

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207960Orig1s000

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

MEMORANDUM

DATE: 24 NOV 2015

TO: NDA 207960

THROUGH: Wendy Wilson-Lee., Acting Branch Chief, OPQ
Yana Mille, OPPQ, OPQ

FROM: David J. Claffey, CMC Lead, OPQ.

David J. Claffey -S

Digitally signed by David J. Claffey -S
DN: c=US, o=US Government, ou=FDA,
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Date: 2015.11.30 17:05:17 -0500

SUBJECT: Established name and labeled strength for NDA 207960 – methylphenidate hydrochloride extended release chewable tablets.

NDA 207960 was submitted with the proposed established name of “methylphenidate hydrochloride extended release chewable tablets” with the strengths expressed in terms of methylphenidate hydrochloride salt. It was pointed out to the applicant that USP <1151> states that the use of the term ‘chewable’ is reserved for dosage forms that must be chewed, rather those that may be chewed:

“Tablets for human use that include “Chewable” in the title must be chewed or crushed prior to swallowing to ensure reliable release of the drug substance(s) or to facilitate swallowing. If tablets are designed so that they may be chewed (but chewing is not required for drug substance release or ease of swallowing), the title should not include a reference to “chewable”. In that case, the product may still be described as “chewable” in the ancillary labeling statement.”

The proposed labeling included language stating that the tablets (b) (4)

This was supported by data in the application. Therefore the proposed product did not appear to meet the definition recommended by USP.

If “chewable” was deleted from the established name, it would become “methylphenidate hydrochloride extended release tablets”. However the USP monograph for products with this title requires it to “contain NLT 90.0% and NMT 110.0% of the labeled amount of methylphenidate hydrochloride”. The proposed product contains just 15% methylphenidate hydrochloride salt, with the remaining 85% as methylphenidate bound to the sodium polystyrene

(b) (4)

A possible means of complying with both the monograph requirements and USP <1151> recommendations is to use the established name “methylphenidate extended release tablets” – as there is no monograph with this exact title. However in order to comply with the salt naming guidance the dosage strengths would then have to be expressed in terms of the free base – from 20, 30 & 40 mg (b) (4) respectively. The applicant was contacted (email 14 SEP 2015) regarding this issue and approach, but they did not find it acceptable (see Attachment). Use of the strengths expressed as the free-base was not the preferred choice by DMEPA or the DPP clinical team as it would confuse the prescribing and dosing of this product. In particular, it is noted that the two smaller strengths are scored. Therefore for the Dosage and Administration Instructions would change from:

For patients 6 years and above, the recommended starting dose is 20 mg given orally once daily in the morning. Dosage may be (b) (4) weekly in increments of 10 mg, 15 mg or 20 mg per day. Daily dosage above 60 mg is not recommended.

to:

For patients 6 years and above, the recommended starting dose is (b) (4) given orally once daily in the morning. Dosage may be (b) (4) weekly in increments of (b) (4) (b) (4) per day. Daily dosage above (b) (4) is not recommended.

Though, the latter option is obviously less intuitive and more confusing, it could be used if absolutely needed. Rounding the strengths was discussed, as decimals are known to lead to dosing errors. However this may lead to confusion as the lowest strength (b) (4) would not be half the higher strength (b) (4)

Final Resolution: After extensive discussion with DPP, DMEPA and the Labeling and Nomenclature Committee (Yana Mille and Richard Lostritto) it was clear that none of the available nomenclature options was ideal so the resolution would have to focus on what would be least confusing for practitioners. As a result, the following option was agreed upon at a 28 OCT 2015 meeting:

The established name will be:

“Methylphenidate hydrochloride extended release chewable tablets” with the strengths expressed in terms of the hydrochloride salt (20, 30 and 40 mg).

The positive aspects of this option are that:

- The strengths are intuitive and are in-line with all other methylphenidate products – of which this product is the one of a long series. (Thus, the “historical” exception to the application of the naming of drug substances that contain salt drug substances is being applied.)
- The strengths of the halved tablets are more intuitive.

- It does not go against USP requirements for similar products, as there is no monograph with this exact title (i.e. with 'chewable')
- The product does at least contain some methylphenidate hydrochloride salt – so the use of the salt in the title does bear some resemblance to drug product composition.

The use of 'chewable' in the established name does however go against the USP <1151> definition of a chewable tablet. Therefore OND/DMEPA/OPQ agreed that references to [REDACTED] (b) (4) [REDACTED] would be removed from the label.

In summary, the patients and prescribers will benefit from the intuitive name and strength in this format. The established and proprietary names will contain the word 'chew' or 'chewable', so removal of instructions from the PI on how exactly to administer does not appear likely to be a problem.

This memorandum will be shared with the Office of Generic Drugs labeling review staff so they are aware of the unique considerations that went into the development of the nomenclature and the labeling for this drug product.

ATTACHMENT

From: Cole, Lisha [mailto:Lisha.Cole@pfizer.com]
Sent: Wednesday, September 30, 2015 4:21 PM
To: Patel, Hiren
Subject: RE: NDA 207960

Hello Hiren,

Please find below and attached our response to the comments provided by the Agency on 14 September 2015 regarding the dosage form designation and established name for the proposed methylphenidate hydrochloride extended release chewable tablet. Please note that we have requests for the Agency at the end of the response.

Kind Regards,
Lisha

FDA comments: We note that the proposed drug product does not meet the USP <1151> definition of a ‘chewable tablet’ as the tablets can be either chewed or swallowed whole whereas USP defines a chewable tablet as one that must be chewed. Therefore the dosage form designation in the established name should be “extended release tablets” rather than “extended release chewable tablets”.

Pfizer response: For both patients and healthcare professionals, it is important that the drug product’s established name and dosage form designation clearly convey that this novel product formulation is both an extended release tablet and a chewable tablet. This is the first *extended release* and *chewable tablet* dosage form for a methylphenidate product.

The proposed drug product was designed as an extended release chewable tablet as described in Module 2.2.1 Introduction of the NDA. This pharmaceutical dosage form is a novel extended release formulation that is designed to be chewed. (b) (4)

(b) (4)
Please note that this novel dosage form is not specifically defined in USP <1151>, which includes recommendations regarding pharmaceutical dosage forms.

Currently approved *extended release tablets* typically **must** be swallowed whole and the currently approved *immediate release chewable tablets* typically **must not** be swallowed whole (i.e. chewed or crushed). Traditional extended release tablets are not designed to be chewed because chewing would result in dose dumping by altering the controlled release mechanism. However, our proposed drug product is novel because it is an extended release chewable tablet that utilizes a (b) (4) that allows it to be chewed without impacting the extended release mechanism. The proposed drug product is a pediatric friendly dosage form which contains flavoring and sweeteners in addition to its chewable design characteristics. In addition, this novel

formulation

(b) (4)

There is an unmet need in the patient population (including young school age children) who have difficulty swallowing tablets, thus our product was designed as a flavored, extended release chewable tablet (b) (4) to address this unmet need. For some patients, especially younger patients, who have difficulty swallowing a tablet whole, chewing may facilitate ingestion of the medication. A systematic review of 41 observational studies and clinical trials for the treatment of ADHD found that, dislike of medication and difficulties swallowing were among the most frequently reported reasons for discontinuing treatment in children and adolescents (Gajria et al. 2014). A survey of 304 parents of 702 children or adolescents found that approximately 34% of children/adolescents had refused to swallow pills, and 26–65% were unable to easily swallow a pill, with percentages increasing in younger children and for larger pills or capsules (Polaha et al. 2008). In a study designed to assess pill swallowing ability, 67/124 (54%) children ages 6–11 years who were willing to try to swallow a tablet could not (Meltzer et al. 2006). Prescribing information for several ADHD medication capsule formulations state that capsules can be opened and the contents sprinkled on applesauce for individuals who cannot swallow the medication (2012; Metadate CD [package insert] 2012; Ritalin LA [package insert] 2012). However, there is a risk of either over- or under-dosing using this method (Childress and Sallee 2013). The patient may be under-dosed if some of the contents of the capsule are spilled while preparing the applesauce for dosing or if the patient does not ingest the entire amount of applesauce prepared. Dose dumping (over dosing) can occur if the patient inadvertently bites down on long-acting beads in the applesauce, releasing the medication prematurely (Childress and Sallee 2013). The development of additional dosing and formulation options that take into account the abilities and preferences of patients ranging from preschool age to adult may improve the acceptability of ADHD medications and reduce non-compliance (Nunn and Williams 2005).

As noted in the rationale for product development section of Module 2.5 Clinical Overview of the NDA, the methylphenidate hydrochloride extended release chewable tablets offer an additional formulation option for patients who cannot or will not swallow tablets or capsules, such as pediatric patients. Given the prevalence of ADHD in the pediatric population, the availability of a pediatric friendly, once-daily extended-release chewable tablet formulation of methylphenidate offers a new dosing option for these patients. It is important for prescribers to understand the capabilities of this dosage form and to understand that is administered differently (i.e. once daily chewed (b) (4) (b) (4)) from the currently available extended release oral products and immediate release chewable tablets. Since a significant segment of the patient population must chew or crush the tablet to facilitate swallowing, the proposed drug product should be designated as an extended release chewable tablet dosage form (b) (4)

To enable the proper display of 'extended release chewable tablets' as the dosage form designation in the SPL version of the USPI, we request that FDA add this option to the metadata choices.

References

Childress A, Sallee FR: The use of methylphenidate hydrochloride extended-release oral suspension for the treatment of ADHD. *Expert Rev Neurother* 13:979-988, 2013.

Gajria K, Lu M, Sikirica V, Greven P, Zhong Y, Qin P, Xie J: Adherence, persistence, and medication discontinuation in patients with attention-deficit/hyperactivity disorder - a systematic literature review. *Neuropsychiatr Dis Treat* 10:1543-1569, 2014.

Meltzer EO, Welch MJ, Ostrom NK: Pill swallowing ability and training in children 6 to 11 years of age. *Clin Pediatr (Phila)* 45:725-733, 2006.

Metadate CD [package insert]. Smyrna, GA, UCB, Inc., 2012.

Nunn T, Williams J: Formulation of medicines for children. *Br J Clin Pharmacol* 59:674-676, 2005.

Polaha J, Dalton WT, III, Lancaster BM: Parental report of medication acceptance among youth: implications for everyday practice. *South Med J* 101:1106-1112, 2008.

Ritalin LA [package insert]. East Hanover, NJ, Novartis Pharmaceuticals Corporation, 2012.

FDA comments: With regards to the “[DRUG]” portion of the established name, it would be misleading if the product was called “methylphenidate hydrochloride extended release tablets” as the USP monograph definition of such a product requires that it “contain NLT 90.0% and NMT 110.0% of the labeled amount of methylphenidate hydrochloride” - the proposed product contains 15% methylphenidate hydrochloride. An appropriate alternative would be to use the established name “methylphenidate extended release tablets”. Note that in order to be in accordance with the Agency guidance “Naming of Drug Products Containing Salt Drug Substances” the primary labeled strength would need to be in terms of methylphenidate free base, rather than the hydrochloride salt. In addition, the name and amount of each of the components (as well as an equivalency statement for the methylphenidate hydrochloride component) will need to appear elsewhere on the label and in the labeling.

Pfizer response: As discussed above, the proposed drug product is a novel pharmaceutical dosage form i.e. an ‘extended release chewable tablet’ and not an ‘extended release tablet’ therefore, the USP monograph for “methylphenidate hydrochloride extended release tablets” is not applicable to the new extended release chewable tablet formulation.

All currently available and approved oral methylphenidate products include the primary labeled strength in terms of the hydrochloride salt. Section II.A.4 of the “Naming of Drug Products containing Salt Drug Substances” Guidance allows for an exception to use the salt name when the name of the salt conveys vital information from a clinical perspective and Section II.C.2.a indicates that the salt name should be retained when the following safety or historical condition is met: ‘The name of the salt is necessary to maintain consistency with other dosage forms of the same active ingredient (salt). For example, if a tablet dosage form that was approved before May 1, 2013 included the salt in its established name and the drug product’s strength is based on the salt form, the naming convention would not change for a new capsule dosage form with the same active ingredient (salt) that is approved after the effective date.’ The proposed drug product meets the above historical condition and therefore the drug part of the established name should be retained as ‘methylphenidate hydrochloride’. To avoid potential confusion in the prescription of this product, it is requested that the proposed drug product primary labeled strength be consistent with currently approved nomenclature as this will also ensure consistency with other dosage forms of the same active ingredient (salt). In accordance with III.B.1.c and Appendix 2, Example 2 of the Naming Guidance, it is proposed to include an equivalency to methylphenidate free base in the label and container labeling (side panel) for the proposed drug product is noted below:

For 20 mg strength: Each tablet contains 20 mg of methylphenidate hydrochloride

(b) (4)

For 30 mg strength: Each tablet contains 30 mg methylphenidate hydrochloride

(b) (4)

For 40 mg strength: Each tablet contains 40 mg methylphenidate hydrochloride

(b) (4)

FDA comments: Therefore we recommend that the drug product's established name be "methylphenidate extended release tablets" with the dosage strength in terms of methylphenidate free base.

Pfizer response: As described above, the proposed drug product is a novel extended release chewable tablet dosage form which is not specifically defined in a USP monograph or pharmaceutical dosage form description. It is a new dosage form of an active ingredient (salt) approved long before May 2013. Therefore we believe that the proposed established name, "methylphenidate hydrochloride extended release chewable tablets" is appropriate, accurate and not misleading. Accurate description of the drug product is important to avoid potential confusion and/or medication errors in the prescription and use of this novel dosage form and to maintain consistency with other dosage forms of the same active ingredient (salt).

Questions to Agency:

1-Does FDA concur with the proposal to retain the dosage form designation as 'extended release chewable tablets'?

2-Does the FDA concur with the proposal to retain the established name as 'methylphenidate hydrochloride extended release chewable tablets' based on applying an exception for historical naming convention for other dosage forms of the same active ingredient (salt)?

If so, an amendment will be submitted to provide the proposed revisions to the label and labeling as noted above and to ensure that the established name of the drug product and the active ingredient are displayed correctly throughout the label. To enable the proper display of 'extended release chewable tablets' as the dosage form designation in the SPL version of the USPI, we request that FDA add this option to the metadata choices.

If not, Pfizer would like to request a brief teleconference to further discuss. Please advise regarding timing for such a discussion.

From: Cole, Lisha

Sent: Friday, September 25, 2015 2:22 PM

To: 'Patel, Hiren'

Subject: RE: NDA 207960

Hello Hiren,

Just wanted to let you know that we are preparing a reply to the comments below and expect to provide them before the end of next week.

Kind Regards,

Lisha

From: Patel, Hiren [<mailto:Hiren.Patel@fda.hhs.gov>]
Sent: Monday, September 14, 2015 3:58 PM
To: Cole, Lisha
Subject: NDA 207960
Importance: High

Dear Lisha,

We note that the proposed drug product does not meet the USP <1151> definition of a 'chewable tablet' as the tablets can be either chewed or swallowed whole whereas USP defines a chewable tablet as one that must be chewed. Therefore the dosage form designation in the established name should be "extended release tablets" rather than "extended release chewable tablets". With regards to the "[DRUG]" portion of the established name, it would be misleading if the product was called "methylphenidate hydrochloride extended release tablets" as the USP monograph definition of such a product requires that it "contain NLT 90.0% and NMT 110.0% of the labeled amount of methylphenidate hydrochloride" - the proposed product contains 15% methylphenidate hydrochloride. An appropriate alternative would be to use the established name "methylphenidate extended release tablets". Note that in order to be in accordance with the Agency guidance "Naming of Drug Products Containing Salt Drug Substances" the primary labeled strength would need to be in terms of methylphenidate free base, rather than the hydrochloride salt. In addition, the name and amount of each of the components (as well as an equivalency statement for the methylphenidate hydrochloride component) will need to appear elsewhere on the label and in the labeling.

Therefore we recommend that the drug product's established name be "methylphenidate extended release tablets" with the dosage strength in terms of methylphenidate free base.

Regards,

Hiren

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Recommend Approval

NDA 207960

Review # 1

1 OCT 2015

QuilliChew ^{(b) (4)} **rx**

Established Name	Methylphenidate Extended-Release Tablets
Strength	^{(b) (4)} (20 mg, 30 mg, 40 mg equivalent salt)
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Pfizer, Inc.
US agent, if applicable	N/A

SUBMISSION(S) REVIEWED	DOCUMENT DATE
Original NDA	February 4, 2015
Quality Amendment	June 19, 2015
Quality Amendment	July 7, 2015
Quality Amendment	July 17, 2015
Quality Amendment	August 10, 2015
Quality Amendment	September 3, 2015
Quality Amendment	September 25, 2015

Quality Review Team

DISCIPLINE	REVIEWER	OFFICE/DIVISION/BRANCH
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Drug Product	Thomas Wong	ONDP/Division of New Drug Products I /Branch I
Process/ Microbiology	Bogdan Kurtyka	OPF/Division 1/Branch 2
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Regulatory Business Process Manager	Dahlia Woody	
Application Technical Lead	David Claffey	

Table of Contents

Table of Contents	2
Quality Review Data Sheet	3
Executive Summary	4
Primary Quality Review	7
2.3.S DRUG SUBSTANCE	7
ASSESSMENT OF THE DRUG PRODUCT	12
2.3.P DRUG PRODUCT	12
R.2 Comparability Protocols.....	19
ASSESSMENT OF THE PROCESS	19
2.3.P DRUG PRODUCT	19
R.2 Comparability Protocols.....	20
ASSESSMENT OF THE FACILITIES	21
2.3.S DRUG SUBSTANCE	21
2.3.P DRUG PRODUCT	23
ASSESSMENT OF THE BIOPHARMACEUTICS	24
ASSESSMENT OF MICROBIOLOGY	35
2.3.P.7 Container/Closure System	35
A APPENDICES	35
ASSESSMENT OF ENVIRONMENTAL ANALYSIS	36
I. Review of Common Technical Document-Quality (Ctd-Q) Module 1	37
Labeling & Package Insert.....	37
II. List of Deficiencies To Be Communicated.....	46
III. Attachments	47

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS
25909	Type II	Tris Pharma	Drug product	Adequate	1 OCT 2015	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	202100	Methylphenidate HCl for extended release oral suspension

2. CONSULTS: N/A

Executive Summary

I. Recommendations: **Recommend Approval**

A. Recommendation and Conclusion on Approvability

The drug product information was referenced to DMF 25909. Drug substance information was referenced to DMF (b) (4). Both DMFs were found adequate to support this application.

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

The holder of DMF 25909 agreed to a postmarketing commitment.

II. Summary of Quality Assessments

Refer to DMF 25909 Review #2 for complete executive summary. The following is based on the limited data provided in the application.

Background: The drug product consists of three dosage strengths (b) (4) of film-coated scored tablets (b) (4). The (b) (4) strength tablets are speckled capsule-shaped and off-white, light pink or dark pink with “NP 12”, “NP 13” or “NP 14” (respectively) debossed on one side and a bisect on the other. They are packed in HDPE bottles with a desiccant.

Established name and dosage strength: The applicant proposed that the dosage form be ‘chewable tablets’. However USP <1151> states that a chewable tablet is one that must be chewed rather than one that may be chewed. As the drug product can be chewed or swallowed whole, the dosage form designation is ‘tablets’ rather than ‘chewable tablets’. Further, the applicant proposes expressing the name and strength in terms of the hydrochloride salt (20, 30 and 40 mg). The established name would then have been ‘methylphenidate hydrochloride extended release tablets’. However USP defines such a product as one which contains 90.0-110.0% methylphenidate hydrochloride. The proposed product contains significantly less methylphenidate hydrochloride – therefore this established name cannot be used. The applicant was informed that a more appropriate established name would be ‘methylphenidate extended release tablets’ with the product strengths expressed in terms of the free base to match the name (in accordance with Agency salt naming guidance).

Drug product development: Drug product development centered on achieving bioavailability comparable to Quillivant XR (methylphenidate hydrochloride for extended release powder oral suspension, NDA 202100). Data supported the PK equivalence of chewing or swallowing whole. Data also supported the use of the functional score. In vitro data found dose dumping at 40% alcohol concentrations.

The drug product is manufactured by Tris Pharma. The manufacturing and testing sites were found to be acceptable.

The drug product specification includes tests typical for an extended release tablet. Tablet hardness, which is critical as this tablet may be chewed, in controlled in-process (detailed in DMF 25909). The major chemical degradant is controlled at 1.5%. This limit was found acceptable as it is a known major metabolite and the limit is in accordance with USP monographs for similar products. Registration batch analysis showed that all batches met specification.

Stability data through 24 months supported the proposed 24 month drug product expiry period when packaged in HDPE bottles with desiccant and stored at 25°C.

Drug substance: Details of the drug substance were referenced to DMF (b) (4). This was found adequate to support this NDA. Drug substance information was also provided in DMF 25909.

A. Summary of Drug Product Intended Use

Proprietary Name of the Drug Product	
Non Proprietary Name of the Drug Product	
Non Proprietary Name of the Drug Substance	
Proposed Indication(s) including Intended Patient Population	
Duration of Treatment	
Maximum Daily Dose	
Alternative Methods of Administration	

B. Biopharmaceutics Considerations

1. BCS Classification:

- Drug Substance: Methylphenidate is highly soluble (aqueous solubility ~150 mg/mL) and the permeability is low (i.e. BCS class III)
- Drug Product: N/A (no BCS designation information)

2. Biowaivers/Biostudies

- Biowaiver Requests: biowaiver request for 20 mg and 30 mg strengths was found adequate.
- PK studies: No PK bridging was necessary
- IVIVC: No IVIVC information submitted

C. Novel Approaches

D. Any Special Product Quality Labeling Recommendations

E. Life Cycle Knowledge Information (see Attachment A)

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead Signature:

David J.
Claffey -S

Digitally signed by David J. Claffey -S
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Date: 2015.10.05 12:25:09 -04'00'

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OVERALL ASSESSMENT AND SIGNATURES: FACILITIES

Reviewer's Assessment and Signature:

Based on a review of the application and an assessment of the facilities, procedures, equipment and data examined during pre-approval and surveillance inspections, the proposed manufacturing, testing and packaging sites for NDA 207960 are acceptable and recommended for approval.

Steven Fong -S  Digitally signed by Steven Fong -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Steven Fong -S, 0.9.2342.19200300.100.1.1=2000287433
Date: 2015.10.02 10:43:11 -04'00'

Steven Fong, M.S., Ph.D.

Microbiologist and Acting Quality Assessment Lead, OPQ.OPF/DIA/Branch I
09/29/2015

Supervisor Comments and Concurrence:

I concur with the facility reviewer's recommendation.

Zhihao Qiu -S  Digitally signed by Zhihao Qiu -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
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Zhihao Peter Qiu, Ph.D.

Branch Chief, OPQ/OPF/DIA/Branch 1
09/29/2015

ASSESSMENT OF THE BIOPHARMACEUTICS

The proposed product is methylphenidate Hydrochloride (MPH) extended-release chewable tablets (ERCT) 20 mg, 30 mg, and 40 mg strengths. MPH is freely soluble in water (solubility ~ 150 mg/mL). The proposed product is formulated by (b) (4)



1. Are the in-vitro dissolution test and acceptance criteria adequate for assuring quality control and consistent bioavailability of the drug product?

The adequacy of the dissolution method parameters, discriminating ability, and acceptance criteria are reviewed in DMF# 25909. The review of NDA 207960 focuses on the proper bridging of formulations during development, adequacy of biowaiver request information, in vitro alcohol dose dumping studies, and the extended-release claim designation.

Applicant’s Response:

Reviewer’s Assessment: ADEQUATE

The finished product dissolution method and acceptance criteria listed in the table below are adequate.

Apparatus	USP II (Paddle)
Speed	75 rpm
Medium	0.4M KH ₂ PO ₄
Volume	900 mL
Temperature	37°C ± 0.5°C
Sampling Volume	5 mL
Proposed Acceptance Criteria	(b) (4) (b) (4) % in 3 h NLT (b) (4) % in 8 h

2. Are the changes in the formulation, manufacturing process, manufacturing sites during the development appropriately bridged to the commercial product?

The Applicant conducted two pilot PK studies to support formulation development: B7491002 and B7491004 to determine the relative bioavailability between early formulations and the commercial formulation. In addition, the Applicant conducted two pivotal studies: one relative BE and food effect study (B7491004) comparing the 40 mg strength of the commercial formulation MPH ERCT to 2 doses of the 20 mg IR product

(METHYLIN[®]) and the effect of food and one pivotal efficacy study (B7491005) conducted in 90 pediatric patients with ADHD to establish efficacy of the proposed product. The efficacy study was conducted using the formulation used in the pivotal BE study (B7491004); therefore, no additional bridging studies were necessary.

Applicant's Response:

Reviewer's Assessment: ADEQUATE

The commercial formulation was used in the pivotal bioavailability study (B7491004) comparing the commercial formulation MPH ERCT to LD (METHYLIN[®]). The pivotal efficacy study was conducted using the commercial formulation. Therefore, no additional bridging studies were necessary.

BIOWAIVER REQUEST

The pivotal BE study compared the 40 mg strength of MPH ERCT to 2 doses of the IR 20 mg tablets (METHYLIN[®]). The Applicant provided a request to waive bioequivalence studies for the lower strengths (20 mg and 30 mg) MPH ERCT.

The formulations of the 3 different strengths are proportional in composition (Table 1), and are manufactured using the same process (refer to process section).

Table 1. Components and Composition of The 20 mg, 30 mg, and 40 mg MPH ERCT

Ingredients	Quantity (mg/tablet)		
	20 mg	30 mg	40 mg
(b) (4)			(b) (4)
Sodium Polystyrene Sulfonate TP			
Methylphenidate Hydrochloride USP	20	30	40
Povidone, USP (b) (4)			(b) (4)
Triacetin USP			
Polyvinyl Acetate (b) (4)			
(b) (4)			
Mannitol USP (b) (4)			
Xanthan Gum NF (b) (4)			
Croscopidone NF (b) (4)			
Microcrystalline Cellulose and Guar Gum (b) (4)			
Aspartame NF			
Citric Acid (b) (4) USP			
(b) (4) Cherry Flavor (b) (4)			
(b) (4)			
D&C Red No. 7			
D&C Red No. 30			
Talc USP (b) (4)			
Magnesium Stearate NF (b) (4)			
(b) (4)			
(b) (4)			

The Applicant provided f_2 score for the 20 mg strength in comparison to the 40 mg strength in 3 different pH media (1.2, 4.5, and 6.8) (Table 2). The Applicant stated that a bracketing approach was taken (i.e. only 20 mg tested and not the 30 mg).

Table 2. Comparison of Similarity Factor (f_2) of 40 mg and 20 mg ERCT Tablets

Reference Batch Used in Biostudy	Strength/Batch Requesting Waiver	Similarity Results ¹
pH 1.2		
40 mg /Batch# TB-103A	20 mg/Batch# TB-104A	71
pH 4.5		
40 mg /Batch# TB-103A	20 mg/Batch# TB-104A	83
pH 6.8		
40 mg /Batch# TB-103A	20 mg/Batch# TB-104A	96
Registration Media		
40 mg /Batch# TB-103A	20 mg/Batch# TB-104A	95

The Applicant provided similarity comparison between the 40 mg strength and the lower strengths in the proposed dissolution method (Figure 1 and Table 3).



(b) (4)

Figure 1. Dissolution profiles of the 20 mg, 30 mg, and 40 mg strengths in the proposed dissolution media

Table 3. Similarity Comparison (f_2) of lower strengths

Strength	f_2
40 mg	-
30 mg	97
20 mg	95

An Information Request (7/28/2015) was sent to the Applicant to request detailed dissolution profiles and data rather than f_2 calculations for the 20 mg and 30 mg strengths in three different media pH (1.2, 4.5, and 6.8) in order to fulfill the biowaiver request. The Applicant responded to the Information Request (Sequence #0012 date 8/10/2015) referencing DMF 25909 (eCTD Sequence #0013 dated 8/7/2015) which contains updated dissolution data for the proposed 20 mg, 30 mg, and 40 mg strengths in pH 1.2, 4.5, 6.8, and the registration media. The data for each strength in each medium is comprised of individual ($n = 12$), mean, and standard deviation (see DMF 25909 section 3.2.P.2 tables 12, 13, 14, 15, 16, 17, 18, and 19 for individual dissolution data). The following table summarizes the similarity factor (f_2) calculated by the reviewer.

Table 4. Summary of similarity factor (f_2) of the 20 and 30 mg strengths in comparison the 40 mg strength in different media.

MEDIUM	20 mg	30 mg
pH 1.2	71	75
pH 4.5	72	77
pH 6.8	96	87
Registration	95	97

Reviewer’s Assessment: ADEQUATE

The formulations are qualitatively similar and quantitatively are proportional in composition. The similarity factors (f2) calculated for the 20 mg and 30 mg dosage strengths relative to 40 mg strength (used in the pivotal BE study) are greater than 50 in different pH media, indicating similarity between the 20 mg, 30 mg, and 40 dosage strengths. In addition, the Applicant has included a formal biowaiver request for the 20 mg and 30 mg strengths. Therefore, the provided data support the biowaiver request.

EXTENDED-RELEASE DESIGNATION

The Applicant provided data to support the extended release claim. The Applicant provided simulation of steady-state PK profiles based on PK profiles obtained from the pivotal BE study. Non-parametric superposition in Phoenix WinNonlin to predict simulated state concentrations were used (Table 5 and Figure 2).

Table 5. Non-Parametric Superposition Parameters Supplied by the Applicant

PK Parameter	Definition/Calculation
T _{max}	Time of maximum observed concentration. For non-steady-state data, the entire curve is considered. For steady-state data, T _{max} corresponds to points collected during a dosing interval. If the maximum observed concentration is not unique, then the first maximum is used.
C _{max}	Maximum concentration between dose time and dose time + Tau (at T _{max}). If not unique, then the first maximum is used.
C _{min}	Minimum concentration between dose time and dose time + Tau (at T _{min}).
C _{avg}	Average concentration calculated as AUC _{tau} /tau
C _{last}	Last measurable concentration
AUC _{last}	Area under the concentration-time curve from zero time until the last measurable concentration (C _{last}) is calculated using the trapezoidal rule.
AUC _{tau}	Area under the concentration versus time curve from zero time to time tau, the dosing interval, calculated using the trapezoidal method. (tau=24 hours)
AUC _t	Partial AUC calculated across the time interval of 0-24 hr, 24-48 hr, 48-72 hr, 72-96 hr, and 96-120 hr.
t _{1/2}	Terminal phase half-life calculate as ln 2/k _{el}
%_Fluctuation	100*(C _{max} -C _{min})/C _{avg} , for C _{min} and C _{max} between dose time and Tau.
Accumulation Index	$\frac{1}{1 - e^{-\lambda_z \tau}}$

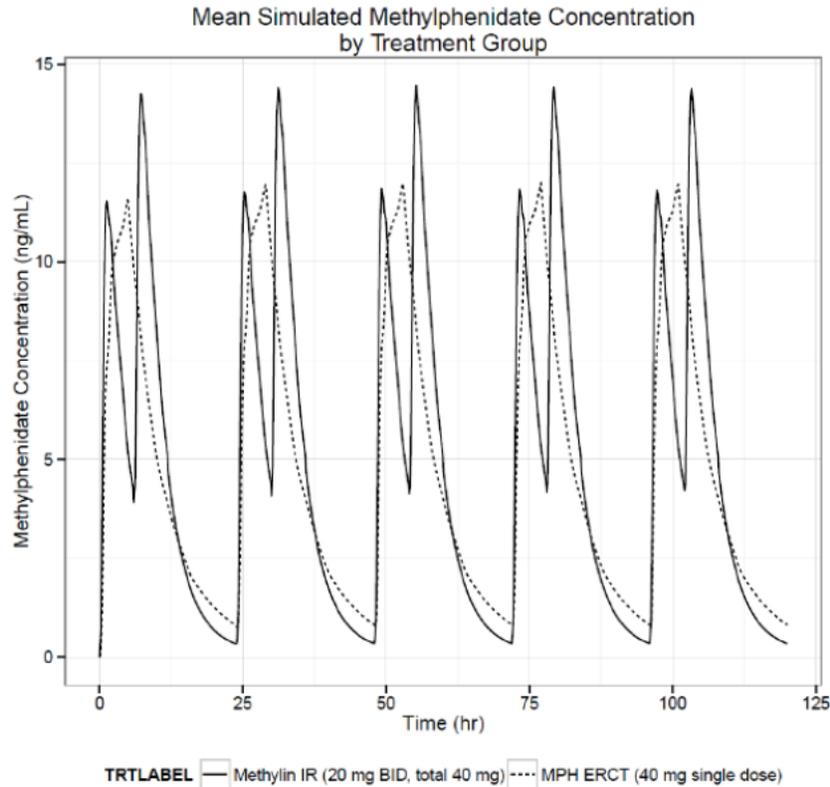
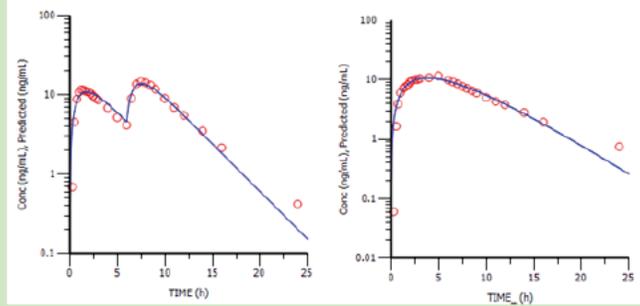


Figure 2. The mean PK profile of each group (ER chewable tablets versus IR formulation) at steady state provided by the Applicant based on non-parametric superposition.

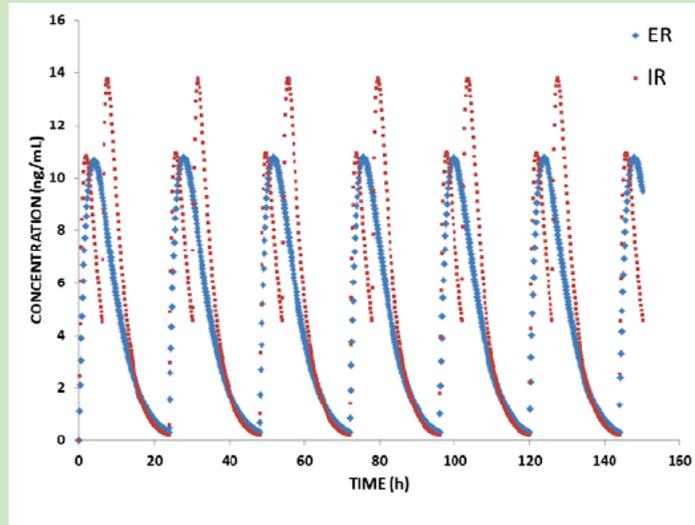
The mean accumulation ratio for the extended release chewable tablet was 1.1% and 1.0% for the split BID dosing of the IR formulation. Peak to trough mean fluctuations value for the IR formulation was 307%. The corresponding mean fluctuation value for the extended release formulation was 268%.

Reviewer’s Assessment: ADEQUATE

The steady-state concentrations were generated (by the reviewer) using compartmental modeling in Phoenix WinNonlin. A one-compartment model with linear elimination was fit to the mean PK data of the IR and ER formulation as shown in the figure below:



The model parameters were used to simulate steady-state concentrations as shown in the following figure:



The following data were obtained from the parametric simulation:

	IR	ER
C_{min} (ng/mL)	0.2	0.3
C_{max} (ng/mL)	13.8	10.7
Fluctuation Index	189%	179%

Based on the provided data, the proposed product has (1) lower dosing frequency (once daily versus twice daily for the IR product), (2) lower fluctuation index (lower C_{max} and higher C_{min}), and (3) a release-controlling (b) (4)

(b) (4). Thus, the proposed product fulfills the requirements for extended-release designation.

IN VITRO ALCOHOL DOSE DUMPING STUDY

To assess the effect of alcohol on MPH extended release chewable tablets, in vitro dissolution with 0%, 5%, 10%, 20% and 40% alcohol was conducted in 0.1 N HCl dissolution media using the proposed dissolution method parameters (Table 6).

Table 6. In vitro Release Profiles in Alcohol Dose Dumping Study

Time (Minutes)	% Drug Release with Alcohol (v/v)				
	0%	5%	10%	20%	40%
15	32	33	34	39	80
30	35	36	38	44	90
45	38	39	41	47	94
60	40	41	43	50	95
75	41	43	45	53	96
90	43	44	47	55	95
105	45	46	48	57	95
120	46	47	50	59	96

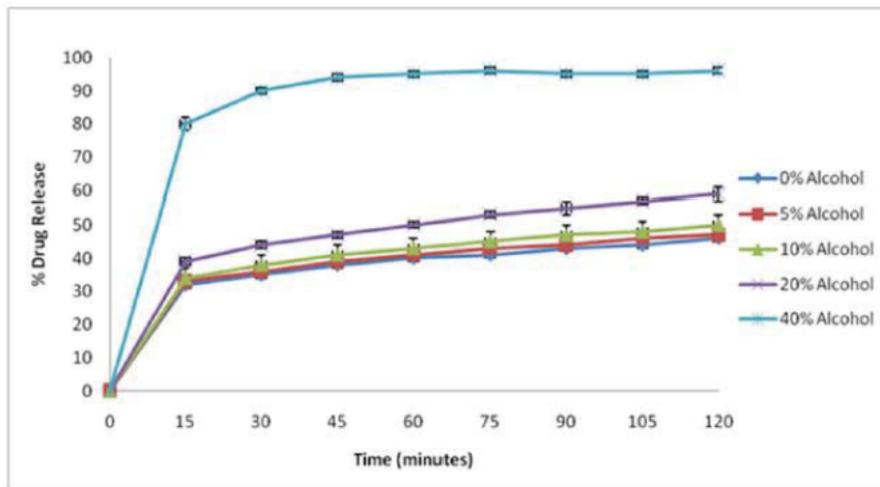


Figure 3. In vitro release profiles of the proposed product various concentrations

The Similarity factor (f_2) calculations (Table 7) indicate that there is a significant effect of alcohol on the release profiles at 20% and 40%.

Table 7. Similarity Factor (f_2) of Release Profiles in Various Alcohol Percentages

% Alcohol	f_2
0	--
5	89.02
10	72.26
20	48.19
40	13.86

Reviewer’s Assessment:

The provided data indicate that that the presence of alcohol may affect the release profiles of the proposed product. Therefore, alcohol consumption should be taken into consideration during the labeling of the proposed product. The specific recommendations

to be included in the product label fall under the purview of the Clinical Review Team and Clinical Pharmacology.

**OVERALL ASSESSMENT AND SIGNATURES:
BIOPHARMACEUTICS**

Reviewer’s Assessment and Signature:

The finished product dissolution method (listed below) was determined to be ADEQUATE. The Applicant’s current in process dissolution method using (b) (4) rpm is discriminating; however they committed to optimize the method to reduce the current sampling times (e.g. less than (b) (4) hrs. sampling time) without compromising its discriminating ability.

Apparatus	USP II (Paddle)
Speed	75 rpm
Medium	0.4M KH ₂ PO ₄
Volume	900 mL
Temperature	37°C ± 0.5°C
Sampling Volume	5 mL
Proposed Acceptance Criteria	(b) (4) (b) (4) % in 3 h NLT (b) (4) % in 8 h

However, the in-process dissolution acceptance criteria was accepted on interim basis only and a post-marketing commitment (PMC) was issued to the DMF holder (1) to develop a new in-process dissolution method with demonstrated discriminatory capability and (2) to select the acceptance criteria for the new in-process method based dissolution profiles from, at least, 5 commercial batches.

The extended-release formulation (40 mg strength) was compared to the reference IR product (METHYLIN®, 2X20 mg tablets) and was used in the pivotal efficacy study. Therefore, no formulation bridging studies were necessary. The Applicant requested a biowaiver for the 20 mg and the 30 mg dosage strength. The similarity factors between the lower and higher strengths were higher than 50. The biowaiver information was found ADEQUATE.

The Applicant provided simulations (non-parametric superposition) to demonstrate the adequacy of the extended-release claim. Internal model-based simulations ran by the reviewer confirmed the findings included in the NDA; the fluctuation index was lower with the ER formulation in comparison to the IR formulation. The extended-release claim was found to be ADEQUATE.

The in vitro Alcohol dose dumping studies indicate that there is a significant effect at the 20% and 40% alcohol concentrations. Specific recommendations in the labeling fall under the purview of the clinical team.

From a Biopharmaceutics perspective, NDA 207960 is recommended for APPROVAL with a post-marketing commitment.

**Salaheldin S.
Hamed**

Digitally signed by Salaheldin S. Hamed
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ou=CDER,
email=salaheldin.hamed@fda.hhs.gov, c=US
Date: 2015.10.02 10:37:37 -04'00'

**Salaheldin S. Hamed, Ph.D
Biopharmaceutics Reviewer
ONDP/Division of Biopharmaceutics**

Secondary Review Comments and Concurrence:

**Sandra
Suarez -A**

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Date: 2015.10.02 11:13:31 -04'00'

**Sandra Suarez-Sharp, Ph.D.
Acting Biopharmaceutics Lead
ONDP/Division of Biopharmaceutics**

ASSESSMENT OF MICROBIOLOGY

3. Are the tests and proposed acceptance criteria for microbial burden adequate for assuring the microbial quality of the drug product?

Applicant's Response: Drug product specification is included in section 3.2.P.5.1.

Reviewer's Assessment: **Satisfactory.**

Drug product specification includes test for microbial purity. The USP<61> and USP<62> are proposed with acceptance limits appropriate for the dosage form.

In addition, see microbial aspects in the review of DMF 25909.

2.3.P.7 Container/Closure System

4. Is the proposed container/closure system for the drug product validated to function as a barrier to microbial ingress? What is the container/closure design space and change control program in terms of validation?

Applicant's Response:

Reviewer's Assessment:

A APPENDICES

A.2 Adventitious Agents Safety Evaluation

5. Are any materials used for the manufacture of the drug substance or drug product of biological origin or derived from biological sources? If the drug product contains material sourced from animals, what documentation is provided to assure a low risk of virus or prion contamination (causative agent of TSE)?

See DMF # 25909 Review #2 for details.

6. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug

substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

See DMF # 25909 Review #2 for details.

OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY

Reviewer's Assessment and Signature: Bogdan Kurtyka, 9/17/2015

The microbiological purity is assured through acceptable test methods and acceptance limits.

Bogdan Kurtyka -S

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Date: 2015.10.05 13:41:40 -04'00'

Secondary Review Comments and Concurrence: I concur

Sharmista Chatterjee, Ph.D.

Branch Chief (Acting), OPF/OPQ

9/18/2015

ASSESSMENT OF ENVIRONMENTAL ANALYSIS

7. Is the applicant's claim for categorical exclusion acceptable?

The applicant claimed for categorical exclusion according to 21 CFR 25.31 (a). In addition, the applicant also stated that Pfizer Inc claims that to our knowledge, no extraordinary circumstances exist.

8. Is the applicant's Environmental Assessment adequate for approval of the application?

Not applicable

Reviewer's Assessment: Acceptable

OVERALL ASSESSMENT AND SIGNATURES: ENVIRONMENTAL**Reviewer's Assessment and Signature:**Thomas M.
Wong -SDigitally signed by Thomas M. Wong -S
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ou=FDA, ou=People, cn=Thomas M Wong
-S, o=9.2342.19200300.100.1.1=1300437649
Date: 2015.10.02 11:08:10 -0400**Thomas Wong, Ph.D., ONDP/Division of New Drug Products I/Branch I****Secondary Review Comments and Concurrence:**Wendy I. Wilson
-SDigitally signed by Wendy I. Wilson -S
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People,
o=9.2342.19200300.100.1.1=1300396790,
cn=Wendy I. Wilson -S
Date: 2015.10.02 11:10:17 -0400**Wendy I. Wilson-Lee, Ph.D.**
Acting Branch Chief
Division New Drug Products I
OPQ/ONDP**I. Review of Common Technical Document-Quality (Ctd-Q) Module 1****Labeling & Package Insert**

The annotated package insert labeling for the text of the proposed package insert is included in Section 1.14.3.1. As this 505(b)(2) NDA relies on the RLD Keppra® Tablets (NDA 021035) the majority of the annotation for labeling elements, content and format is referenced to the RLD current FDA approved labeling. Any SPRITAM® (levetiracetam) triturate specific information is annotated in Section 1.14.3.1 to the appropriate sections of the NDA supporting the proposed labeling statements. Therefore only the annotated carton and blister labeling will appear in this section.

1. Package Insert**(a) “Highlights” Section (21CFR 201.57(a))**

Item	Information Provided in NDA	Reviewer's Assessment
Product title, Drug name (201.57(a)(2))		
Proprietary name and established name	Proprietary name: ??????? Established name: methylphenidate hydrochloride	At the time of this review, the proposed proprietary name has not yet been approved by DMEPA.
Dosage form, route of administration	Extended-release chewable tablets for oral administration	Acceptable
Controlled drug substance symbol (if applicable)	Not applicable. The product is no controlled substance.	N/A
Dosage Forms and Strengths (201.57(a)(8))		
A concise summary of dosage forms and strengths	Extended-release chewable tablet: 20 mg, 30 mg, and 40 mg. The 20 mg and 30 mg tablets are scored (bisected) and may be divided into equal halves for dose adjustments.	The expression of the tablet strength does not comply with MAPP 5021.1 - Naming of Drug Products Containing Salt Drug Substances, and USP Salt Policy. The expression of the strength should be (based on the conversion factor of (b) (4)): (b) (4) 20 mg methylphenidate hydrochloride), (b) (4) 30 mg methylphenidate hydrochloride), (b) (4) 40 mg methylphenidate hydrochloride).

Conclusion: Acceptable. Final package insert language will be finalized with other review disciplines during labeling meetings.

(b) “Full Prescribing Information” Section

3: Dosage Forms and Strengths (21CFR 201.57(c)(4))

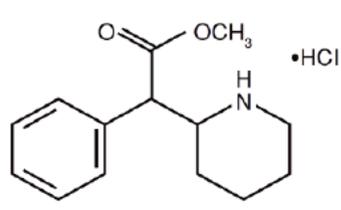
3 DOSAGE FORMS AND STRENGTHS

Extended-release chewable tablets: 20 mg, 30 mg and 40 mg. The 20 mg and 30 mg tablets are scored (bisected) and may be divided into equal halves for dose adjustments.

Item	Information Provided in NDA	Reviewer’s Assessment
Available dosage forms	Extended-release chewable tablet.	Acceptable
Strengths: in metric system	20 mg, 30 mg, and 40 mg.	The expression of the tablet strength does not comply with MAPP 5021.1 - Naming of Drug Products Containing Salt Drug Substances, and USP Salt Policy. The expression of the strength should be (based on the conversion factor of (b)(4)): (b)(4) 20 mg methylphenidate hydrochloride (b)(4) 30 mg methylphenidate hydrochloride (b)(4) 40 mg methylphenidate hydrochloride).
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	The 20 mg extended-release chewable tablet is available as a speckled, off-white, capsule-shaped coated tablet, debossed with “NP 12” on one side and scored (bisected) on the other side. The 30 mg extended-release chewable tablet is available as a speckled, light pink color, capsule-shaped coated tablet, debossed with “NP 13” on one side and scored (bisected) on the other side. The 40 mg extended-release chewable tablet is available as a speckled, dark pink to peach color, capsule-shaped coated tablet, debossed with “NP 14” on one side and plain on the other side.	Acceptable with revision in tablet strength expression.

Conclusion: Acceptable. Final package insert language will be finalized with other review disciplines during labeling meetings

#11: Description (21CFR 201.57(c)(12))

<p>11 DESCRIPTION</p> <p><TRADENAME> (methylphenidate HCl) is available (b) (4) 20 mg, 30 mg and 40 mg (b) (4)</p> <p>(b) (4) <TRADENAME> contains approximately 30% immediate-release and 70% extended-release methylphenidate.</p> <p>(b) (4)</p> <p>The <TRADENAME> extended-release chewable tablets are cherry flavored.</p> <p>Methylphenidate HCl is a central nervous system (CNS) stimulant. The chemical name is methyl α-phenyl-2-piperidineacetate hydrochloride, and its structural formula is shown in Figure 1.</p> <p>Figure 1. Methylphenidate HCl Structure</p>  <p>$C_{14}H_{19}NO_2 \cdot HCl$ Mol. Wt. 269.77</p> <p>Methylphenidate HCl is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone.</p> <p><TRADENAME> also contains the following inactive ingredients: sodium polystyrene sulfonate, povidone, polyvinyl acetate, triacetin, microcrystalline cellulose, mannitol, xanthan gum, guar gum, crospovidone, aspartame, citric acid, cherry flavor, talc, silicon dioxide, magnesium stearate, polyvinyl alcohol, D&C red #30 (for 30 mg strength), D&C red #7 (for 40 mg strength).</p>
--

Item	Information Provided in NDA	Reviewer's Assessment
Proprietary name and established name	To be determined	At the time of this review, the proposed proprietary name has not yet been approved by DMEPA.
Dosage form and route of administration	Extended-release chewable tablets for oral administration*	Acceptable
Active moiety expression of strength with equivalence statement for salt (if applicable)	20 mg, 30 mg, and 40 mg.	The expression of the strength should be (based on the conversion factor of (b) (4)): (b) (4) 20 mg methylphenidate hydrochloride) (b) (4) 30 mg methylphenidate hydrochloride), (b) (4) 40 mg methylphenidate hydrochloride).
Inactive ingredient information	The inactive ingredients are listed.	Acceptable

(quantitative, if injectables 21CFR201.100(b)(5)(iii)), listed by USP/NF names.		
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	It is a central nervous system stimulant indicated for the treatment of Attention Deficit Hyperactivity Disorder.	Acceptable
Chemical name, structural formula, molecular weight	See above photocopy of the package insert	Acceptable
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa, solubility, or pH)	Methylphenidate HCl is a white, odorless crystalline powder. Its solutions are acid to litmus. It is freely soluble in water and in methanol, soluble in alcohol, and slightly soluble in chloroform and in acetone	Acceptable
Warning and precaution statements	<i>Phenylketonurics:</i> <TRADENAME> extended-release chewable tablets contain phenylalanine, a component of aspartame. Phenylalanine can be harmful to patients with phenylketonuria ^(b) ₍₄₎	Acceptable. Declaration of phenylalanine complies with 21 CFR 172.804 – Aspartame.
* See above photocopy of the package insert.		

Conclusion: Acceptable. Final package insert language will be finalized with other review disciplines during labeling meetings.

#16: How Supplied/Storage and Handling (21CFR 201.57(c)(17))

16 HOW SUPPLIED/STORAGE AND HANDLING

16.1 How Supplied

<p><TRADENAME> is supplied as extended-release chewable tablets in 20 mg, 30 mg and 40 mg strengths. (b) (4)</p>			
<p>(b) (4)</p>			
<p>The 20 mg extended-release chewable tablet is available as a speckled, off-white, capsule-shaped coated tablet, debossed with "NP 12" on one side and scored (b) (4) on the other side.</p>			
<p>The 30 mg extended-release chewable tablet is available as a speckled, light pink color, capsule-shaped coated tablet, debossed with "NP 13" on one side and scored (b) (4) on the other side.</p>			
<p>The 40 mg extended-release chewable tablet is available as a speckled, dark pink to peach color, capsule-shaped coated tablet, debossed with "NP 14" on one side and plain on the other side.</p>			
<p>The product is supplied in bottles of 100.</p>			
<p align="center"><TRADENAME> Extended-Release Chewable Tablets</p>			
Package Configuration	Tablet Strength (mg)	NDC	Print
Bottles of 100	20 mg	NDC 24478-120-01	NP 12
Bottles of 100	30 mg	NDC 24478-130-01	NP 13
Bottles of 100	40 mg	NDC 24478-140-01	NP 14

16.2 Storage and Handling

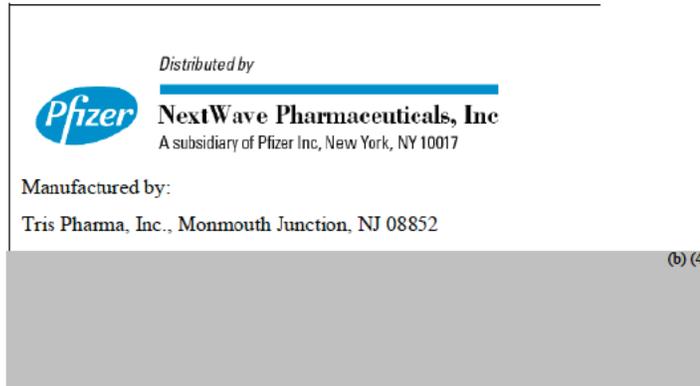
Store at 25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature.]

Disposal

Comply with laws and regulations on drug disposal. (b) (4)

Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	Expression of product strength is in salt form.	Not acceptable. Should be expressed as the free base form which is active moiety. See Assessment of "Full Prescribing Information" Section # 3: Dosage Forms and Strengths for detail.
Available units (e.g., bottles of 100 tablets)	Bottle of 100	Acceptable
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See above reproduced Full Prescribing Information Section # 16 for detail	Acceptable with revision of tablet strength expression.
Special handling (e.g., protect from light, do not freeze)	None	Acceptable
Storage conditions	Store at 25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).	Acceptable. Available stability data supports the stated storage conditions.

Manufacturer/distributor name listed at the end of PI, following Section #17



Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	See above reproduced PI	Acceptable

Conclusion: Acceptable. Final package insert language will be finalized with other review disciplines during labeling meetings.

2. Labels

1) Immediate Container (HDPE bottle) Label



(b) (4)



Reviewer's Assessment:

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	The font size and prominence of both proprietary (proposed) and establish name is adequate.	At the time of this review, the proposed proprietary name has not yet been approved by DMEPA. Final decisions on font size and prominence will be made jointly with DMEPA
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))	Expression of product strength is in salt form.	Not acceptable. Should be expressed as the free base form which is active moiety. See Assessment of "Full Prescribing Information" Section # 3: Dosage Forms and Strengths for detail.
Net contents (21 CFR 201.51(a))	100 tablets	Acceptable
Lot number per 21 CFR 201.18	Space is provided for entry.	Acceptable
Expiration date per 21 CFR 201.17	Space is provided for entry.	Acceptable
"Rx only" statement per 21 CFR 201.100(b)(1)	"Rx only" statement is present	Acceptable
Storage	Store at 25°C (77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).	Acceptable
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)	NDC number for each strength is printed on the label	Acceptable
Bar Code per 21 CFR 201.25(c)(2)**	Printed on the label	Acceptable
Name of manufacturer/distributor	Printed on the label	Acceptable
Others	Keep out of reach of children. (b) (4)	Acceptable

*21 CFR 201.51(h) A drug shall be exempt from compliance with the net quantity declaration required by this section if it is an ointment labeled "sample", "physician's sample", or a substantially similar statement and the contents of the package do not exceed 8 grams.

**Not required for Physician's samples. The bar code requirement does not apply to prescription drugs sold by a manufacturer, repacker, relabeler, or private label distributor directly to patients, but versions of the same drug product that are sold to or used in hospitals are subject to the bar code requirements.

Conclusion: **Acceptable.** Final container label will be finalized with other review disciplines during labeling meetings.

2) Cartons

There is no secondary packaging for the bottles of tablets.

OVERALL ASSESSMENT AND SIGNATURES: LABELING

Reviewer's Assessment and Signature:

Thomas M. Wong
-S

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ou=FDA, ou=People, cn=Thomas M. Wong S
-S, 2.5.4.19200300.100.1.1=1300396790
Date: 2015.10.02 10:59:24 -0400

Secondary Review Comments and Concurrence:

Wendy I. Wilson -S

Digitally signed by Wendy I. Wilson -S
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ou=People, 2.5.4.19200300.100.1.1=1300396790,
cn=Wendy I. Wilson -S
Date: 2015.10.02 11:05:54 -0400

II. List of Deficiencies To Be Communicated

None.

III. Attachments

A. Lifecycle Knowledge Management

a) Drug Product

NOTE: some of this information in the table below is part of DMF 25909 and may need **REDACTION** if released to the applicant.

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/ Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay, Stability	Drug substance appears relatively stable, but can (b)(4) product is controlled in the drug product specification.	L	Release testing, use of dessicant	Acceptable	Ensure that data are provided for hardness if desiccant will be removed.
Physical stability of Tablet Hardness, Friability	The tablet is expected to be more fragile than typical oral tablets and it is stored in 100-count bottles. Includes a coating, so fri	M	In process hardness and friability testing. Use of dessicant in bottle	Acceptable	Ensure that data are provided for hardness if desiccant will be removed.
Content Uniformity	Tested at release. Will require evaluation as the (b)(4) likely have different particle size distribution than the excipients and the unbound drug substance. Contains a functional score for the lower strengths – will require evaluation.	M	Assay content uniformity at release. Dissolution content uniformity will be carried out during validation and scale up.	Acceptable	(b)(4)
Physical stability (solid state)	(b)(4) The multiple modified release coatings are susceptible to degradation. Extended release	L	(b)(4) studies showed that chewing is unlikely to impact the ER coating. Stability data indicate that the	Acceptable	N/A

	coating could be compromised with chewing.		coating is stable.		
Palatability	(b) (4)	M	Several flavors and sweeteners are added. No data on issues during clinical studies. (b) (4)	Acceptable	N/A
Microbial Limits		L	Data found acceptable	Acceptable	
Disintegration	Test required?	M	N/A As tablet is not designed to disintegrate.	Acceptable	
Dissolution	Drug substance appears relatively stable, (b) (4) product is controlled in the drug product specification.	M	Acceptance criteria for both in-process and release dissolution tests were discussed with the applicant during the review cycle.	Acceptable	
Alcohol dose dumping			Invitro data found dose dumping at higher ethanol concentration. Information will be added to label	Acceptable	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

Application #: 207960 **Submission Type:** 505 (b)(2)

Established/Proper Name:
Methylphenidate HCl Extended
Release Chewable Tablets

Applicant: Pfizer Inc. **Letter Date:** 4 February 2015

Dosage Form: Chewable
Tablet

Chemical Type: 3 **Stamp Date:** 4 February 2015

Strength: 20, 30, 40 mg

A. FILING CONCLUSION				
	Parameter	Yes	No	Comment
1.	DOES THE OFFICE OF PHARMACEUTICAL QUALITY RECOMMEND THE APPLICATION TO BE FILED?	X		The Application is fileable.
2.	If the application is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			
3.	Are there any potential review issues to be forwarded to the Applicant, not including any filing comments stated above?	X		Refer to biopharmaceutics comment to be conveyed to the applicant. Other comments are being prepared for the DMF holder. Note the DMF comments may need to be redacted if this document is released to the Applicant.

B. NOTEWORTHY ELEMENTS OF THE APPLICATION		Yes	No	Comment
Product Type				
1.	New Molecular Entity ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
2.	Botanical ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
3.	Naturally-derived Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
4.	Narrow Therapeutic Index Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
5.	PET Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
6.	PEPFAR Drug	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
7.	Sterile Drug Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
8.	Transdermal ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
9.	Pediatric form/dose ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
10.	Locally acting drug ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
11.	Lyophilized product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
12.	First generic ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
13.	Solid dispersion product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
14.	Oral disintegrating tablet ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
15.	Modified release product ¹	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
16.	Liposome product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
17.	Biosimilar product ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Combination Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
19.	Other	<input checked="" type="checkbox"/>	<input type="checkbox"/>	Extended Release Chewable Tablet

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Regulatory Considerations				
20.	USAN Name Assigned	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
21.	End of Phase II/Pre-NDA Agreements	<input checked="" type="checkbox"/>	<input type="checkbox"/>	PreIND meeting and PreNDA meeting with questions about stability protocol, tablet score
22.	SPOTS (Special Products On-line Tracking System)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
23.	Citizen Petition and/or Controlled Correspondence Linked to the Application	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
24.	Comparability Protocol(s) ²	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
25.	Other	<input type="checkbox"/>	<input type="checkbox"/>	
Quality Considerations				
26.	Drug Substance Overage	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
27.	Design Space	Formulation	<input type="checkbox"/>	<input checked="" type="checkbox"/>
28.		Process	<input type="checkbox"/>	<input checked="" type="checkbox"/>
29.		Analytical Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>
30.		Other	<input type="checkbox"/>	<input checked="" type="checkbox"/>
31.	Real Time Release Testing (RTRT)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
32.	Parametric Release in lieu of Sterility Testing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
33.	Alternative Microbiological Test Methods	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
34.	Process Analytical Technology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
35.	Non-compendial Analytical Procedures and/or specifications	Drug Product	<input type="checkbox"/>	<input checked="" type="checkbox"/>
36.		Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>
37.		Microbial	<input type="checkbox"/>	<input checked="" type="checkbox"/>
38.	Unique analytical methodology ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
39.	Excipients of Human or Animal Origin	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
40.	Novel Excipients	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
41.	Nanomaterials ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
42.	Hold Times Exceeding 30 Days	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
43.	Genotoxic Impurities or Structural Alerts	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
44.	Continuous Manufacturing	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
45.	Other unique manufacturing process ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
46.	Use of Models for Release (IVIVC, dissolution models for real time release).	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
47.	New delivery system or dosage form ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
48.	Novel BE study designs	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
49.	New product design ¹	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
50.	Other	<input type="checkbox"/>	<input type="checkbox"/>	Chewable tablets

¹Contact Office of Testing and Research for review team considerations

²Contact Post Marketing Assessment staff for review team considerations

C. FILING CONSIDERATIONS					
	Parameter	Yes	No	N/A	Comment
GENERAL/ADMINISTRATIVE					
1.	Has an environmental assessment report or categorical exclusion been provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
2.	Is the Quality Overall Summary (QOS) organized adequately and legible? Is there sufficient	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS				
information in the following sections to conduct a review? <input type="checkbox"/> Drug Substance <input type="checkbox"/> Drug Product <input type="checkbox"/> Appendices <ul style="list-style-type: none"> <input type="checkbox"/> Facilities and Equipment <input type="checkbox"/> Adventitious Agents Safety Evaluation <input type="checkbox"/> Novel Excipients <input type="checkbox"/> Regional Information <ul style="list-style-type: none"> <input type="checkbox"/> Executed Batch Records <input type="checkbox"/> Method Validation Package <input type="checkbox"/> Comparability Protocols 				
FACILITY INFORMATION				
3. Are drug substance manufacturing sites, drug product manufacturing sites, and additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet? For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? For each site, does the application list: <ul style="list-style-type: none"> <input type="checkbox"/> Name of facility, <input type="checkbox"/> Full address of facility including street, city, state, country <input type="checkbox"/> FEI number for facility (if previously registered with FDA) <input type="checkbox"/> Full name and title, telephone, fax number and email for on-site contact person. <input type="checkbox"/> Is the manufacturing responsibility and function identified for each facility, and <input type="checkbox"/> DMF number (if applicable) 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
4. Is a statement provided that all facilities are ready for GMP inspection at the time of submission? For BLA: <ul style="list-style-type: none"> <input type="checkbox"/> Is a manufacturing schedule provided? <input type="checkbox"/> Is the schedule feasible to conduct an inspection within the review cycle? 	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
DRUG SUBSTANCE INFORMATION				
5. For DMF review, are DMF # identified and authorization letter(s), included US Agent Letter of Authorization provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	No LoA to the drug substance manufacturer – but may not be needed as it is in the drug product DMF.
6. Is the Drug Substance section [3.2.S] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	Most information is in the cross referenced DMF for the drug substance.

**OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW**

C. FILING CONSIDERATIONS				
	<ul style="list-style-type: none"> <input type="checkbox"/> general information <input type="checkbox"/> manufacture <ul style="list-style-type: none"> ○ Includes production data on drug substance manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots – BLA only ○ Includes complete description of product lots and their uses during development – BLA only <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) – BLA only <input type="checkbox"/> reference standards or materials <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment 			
DRUG PRODUCT INFORMATION				
7.	<p>Is the Drug Product section [3.2.P] organized adequately and legible? Is there sufficient information in the following sections to conduct a review?</p> <ul style="list-style-type: none"> <input type="checkbox"/> Description and Composition of the Drug Product <input type="checkbox"/> Pharmaceutical Development <ul style="list-style-type: none"> ○ Includes descriptions of changes in the manufacturing process from material used in clinical to commercial production lots ○ Includes complete description of product lots and their uses during development <input type="checkbox"/> Manufacture <ul style="list-style-type: none"> ○ If sterile, are sterilization validation studies submitted? For aseptic processes, are bacterial challenge studies submitted to support the proposed filter? 	☒	<input type="checkbox"/>	<input type="checkbox"/>

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS				
	<ul style="list-style-type: none"> <input type="checkbox"/> Control of Excipients <input type="checkbox"/> Control of Drug Product <ul style="list-style-type: none"> ○ Includes production data on drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es) ○ Includes data to demonstrate process consistency (i.e. data on process validation lots) ○ Includes data to demonstrate comparability of product to be marketed to that used in the clinical trials (when significant changes in manufacturing processes or facilities have occurred) ○ Analytical validation package for release test procedures, including dissolution <input type="checkbox"/> Reference Standards or Materials <input type="checkbox"/> Container Closure System <ul style="list-style-type: none"> ○ Include data outlined in container closure guidance document <input type="checkbox"/> Stability <ul style="list-style-type: none"> ○ Includes data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment <input type="checkbox"/> APPENDICES <input type="checkbox"/> REGIONAL INFORMATION 			
BIOPHARMACEUTICS				
8.	<p>Does the application contain dissolution data?</p> <ul style="list-style-type: none"> • Is the dissolution test part of the DP specifications? • Does the application contain the dissolution method development report including data supporting the discriminating ability? 	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<p>Yes. Dissolution is part of the DP specification. The proposed dissolution method is as follows: <u>Apparatus:</u> USP II (Paddle) <u>Temp:</u> 37 °C <u>Volume:</u> 900 mL <u>Rotational Speed:</u> 75 rpm <u>Medium:</u> 0.4M K₂H₂PO₄ <u>Sampling Times:</u> ^{(b) (4)} 3 h, and 8 h</p> <p>Section 3.2.P.2 of DMF 025909 contains dissolution method. The proposed dissolution method is based on the method approved for the extended-release powder for oral suspension. The applicant investigates the effect paddle speed and medium pH on dissolution. The applicant provides dissolution data for 7 batches of drug product to justify the selection of dissolution method acceptance criteria. The Applicant investigates the effect of coating level,</p>

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

C. FILING CONSIDERATIONS					
				coating (b) (4) and formulation composition to investigate the discriminating ability of dissolution method The proposed acceptance criterion is: (b) (4) % at 3 h NLT (b) (4) % at 8 h The dissolution method parameters and the proposed acceptance criteria will be a review issue	
9.	If the Biopharmaceutics team is responsible for reviewing the in vivo BA or BE studies: • Does the application contain the complete BA/BE data? • Are the PK files in the correct format? • Is an inspection request needed for the BE study(ies) and complete clinical site information provided?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The Applicant provides 2 pilot PK studies to compare the bioavailability formulation Prototype 1 and Prototype 2 to the extended-release powder for oral suspension. The Applicant combines the comparison of the final formulation (which is used in the Phase III study and is the To-be-marketed formulation) to the IR product and the food effect study in one study. Biopharmaceutics will review the relative bioavailability of the proposed formulation and the IR product. In addition, Biopharmaceutics will review the PK data provided in the 2 pilot studies and Phase I bioavailability study to assess the prolonged release claim. The review of the food effect aspect falls under the purview of Clinical Pharmacology.
10.	Are there adequate in vitro and/or in vivo data supporting the bridging of formulations throughout the drug product's development and/or manufacturing changes to the clinical product? <i>(Note whether the to-be-marketed product is the same product used in the pivotal clinical studies)</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	The basis for approval of this NDA is a Phase I relative bioavailability and food effect study comparing the proposed MPH ERCT to the approved IR product and Phase III classroom efficacy study. The formulation used in the combined relative bioavailability and food effect study is the formulation used in Phase III and the To-be-marketed formulation.
11.	Does the application include a biowaiver request? If yes, are supportive data provided as per the type of waiver requested under the CFR to support the requested waiver? Note the CFR section cited.	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	A relative bioavailability study was conducted using the highest dosage strength, 40 mg. However, no biowaiver request was included for the two lower strengths 20 mg and 30 mg. A comment will be included in the IR.
12.	For a modified release dosage form, does the application include information/data on the in-vitro alcohol dose-dumping potential?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The Applicant provides dissolution data in 5%, 10%, 20%, and 40% (v/v) alcohol in dissolution media.
13.	For an extended release dosage form, is there enough information to assess the extended release designation claim as per the CFR?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	The Applicant provides in vivo data after a single dose of the proposed MP ERCT and IR Product. However, no PK data at

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FILING REVIEW

C. FILING CONSIDERATIONS					
					steady-state to compare the two products. The Applicant references the similarity between the proposed MP ECRT and the extended-release oral suspension product. However, only prototype 2 formulation is compared to the oral suspension in a pilot BE study and not the final proposed formulation. The Applicant mentions that the dissolution profiles of the oral suspension and the proposed formulation are similar in the range of (b) (4) % of label claim but no data was provided.
14.	Is there a claim or request for BCS I designation? If yes, is there sufficient permeability, solubility, stability, and dissolution data?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
REGIONAL INFORMATION AND APPENDICES					
15.	Are any study reports or published articles in a foreign language? If yes, has the translated version been included in the submission for review?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
16.	Are Executed Batch Records for drug substance (if applicable) and drug product available?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
17.	Are the following information available in the Appendices for Biotech Products [3.2.A]? <ul style="list-style-type: none"> <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients 	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
18.	Are the following information available for Biotech Products: <ul style="list-style-type: none"> <input type="checkbox"/> Compliance to 21 CFR 610.9: If not using a test method or process specified by regulation, data are provided to show the alternate is equivalent to that specified by regulation. For example: <ul style="list-style-type: none"> <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> Mycoplasma Compliance to 21 CFR 601.2(a): Identification by lot number and submission upon request, of sample(s) representative of the product to be marketed with summaries of test results for those				

OFFICE OF PHARMACEUTICAL QUALITY
FILING REVIEW

C. FILING CONSIDERATIONS				
samples				

Product Property/Impact of change/CQAs	Factors affecting CQA	O	S	D	FMECA RPN	Comment
Assay, Stability	Drug substance appears relatively stable. (b) (4) product is controlled in the drug product specification.	1	2	6	12	
Physical stability of Tablet Hardness, Friability	The tablet is expected to be more fragile than typical oral tablets and it is stored in 100-count bottles. Includes a coating, so fri	4	2	5	40	Will require evaluation. There is no test for hardness or friability at release or on stability.
Content Uniformity	Tested at release. Will require evaluation as the (b) (4) likely have different particle size distribution than the excipients and the unbound drug substance. Contains a functional score for the lower strengths – will require evaluation.	3	3	4	36	
Physical stability (solid state)	(b) (4) The multiple modified release coatings are susceptible to degradation. Extended release coating could be compromised with chewing.	2	2	5	20	
Palatability	(b) (4)	3	3	4	36	
Microbial Limits		1	2	3	6	
Disintegration	Test required?					

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FILING REVIEW**

Dissolution		3	4	3	48	Medium Risk: based on the data submitted, critical process parameters (such as complexation and pre-coating) were not investigated. The discriminating ability of the method could not be adequately demonstrated based on the data provided. As such, dissolution may not be able to detect large batch-to-batch variations.
Alcohol dose dumping		4	4	4	64	The product exhibit high degree of in vitro dose dumping in presence of 40% alcohol. The clinical relevance will be a matter of review.

RPN 25-60 is considered **moderate** risk; RPN > 60 is considered as **high** risk.

General CMC Notes:

Drug substance: Check that we do not need LoA to drug substance DMF in the NDA.

Drug product: All data is referred to DMF 25909. This was reviewed in the context of the IND, but will require a complete reevaluation in the context of the proposed NDA. Tablets of three strengths are proposed. (b) (4)

1. (b) (4)
2. (b) (4)
3. (b) (4)

(b) (4)

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FILING REVIEW

(b) (4)



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Table 3.2.P.5.1-1. Release Specifications for Methylphenidate HCl Extended-Release Chewable Tablets – 20 mg

Test/ Method	Method Number	Acceptance Criteria
Description	M-074-ASY	Speckled, off white, capsule shaped coated tablet, debossed with "NP 12" on one side and bisect on the other side
Identity By UPLC	M-074-ASY	
(A) By Retention Time		The retention time of the major peak in the chromatogram of the sample preparation corresponds to that in the chromatogram of the standard preparation as obtained in the assay
(B) By UV-PDA		The Lambda Max of the major peak in the spectrum of the sample preparation corresponds to that in the spectrum of the standard preparation as obtained in the assay
Uniformity of Dosage Units – Content Uniformity	M-074-ASY	Meets the requirements USP <905>AV<15.0
Assay	M-074-ASY	(b) (4) % of the labeled amount
Dissolution	M-074-DIS	3-hr (b) (4) 8-hr (b) (4)
Impurities	M-074-IMP1	Specified Impurities: (b) (4)
(b) (4)		

(b) (4)

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FILING REVIEW

DMF 25909

1. *It is not clear which? medium pH is proposed in your dissolution method. In the dissolution method development report, dissolution data summarized in Table 13 for Lot TB-104A do not match with any of the dissolution data (at pH 1.2, 4.5, and 6.8) for the same Lot in Table 19. Similarly, for Lot TB-103A data in Table 13 do not match with any dissolution data for the same lot in Table 29. Clarify the differences observed in both cases.* (b) (4)
(b) (4)
2. *The dissolution testing was performed* (b) (4)
(b) (4)
(b) (4) Provide data using the proposed dissolution method parameters (i.e. 75 rpm).
3. *Provide data (tabulated and graphical form) showing the capability of the PROPOSED dissolution method to discriminate toward critical attributes* (b) (4)
(b) (4) In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e. aberrant formulations and manufacturing conditions) for the most relevant formulation and manufacturing variables (e.g. drug substance particle size, hardness, etc.).
4. *There is no IVIVC approved for your proposed product. Therefore, the selection of the dissolution acceptance criteria limits for the ER portion of your drug product should be based on the mean target value $\pm 10\%$ variation and NLT 80% for the last specification time-point. In addition, the IR component should release the drug in a range between* (b) (4) % of the labeled amount
(b) (4) Revised the specifications table with the updated acceptance criteria for the dissolution test.
5. *Include the individual dissolution data in tabular and graphical format using the proposed dissolution method and provide the dissolution profile comparisons (e.g., f2 testing) for the two batches (Prototype 1 and 2) tested in BE study B7491003 (pilot).*

NDA 207960

1. *The submission of bioequivalence (BE) and/or bioavailability (BA) information for the lower strengths of your proposed product may be waived if the following CFR requirements are met:*
 - *Inclusion of the biowaiver request as part of the NDA submission;*
 - *All the strengths of your proposed drug product have the same dosage form;*
 - *There is BA/BE data for the highest strength;*

OFFICE OF PHARMACEUTICAL QUALITY

FILING REVIEW

- *The lower strengths are proportionally similar in its active and inactive ingredients to the highest strength of your proposed product;*
 - *All the strengths of your proposed product have the same manufacturing process and have the same drug release mechanism; and*
 - *Dissolution profile comparisons between the highest and lower strengths in three different dissolution media (e.g., pH 1.2, 4.5 and 6.8) meet the similarity requirements (e.g. f2 testing).*
2. The following information should be submitted to support the extended release designation claim (refer also to CFR 320.25f):
- *The BA profile established for the drug product rules out the occurrence of any dose dumping;*
 - *The drug product's steady-state performance is comparable (e.g., degree of fluctuation is similar or lower) to a currently marketed non-controlled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.*
 - *The drug product's formulation provides consistent pharmacokinetic performance between individual dosage units;*
 - *The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.*

David J.
Claffey -S

Digitally signed by David J. Claffey -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=13002255
65, cn=David J. Claffey -S
Date: 2015.04.21 21:07:16 -0400'