] (b) (4)

c. [redacted] (b) (4)

D. **Biopharmaceutics**

1. The proposed dissolution method [redacted] (b) (4) is not acceptable at this stage because the discriminating ability of the method has not been adequately investigated. Described below are our recommendations with respect to proper investigation for the discriminating ability of the proposed dissolution method:

- Provide a list of critical material attributes (CMA) and critical process parameters (CPP) affecting the dissolution and establish that your method is discriminating with regard to those CMAs and CPPs which affect dissolution. In general, the testing conducted to demonstrate the discriminating ability of the dissolution method should compare the dissolution profiles of the proposed drug product(target) and the formulations/product that are intentionally manufactured with meaningful variations, i.e., aberrant formulations and manufacturing conditions with **± 10-20%** change to the specification-ranges of these variables for the most relevant CMA's and CPPs.
  In addition, if available, data can be submitted showing that the selected dissolution method is able to reject batches that are not bioequivalent. Supportive dissolution data may also be submitted showing that the selected dissolution method can detect the change(s) in the drug product occurring during the accelerated and stress conditions.

2. Provide complete dissolution profile data (individual, mean, ranges, % CV) for all strengths of your proposed test product including dissolution data for the earlier time points during the stage-1 (e.g., at 10 minutes, 15 minutes and 20 minutes) and stage-2 (e.g., at 2.25, 2.5 and 3 hrs) dissolution testing using the proposed dissolution method and the dissolution method recommended [redacted] (b) (4)

If you would like to respond to these initial deficiencies before the end of this review-cycle, we request a complete written response to this discipline review letter no later than 10/22/2018. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
QUALITY

If you do not submit a complete written response by 10/22/2018, these initial deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

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.

If you have any questions, please contact Qinghua Ge, Regulatory Business Process Manager, at Qinghua.Ge@fda.hhs.gov or (240) 402-7623.

Sincerely,

{See appended electronic signature page}

Qinghua Ge
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Qinghua
Ge

Digitally signed by Qinghua Ge
Date: 9/25/2018 08:59:15AM
GUID: 5a204ebd0016c8f54124c662a855562b

[redacted]

ANDA 211796

DISCIPLINE REVIEW LETTER

Granules Pharmaceuticals Inc.
3701 Concorde Parkway
Chantilly, VA 20151
Attention: Vamsi Nama
Director Regulatory Affairs

Dear Vamsi Nama:

This letter is in reference to your abbreviated new drug application (ANDA) received for review on April 2, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for Methylphenidate Hydrochloride Extended-Release Capsules, 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.

We have concluded the BIOEQUIVALENCE review of this ANDA and have identified the following initial deficiencies:

Per your bioanalytical report for the pivotal fasting study #2018-4413, the original run [redacted] (b) (6) was "incomplete" due to "Sample processing error." This batch was re-extracted and analyzed in run [redacted] (b) (6). However, you did not provide real-time documentation providing details of the "sample processing error." In this regard, SOP [redacted] (b) (4) ('Repeat Sample Analysis Procedure and Acceptance Criteria') does not specify criteria for "sample processing error." Please provide a detailed explanation of the reason for re-extraction of the original run [redacted] (b) (6) in the pivotal fasting BE study with supporting real-time documentation. Please also provide the analytical raw data for said run and the resulting methylphenidate concentration values in SAS Transport format as applicable (.xpt).

DISCIPLINE REVIEW LETTER
BIOEQUIVALENCE
REFERENCE # 25935124

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the Generic Drug User Fee Amendments of 2017 (GDUFA II) Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect

[1] GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review of your entire application.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

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.

If you have any questions, please contact Jenny Choi, Bioequivalence Project Manager, at jenny.choi@fda.hhs.gov or (240) 402-3433.

Sincerely,

{See appended electronic signature page}

Jenny Choi, Pharm.D.
OFFICE OF GENERIC DRUGS
OFFICE OF BIOEQUIVALENCE
Center for Drug Evaluation and Research
U.S. Food and Drug Administration

Jenny Choi

Digitally signed by Jenny Choi
Date: 9/17/2018 10:31:42PM
GUID: 555e0102000a87a04c594eb0537bc868

[redacted]

ANDA 211796

DISCIPLINE REVIEW LETTER

Granules Pharmaceuticals Inc.
3701 Concorde Parkway
Chantilly, VA 20151
Attention: Vamsi Nama
Director Regulatory Affairs

Dear Mr. Nama:

This communication is in reference to your abbreviated new drug application (ANDA) dated March 31, 2018, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act for Methylphenidate Hydrochloride Extended-Release Capsules (LA), 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.

We have completed the Labeling review of this ANDA and have the following preliminary thoughts on possible deficiencies:

Labeling Deficiencies determined on June 13, 2018, based on your submission dated March 31, 2018:

1. GENERAL COMMENT
   Please provide a statement to ensure adequate number of medication guide(s) will be provided for each package size.

2. CONTAINER LABEL
   a. Please confirm that the container closure system meets 21 CFR 1302.06 for tamper evident sealing.
   b. Add "(LA)" at the end of the established name in the principal display panel (PDP) to read as follows: Methylphenidate Hydrochloride Extended-Release Capsules (LA).
   c. Increase the prominence and relocate the controlled substance sign to appear closer to the established name.
   d. Relocate the period to appear inside the bracket for "See USP Controlled Room Temperature.]" statement.
   e. Revise [redacted] (b) (4) to read "Usual Dosage" on the side panel.
   f. Please include one of the following statements on the side panel: Contains FD&C Yellow No. 5 (tartrazine) as a color additive" [redacted] (b) (4) .
   g. [redacted] (b) (4).

3. PRESCRIBING INFORMATION
   a. DESCRIPTION: [redacted] (b) (4).

   b. PRECAUTIONS: We note that your drug product contains FD&C Yellow #5, tartrazine. Please include the following statement at the end of the PRECAUTIONS section to read as follows: "This product contains FD&C Yellow No. 5 (tartrazine) which may cause allergic-type reactions (including bronchial asthma) in certain susceptible persons. Although the overall incidence of FD&C Yellow No. 5 (tartrazine) sensitivity in the general population is low, it is frequently seen in patients who also have aspirin hypersensitivity."

4. MEDICATION GUIDE
   a. What are the ingredients in methylphenidate hydrochloride extended-release capsules?
      Include the following statement at the end of this section: Methylphenidate Hydrochloride Extended-Release Capsules contain FD&C Yellow #5 (tartrazine).
   b. [redacted] (b) (4)

5. STRUCTURED PRODUCT LABELING (SPL)
   [redacted] (b) (4)

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.

Additionally, we remind you that it is it your responsibility to continually monitor available labeling resources such as DRUGS@FDA, the Electronic Orange Book, and the United States Pharmacopeia – National Formulary (USP-NF) online for recent updates, and make any necessary revisions to your labels and labeling.

It is also your responsibility to ensure your ANDA addresses all listed exclusivities that claim the approved drug product. Please ensure that all exclusivities and patents listed in the electronic OB are addressed and updated in your application. Ensure your labeling aligns with your patent and exclusivity statements.

If you would like to respond to these possible deficiencies before the end of this review-cycle, we request a complete written response no later than July 12, 2018. We will not process or review a partial response. Facsimile or e-mail responses will also not be accepted. Prominently identify the submission with the following wording in bold capital letters at the top of the first page of the submission:

DISCIPLINE REVIEW LETTER
LABELING

If you do not submit a complete written response by July 12, 2018, these possible deficiencies may be incorporated in a complete response letter.

Please note that we are providing these preliminary thoughts on possible deficiencies to you before a complete review of your entire application. As contemplated in the GDUFA II Commitment Letter[1], these possible deficiencies do not reflect a complete review of your application and should not be construed as such. In addition, these possible deficiencies do not necessarily reflect input from supervisory levels. You should be aware that these deficiencies may be modified as we complete our review.

If you respond to these issues during this review cycle, depending on the timing of your response, we may not be able to consider your response before taking action on your application.

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.

If you have any questions, please contact Hyon J. Kim, Labeling Project Manager, at Hyon.Kim@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Hyon J. Kim, Pharm.D., PMP
Labeling Project Manager
Division of Labeling Review
Office of Regulatory Operations
Office of Generic Drugs
Center for Drug Evaluation and Research

[1] The term "GDUFA II Commitment Letter" refers to the GDUFA Reauthorization Performance Goals and Program Enhancements Fiscal Years 2018-2022 (available at: https://www.fda.gov/downloads/ForIndustry/UserFees/GenericDrugUserFees/UCM525234.pdf).

Hyon
Kim

Digitally signed by Hyon Kim
Date: 6/29/2018 07:53:10AM
GUID: 5638fc9e00454a67b6922d20c44f771b

[redacted]

ANDA 211796

EARLY INFORMATION REQUEST

Granules Pharmaceuticals Inc.
Attention: Vamsi Nama
Regulatory Affairs Director
3701 Concorde Parkway
Chantilly, VA 20151

Dear Sir/Madam:

Please refer to your Abbreviated New Drug Application (ANDA) dated April 2, 2018, submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (the Act) for Methylphenidate Hydrochloride Extended-Release Capsules 10 mg, 20 mg, 30 mg, 40 mg, and 60 mg.

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 30 days, in order to continue our evaluation of your ANDA.

Comments and information requests:

Drug Product

1. Please submit samples of all configurations of your finished product as well as the reference product for evaluation. Please inform us if any special handling requirements are advised. The samples can be mailed to the address below.

   FDA/CDER/OPQ/OPRO
   Attn: Qinghua Ge
   10903 New Hampshire Ave
   WO Bldg 75, Room 4621A
   Silver Spring, MD 20993

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

If you have any questions, please contact Qinghua Ge, Regulatory Business Process Manager, at 240-402-7623.

Sincerely,

{See appended electronic signature page}

Qinghua Ge

Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Qinghua
Ge

Digitally signed by Qinghua Ge
Date: 6/04/2018 09:39:44AM
GUID: 5a204ebd0016c8f54124c662a855562b

[redacted]

ANDA 211796

ACKNOWLEDGEMENT
ANDA RECEIPT

Granules Pharmaceuticals Inc.
3701 Concorde Parkway
Chantilly, VA 20151
Attention: Vamsi Nama

Dear Vamsi Nama:

This is in reference to your abbreviated new drug application (ANDA) submitted pursuant to section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The Food and Drug Administration (FDA or the Agency) has made a threshold determination that this ANDA is substantially complete. This ANDA is received for review.

NAME OF DRUG: Methylphenidate Hydrochloride Extended-release Capsules, 10 mg, 20 mg, 30 mg, 40 mg and 60 mg

DATE OF APPLICATION: March 30, 2018

DATE (RECEIVED) ACCEPTABLE FOR REVIEW: April 2, 2018

Reference is made to the information request dated May 14, 2018 and to any amendments thereafter.

This original ANDA is subject to the provisions of the Generic Drug User Fee Amendments of 2017 (GDUFA II). The GDUFA goal date for review of this standard original ANDA is February 1, 2019.

A drug with a name recognized in the USP National Formulary (USP–NF) generally must comply with applicable compendial standards or the drug will be deemed adulterated, misbranded, or both. (See section 501(b) and 502(e)(3)(b) and (g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act); also 21 CFR 299.5(a) and (b)). Such drugs must also comply with compendial standards for strength, quality, and purity, unless labeled to show all respects in which the drug differs or they will be deemed adulterated. (See section 501(b) of the FD&C Act and 21 CFR 299.5(c)). If the proposed specifications for your product do not conform with an applicable official USP monograph, you are advised to contact USP upon receipt of this Acknowledgement Letter to initiate a monograph revision through the USP Pending Monograph Process (PMP). Please note that initiation of the PMP does not mean that the proposed specifications will necessarily be approved by FDA; revisions to the USP monograph will be contingent upon FDA approval of the proposed specifications in this application.

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.

Please identify any related communications with the ANDA number referenced above. If you have any questions, contact Dat Doan, Project Manager Team Leader, at Dat.Doan@FDA.HHS.GOV[1] or 240-402-8926. We also recommend that you sign up for Generic Drug e-mail updates,[2] which provide updates and information generally related to generic drug regulation.

Sincerely,

{See appended electronic signature page}

Bankim Patel, RPh
Team Leader
Division of Filing Review
Office of Regulatory Operations
Office of Generic Drugs

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1 A secure email address is recommended for applicants to utilize when communicating with the Agency. If you have not already established a secure email with FDA, you may send a request for a secure email address to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications. Formal regulatory submissions must be submitted according to FDA regulations and current guidances.

2 https://service.govdelivery.com/accounts/USFDA/subscriber/new?topic_id=USFDA_476

Bankim
Patel

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