CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212994Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 212994
Assessment 1

Drug Product Name	Serdexmethylphenidate and Dexmethylphenidate (SDX/d-MPH)
Dosage Form	capsule
Strength	26.1/5.2 mg SDX/d-MPH 39.2/7.8 mg SDX/d-MPH 52.3/10.4 mg SDX/d-MPH
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Commave Therapeutics SA
US agent, if applicable	James Bammert

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document #1; eCTD 0001	2 Mar 20	All, original NDA
Supporting document #12; eCTD 0012	1 Sep 20	Drug substance, drug product, biopharmaceutics, process/manufacturing
Supporting document #13; eCTD 0013	11 Sep 20	Drug product
Supporting document #17; eCTD 0017	30 Sep 20	Drug substance, drug product, biopharmaceutics, process/manufacturing

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sam Bain	Donna Christner
Drug Product	Renish Delvadia	Julia Pinto
Manufacturing	Yoon Oh	Tony Huang
Microbiology	N/A	N/A
Biopharmaceutics	Jia Yin	Ta-Chen Wu

Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Renish Delvadia	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends approval of this application based on drug substance, drug product, process/facilities and biopharmaceutics reviews.

The data provided by the Applicant support the proposed 24 month shelf-life when stored at 20°–25° (68°–77° F).

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

The drug product title will be serdexmethylphenidate and dexmethylphenidate [SDX/d-MPH] however for reference the salt forms will be included here: serdexmethylphenidate chloride and dexmethylphenidate hydrochloride.

The SDX/d-MPH Capsules are (b) (4) capsules manufactured using (b) (4) SDX and (b) (4) (b) (4) d-MPH HCl active drug substances. The capsules are comprised of hypromellose.
The final drug product contains fixed ratios of 30% d-MPH HCl and 70% d-MPH HCl equivalents from the SDX drug substance.
SDX/d-MPH Capsules are packaged in a white high-density polyethylene (HDPE) bottle with a (b) (4) closure.

The data provided by the Applicant support the proposed 24 month shelf-life when stored at 20°–25° (68°–77° F).

Proposed Indication(s) including Intended Patient Population	For the treatment of attention-deficit/hyperactivity disorder (ADHD) in patients 6 years of age and older

Duration of Treatment	chronic
Maximum Daily Dose	52.3 mg serdexmethylphenidate /10.4 mg d-methylphenidate as free base or 56 mg serdexmethylphenidate Chloride /12 mg d-methylphenidate HCl as salt
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance, Serdexmethylphenidate Chloride (SDX), is manufactured (b) (4) (b) (4) Dexmethylphenidate (d-MPH), is actually the other drug substance for the drug product of this NDA. The choices (b) (4) (b) (4) are consistent with ICH Q11 guidelines and were found acceptable by the Agency in the pre-NDA meeting on 31-JAN-2019. (b) (4) (b) (4)

The drug substance container closure system components, (b) (4) (b) (4) are adequate.

The drug substance is stable (b) (4) (b) (4). Based upon the submitted data, the proposed retest period of (b) (4) months for the drug substance is acceptable.

For the drug substance Dexmethylphenidate Hydrochloride, the NDA applicant references Type II DMF (b) (4), which has been found adequate by the Agency. The applicant has provided the DMF holder's synthetic scheme for the drug substance in the NDA. The DMF holder is actually the NDA applicant as well.

The drug substance is manufactured via (b) (4) (b) (4). Based upon the synthetic process, the drug substance is not expected to contain any genotoxic impurity.

The drug substance specification is the same as that of the DMF holder. It is also in line with the USP monograph of Merthylphenidate Hydrochloride, which is the racemic mixture of the drug substance and its enantiomer. All individual impurity limits are within ICH Q3A guidelines except for one, (b) (4), at NMT (b) (4)%, which is the same as that in the listed drug (NDA 021802) for this 505(b)(2) NDA 212994.

Based upon stability data in DMF (b) (4), the DMF holder currently has a retest period of (b) (4) years for the substance, for the shelf-life storage condition of the long-term stability testing condition (b) (4)

Drug Product: Adequate

The proposed drug product, serdexmethylphenidate (as serdexmethylphenidate chloride; also referred to SDX or KP145 in the submission and this review) and dexmethylphenidate (as dexmethylphenidate HCl, also referred to as d-MPH) capsules, is formulated as an immediate release fixed-dose combination of SDX with d-MPH. The three proposed strengths of SDX/d-MPH Capsules (i.e., SDX 'base'/ d-MPH base [mg] : 26.1/5.2, 39.2/7.8, and 52.3/10.4) are (b) (4) (b) (4) capsules manufactured (b) (4). SDX is a prodrug of d-MPH.
Capsules are packaged in white high-density polyethylene (HDPE) bottles with (b) (4) closures.

Both APIs are highly soluble in aqueous solutions at ambient temperature and therefore easy to extract using a small volume of aqueous vehicles. Also, the formulation is a (b) (4) powder (b) (4) (b) (4), it can be readily snorted without need for any manipulation.

The data provided by the Applicant support the proposed 24-months of shelf-life for the all three strengths.

Labeling: Adequate

Manufacturing: Adequate

(b) (4)

All facilities proposed for commercial manufacturing are acceptable for proposed responsibilities.

Biopharmaceutics: Adequate

In support of the application, the Applicant conducted a pivotal BA/BE study and a food effect study on the highest proposed strength (SDX/d-MPH 56/12 mg), as well as a dose proportionality study using all strengths of the proposed drug product. No biowaiver request was made by the Applicant.

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting 1) formulation bridging between the pivotal clinical batch and the commercial batch, 2) the proposed dissolution method and acceptance criterion, and 3) the alcohol dose-dumping potential of the proposed drug product. The key review findings are summarized as follows:

1) Formulation Bridging: The formulation used in all pivotal clinical studies is the same as the proposed commercial formulation. No in vitro or in vivo formulation bridging study is needed.

2) Dissolution Method and Acceptance Criterion: The revised dissolution method (USP Apparatus 2, 50 rpm, 500 mL 0.1N HCl) for all strengths of the proposed drug product is considered acceptable, per the 2018 Dissolution Guidance for oral drug product containing highly soluble drug substance (SDX and d-MPH). The dissolution test condition is as recommended in the Guidance. Further investigation for discriminating ability of the dissolution method is deemed unnecessary also per the same Guidance. The Applicant's proposed dissolution acceptance criterion of NLT (b) (4) % (Q) at 30 minutes is acceptable based on the provided dissolution profile data.

3) Alcohol Dose-Dumping Potential: The provided dissolution profile data show that drug releases from the lowest and the highest strengths (28 mg/6 mg and 56 mg/12 mg) were not significantly affected in the presence of 5% or 40% (v/v) alcohol. Considering the dosage form, drug release characteristics, and location of the reported prodrug conversion, the results are acceptable, and no additional investigation is necessary.

RECOMMENDATION:
Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212994 for (b) (4) (SDX/d-MPH) Immediate Release Capsules is deemed adequate for approval.

Microbiology (if applicable): Choose an item.

N/A

C. Risk Assessment

From Initial Risk Identification			Assessment		
Attribute/ CQA	**Factors that can impact the CQA**	**Initial Risk Ranking**	**Risk Mitigation Approach**	**Final Risk Evaluation**	**Lifecycle Considerations / Comments**
Assay, Stability	• Formulation • Container closure • Raw materials • Process parameters • Scale/ equipment • Site	L	(b) (4)	Acceptable	

Physical stability (solid state)	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L	(b) (4)	Acceptable	
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L		Acceptable	
Microbial limits	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L		Acceptable	
Dissolution	• Formulation • Raw materials • Process parameters • Scale/ equipment • Site	L		Acceptable	

D. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (Deficiencies that affect multiple sub-disciplines)

2. Drug Substance Deficiencies

3. Drug Product Deficiencies

4. Labeling Deficiencies

5. Manufacturing Deficiencies

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

8. Other Deficiencies (Specify discipline, such as Environmental)

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)		3	12 Aug 20	Last reviewed by Steve Kinsley
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		

Action codes for DMF Table:
1 – DMF Reviewed.
2 –Type 1 DMF
3 – Reviewed previously and no revision since last review
4 – Sufficient information in application
5 – Authority to reference not granted
6 – DMF not available

7 – Other (explain under "Comments")

B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	21802	Focalin XR
IND	130463	

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics				
Pharmacology/Toxicology				
CDRH-ODE				
CDRH-OC				
Clinical				
Other				

Valerie Amspacher

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Date: 11/02/2020 01:07:22PM
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1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	(b) (4)	In July 30, 2020 correspondence the Applicant withdraw the conditionally approved name, (b) (4) Change (b) (4) to AZSTARYS throughout the document accordingly.
Established name(s)	(b) (4) (serdexmethylphenidate and dexmethylphenidate) capsules	Acceptable
Route(s) of administration	capsules, for oral use	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Change to "Capsules (serdexmethylphenidate/ dexmethylphenidate): 26.1/5.2 mg, 39.2/7.8 mg, 52.3/10.4 mg" Serdexmethyphenidate strengths need to be corrected to one decimal accuracy throughout the document . i.e., 26.1/5.2 mg, 39.2/7.8 mg, 52.3/10.4 mg

Reference ID: 4695893

Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

Reference ID: 4695893

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	(b) (4) may be taken whole or the capsule may be opened and the entire contents sprinkled into water or applesauce. (b) (4)	Acceptable

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Capsules	Adequate
Strength(s) in metric system	(b) (4) [redacted]	Change to: "Capsules: •26.1/5.2 mg – blue cap/grey body, imprinted with "286" on cap and "KP415" on the body •39.2/7.8 mg – dark blue cap/grey body, imprinted with "429" on cap and "KP415" on the body •52.3/10.4 mg – orange cap/grey body, imprinted with "5612" on cap and "KP415" on the body)"
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance	Applied	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	See above	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	N/A
For injectable drug products for parental administration, use appropriate labeling term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	N/A

1.2.3 Section 11 (DESCRIPTION)

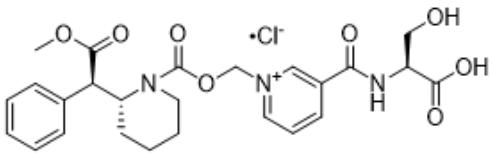
Reference ID: 4695893

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	(b) (4)	Change to AZSTARYS (serdexmethylphenidate and dexmethylphenidate) capsules)
Dosage form(s) and route(s) of administration	Capsule; oral	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	(b) (4)	Change to "AZSTARYS contains 26.1/5.2, 39.2/7.8 or 52.3/10.4 mg of serdexmethylphenidate/ dexmethylphenidate (equivalent to 28/6, 42/9 or 56/12 mg of serdexmethylphenidate chloride/ dexmethylphenidate hydrochloride, respectively., The combined molar dose of serdexmethylphenidate and dexmethylphenidate in each dosage strength of (b) (4) is equivalent to 20, 30 or 40 mg dexmethylphenidate hydrochloride, respectively (equivalent to 17.3, 25.9 or 34.6 mg dexmethylphenidate free base, respectively). "

List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	(b) (4) (b) (4) inactive ingredients: colloidal silicon dioxide, crospovidone, hypromellose, magnesium stearate, microcrystalline cellulose, and talc. Each strength capsule also contains colorant ingredients in the capsule shell as follows: • (b) (4)/5.2 mg: Back Iron Oxide, FD&C Blue No. 1, Titanium Dioxide • (b) (4)/7.8 mg: Black Iron Oxide, FD&C Blue No. 1, FD&C Red No. 40, Titanium Dioxide • (b) (4)/10.4 mg: Black Iron Oxide, FD&C Red No. 40, FD&C Yellow No. 6, Titanium Dioxide	Correct the strength to one decimal accuracy.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	dexmethylphenidate, a CNS stimulant	Pharmacological class of serdexmethylphenidate not included in the label.
Chemical name, structural formula, molecular weight	See excerpt from the proposed label below this table	Adequate.

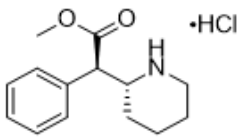
If radioactive, statement of important nuclear characteristics.		
Other important chemical or physical properties (such as pKa or pH)	See excerpt from the proposed label below this table	Adequate
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., “synthesized and developed by Drug Company X,” “structurally unique molecular entity”	N/A	

The chemical name of serdexmethylphenidate chloride is 3-(((*1S*)-1-carboxy-2-hydroxyethyl)carbamoyl)-1-((((*2R*)-2-(2-(*1R*)-methoxy-2-oxo-1-phenylethyl)piperidine-1-carbonyl)oxy)methyl)pyridinium chloride. Its molecular formula is $C_{25}H_{30}N_3O_8^+ \bullet Cl^-$, and its structural formula is:



Serdexmethylphenidate chloride (b) (4) is a white to off-white crystalline powder. Its solutions are acid to litmus. It is freely soluble in water, soluble in methanol, and slightly soluble in alcohol and acetone. Its molecular weight is 535.98 g/mol.

The chemical name of dexmethylphenidate hydrochloride is methyl (*R*)-2-phenyl-2-((*R*)-piperidin-2-yl)acetate hydrochloride. Its molecular formula is $C_{14}H_{19}NO_2 \bullet HCl$, and its structural formula is:



Dexmethylphenidate hydrochloride is a white to off-white 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.

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	capsules	
Strength(s) in metric system	(b) (4)/5.2 mg, (b) (4)/7.8 mg, (b) (4)/10.4 mg	Correct the strength to one decimal accuracy.
Available units (e.g., bottles of 100 tablets)	Bottles of 100	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	See excerpt below this table from the proposed label	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

- (b) (4)***/5.2 mg Capsules*** – blue cap/grey body (imprinted with "286" on cap and "KP415" on the body)
  Bottles of 100..... NDC (b) (4)
- (b) (4)***/7.8 mg Capsules*** – dark blue cap/grey body (imprinted with "429" on cap and "KP415" on the body)
  Bottles of 100..... NDC (b) (4)
- (b) (4)***/10.4 mg Capsules*** – orange cap/grey body (imprinted with "5612" on cap and "KP415" on the body)
  Bottles of 100..... NDC (b) (4)

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Information Provided in the NDA	Assessor's Comments

Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to “Dispense in original container,” provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	Protect from moisture. Dispense in tight container (USP). Disposal Comply with local laws and regulations on drug disposal of CNS stimulants. Dispose of remaining, unused, or expired (b) (4) 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 (b) (4) 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 (b) (4) in the household trash.	Adequate
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°C to 25°C (68°F to 77°F). Excursions permitted between 15°C to 30°C (59°F to 86°F). [See USP Controlled Room Temperature].	Adequate
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: “Not made with natural rubber latex. Avoid statements such as “latex-free.”	N/A	N/A
Include information about child-resistant packaging	N/A	N/A

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.

1.2.6 Manufacturing Information After Section 17 (for drug products)

Item	Information Provided in the NDA	Assessor's Comments
Manufacturing Information After Section 17		
Name and location of business (street address, city, state and zip code) of the manufacturer, distributor, and/or packer	(b) (4)	Adequate

2.0 CARTON AND CONTAINER LABELING

3.1 Container Label

3.2 Carton Labeling

N/A

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Azstarys serdexmethyphenedate and methylphenidate capsules	Adequate
Dosage strength	26.1 mg/5.2 mg, 39.2 mg/7.8 mg, 52.3 mg/10.4 mg	Adequate
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Included	Adequate
Net contents (e.g. tablet count)	100	Adequate
"Rx only" displayed on the principal display	Yes	Adequate
NDC number	Included	Adequate
Lot number and expiration date	Included	Adequate
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Included	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Included	Noted

Reference ID: 4695893

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Included	Adequate
Medication Guide (if applicable)	References	Adequate
No text on Ferrule and Cap overseal	N/A	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available	N/A	

Assessment of Carton and Container Labeling: *Adequate*

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date: Renishkumar Delvadia, 10/20/2020

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto, 10/20/2020

Reference ID: 4695893

Renishkumar Delvadia

Digitally signed by Renishkumar Delvadia
Date: 10/30/2020 07:08:35AM
GUID: 5388ee7d000671ff7781f1835a3ff7b9

Julia Pinto

Digitally signed by Julia Pinto
Date: 10/30/2020 11:02:50AM
GUID: 5050dbcb00001294a888a4bdc20a3a58

BIOPHARMACEUTICS ASSESSMENT

NDA: 212994
Submission Type: 505(b)(2)
Drug Product Name / Strength: (b) (4) (Serdexmethylphenidate chloride (SDX) and Dexmethylphenidate hydrochloride (d-MPH))/ 28 mg/6 mg, 42 mg/9 mg, 56 mg/12 mg
Dosage Form: Immediate Release Capsule
Route of Administration: Oral
Applicant: Commave Therapeutics SA
Indication: Treatment of attention deficient hyperactivity disorder (ADHD) in patients 6 years and older
Submission Date: 3/2/2020
Primary Reviewer: Jia Yin, Ph.D.
Secondary Reviewer: Ta-Chen Wu, Ph.D.

Background: The Applicant seeks approval for (b) (4) (Serdexmethylphenidate chloride (SDX) and Dexmethylphenidate hydrochloride (d-MPH)) via 505(b)(2) pathway for the treatment of attention deficient hyperactivity disorder (ADHD) in patients 6 years and older. The listed drug (LD) is Focalin XR® (dexmethylphenidate hydrochloride extended release capsule) under NDA 021802 (approved in May 2005). The proposed drug product is an immediate-release formulation containing a fixed dose combination of two drug substance: serdexmethylphenidate chloride (SDX) and dexmethylphenidate hydrochloride (d-MPH). Serdexmethylphenidate chloride is an inactive prodrug of d-MPH and is claimed as a new chemical entity (NCE) by the Applicant.

In support of the application, the Applicant conducted a pivotal BA/BE study and a food effect study on the highest proposed strength (SDX/d-MPH 56/12 mg), as well as a dose-proportionality study using all strengths of the proposed drug product. No biowaiver request was made by the Applicant.

REVIEW SUMMARY

The Biopharmaceutics review was focused on the evaluation of the adequacy of the overall information/data supporting **1)** formulation bridging between the pivotal clinical batch and the commercial batch, **2)** the proposed dissolution method and acceptance criterion, and **3)** the alcohol dose-dumping potential of the proposed drug product. The key review findings are summarized as follows:

Reference ID: 4695893

1) ***Formulation Bridging:*** The formulation used in all pivotal clinical studies is the same as the proposed commercial formulation. No in vitro or in vivo formulation bridging study is needed.

2) ***Dissolution Method and Acceptance Criterion:*** The revised dissolution method (USP Apparatus 2, 50 rpm, 500 mL 0.1N HCl) for all strengths of the proposed drug product is considered acceptable, per the 2018 Dissolution Guidance for oral drug product containing highly soluble drug substance (SDX and d-MPH). The dissolution test condition is as recommended in the Guidance. Further investigation for discriminating ability of the dissolution method is deemed unnecessary also per the same Guidance. The Applicant's proposed dissolution acceptance criterion of NLT (b) (4) (Q) at 30 minutes is acceptable based on the provided dissolution profile data.

3) ***Alcohol Dose-Dumping Potential:*** The provided dissolution profile data show that drug releases from the lowest and the highest strengths (28 mg/6 mg and 56 mg/12 mg) were not significantly affected in the presence of 5% or 40% (v/v) alcohol. Considering the dosage form, drug release characteristics, and location of the reported prodrug conversion, the results are acceptable, and no additional investigation is necessary.

RECOMMENDATION:

Based on the review of the overall information, from a Biopharmaceutics perspective, NDA 212994 for (b) (4) (SDX/d-MPH) Immediate Release Capsules is deemed adequate for approval.

Reference ID: 4695893

BIOPHARMACEUTICS ASSESSMENT

I. List Submissions Being Reviewed

Received Date	Submission
3/2/2020	Original submission
9/30/2020	Response to information request (IR) dated 8/11/2020

II. Drug Product

The proposed drug product is an immediate-release formulation containing a fixed-dose combination with a molar ratio of 70% serdexmethylphenidate chloride (SDX) and 30% dexmethylphenidate hydrochloride (d-MPH) (**Table 1**). The SDX/d-MPH capsules are (b) (4) capsules manufactured using (b) (4) (b) (4) SDX and (b) (4) d-MPH (**Table 2**).

Table 1 The amount of SDX and d-MPH in each strength

SDX/d-MPH capsule dosage (in total d-MPH HCl) [mg]	actual mg SDX Cl/d-MPH HCl	d-MPH HCl eq. [mg]	molar dose ratio	SDX 'base'/ d-MPH base [mg]
20	28/6	(b) (4)	70:30	(b) (4) 5.2
30	42/9		70:30	7.8
40	56/12		70:30	10.4

Table 2 Composition of the capsule (b) (4) of the proposed product

Component	Function	w/w%	Strength (SDX/d-MPH)		
			28 mg/6 mg	42 mg/9 mg	56 mg/12 mg
(b) (4)			Quantity (mg/capsule)		
Serdexmethylphenidate chloride	API	(b) (4)	28.00	42.00	56.00
Dexmethylphenidate hydrochloride	API		6.00	9.00	12.00
Microcrystalline cellulose, USP/NF	(b) (4)				
Crospovidone, USP/NF					
Magnesium stearate, USP/NF					
(b) (4)					
Talc, USP/NF					
Colloidal silicon dioxide, USP/NF					
(b) (4)					
Total (b) (4) per Capsule					(b) (4)

Dexmethylphenidate hydrochloride is the active API. The immediate-release formulation of d-MPH provides an early onset of the pharmacological effect. Serdexmethylphenidate

Reference ID: 4695893

chloride is an inactive prodrug of d-MPH. Based on the Applicant's pharmacokinetic (PK) findings, less than 3% of orally administered SDX is absorbed systematically. More than 97% oral dose of SDX stays within the gastrointestinal (GI) tract and converts slowly in the lower intestine to d-MPH. The exact mechanism underlying the conversion of SDX to d-MPH remains unknown. Due to the intrinsic property of the prodrug (SDX) molecule, the proposed product exhibits an extended-release PK profile of the active API, d-MPH.

As SDX/d-MPH 28 mg/6 mg, 42 mg/9mg, and 56 mg/12 mg is equivalent to total d-MPH 20 mg, 40 mg, and 60 mg. In the following review, strength 28 mg/6 mg, 42 mg/9mg, and 56 mg/12 mg and strength 20 mg, 40 mg, and 60 mg will be used interchangeably.

III. Formulation Bridging

The formulation development started with (b) (4) (b) (4). The first formulation (Formulation1) was used in initial PK studies. The results indicated relative low d-MPH exposure during the first several hours post-dose. In order to provide an earlier onset and adequate d-MPH exposure through the day, (b) (4) (b) (4) was added to the formulation. The final formulation (Formulation 3) was used in all pivotal clinical studies and is also the proposed commercial formulation (**Table 3**). No in vitro or in vivo formulation bridging study is needed.

Table 3. Formulations used in clinical studies

Study Description	Dosage type; Strength; Route	Formulation Reference	Final Formulation
Pharmacokinetics (PK) / Bioavailability (BA)			
KP415.102: Single Oral Dose PK	SDX capsule; 20 mg, 40 mg, 60 mg; oral	Table 6	No
KP415.108: Pilot Food Effect Study	SDX capsule; 60 mg; oral	Table 6	No
KP415.105: PK study in children and adolescents with ADHD	SDX/d-MPH capsule; 28 mg/6 mg; 56 mg/ 12 mg; oral	Table 8 (CTM)	**Yes**
KP415.104: Food Effect Study	SDX/d-MPH capsule; 56/12 mg; oral	Table 8 (Registration Batch)	**Yes**
KP415.110: PK Dose Proportionality and Steady State Study of SDX/d-MPH Capsules	SDX/d-MPH capsule; 28/6 mg, 42/9 mg, 56/12 mg; oral	Table 8 Registration Batch)	**Yes**
KP415.107: Bioavailability Study Comparing SDX/d-MPH Capsules to Focalin® XR	SDX/d-MPH capsule; 56/12 mg; oral	Table 8 (Registration Batch)	**Yes**
Efficacy/Safety			
KP415.E01: Laboratory classroom efficacy study with SDX in children with ADHD	SDX/d-MPH capsule; 28/6 mg, 42/9 mg, 56/12 mg; oral	Table 8 (CTM)	**Yes**
KP415.S01: Open-label Safety study with SDX in children with ADHD	SDX/d-MPH capsule; 28/6 mg, 42/9 mg, 56/12 mg; oral	Table 8 (Registration Batch)	**Yes**
Human Abuse Potential			
KP415.A01: Oral Human Abuse Potential Study	SDX capsule; 60 mg; oral	Table 7	No

IV. Dissolution Method

Reviewer's Assessment:

Reference ID: 4695893

The initially proposed dissolution method was deemed unacceptable due to inadequate justification (b) (4)

(b) (4)

In addition, the Applicant did not investigate the discriminating ability of the proposed dissolution method. An Information request (IR) was sent out on 8/11/2020 (**Appendix 1**), requesting the Applicant to develop a (b) (4) method for (b) (4) the proposed drug product and submit a complete dissolution method development report, including data to support the discriminating ability of the proposed dissolution method. In response, the Applicant modified the initially proposed dissolution method

(b) (4)

(b) (4) to be in line with dissolution condition in 2018 FDA Dissolution Guidance for oral drug product containing highly soluble drug substance. Referring to the same Guidance, the Applicant stated that as the dissolution condition in the Guidance is adopted, the demonstration of the discriminating ability of the dissolution method is not required.

This Reviewer determined that justification for selection of dissolution parameters (USP Apparatus 2, 50 rpm, 500 mL 0.1N HCl) is reasonable, as both APIs (SDX and d-MPH) are highly soluble and the Applicant adopted the dissolution condition in the 2018 Dissolution Guidance for oral drug product containing highly soluble drug substance. It is noted that the provided dissolution data using the modified dissolution method showed large variability at time points up to 30 minutes, likely attributed by the HPMC capsule shell. This Reviewer also agreed that no additional investigation of discriminating ability is necessary based on the high solubility of the both APIs and drug release characteristics of the drug product, as per the same 2018 Guidance.

Proposed Dissolution Method

The initially proposed dissolution method (**Table 4**) was deemed unacceptable and an information request (IR) was sent to the Applicant on 8/11/2020 regarding the dissolution method. In response (**Appendix 1**), the Applicant proposed a new dissolution method (**Table 5**).

Reference ID: 4695893

Table 4. Proposed dissolution method in the original submission

(b) (4)

[redacted]

Table 5. Proposed dissolution method in response to IR dated 8/11/2020

Apparatus:	USP Apparatus II (Rotating Paddles)
Sample Size:	N=12 single capsules with (b) (4) sinkers (Release)
	N=6 single capsules with (b) (4) sinkers (Stability)
Paddle Speed:	50 RPM
Media Temperature:	37.0°C ± 0.5°C
Sampling Times, profile:	10, 15, 20, 30, and 45 minutes
Dissolution Medium:	0.1N Hydrochloric Acid, degassed
Medium Volume:	500 mL

(b) (4)

[redacted]

Reference ID: 4695893

(b) (4)

Reviewer's Assessment

The justification (b) (4) in the originally proposed method (b) (4) is inadequate. (b) (4)

(b) (4)

(b) (4) An information request (IR) was sent to the Applicant on 8/11/2020, requesting the Applicant to develop a (b) (4) method for (b) (4) (b) (4) the proposed drug product (**Appendix 1**). In response, the Applicant changed the dissolution (b) (4) of the proposed product, referring to the dissolution condition in 2018 FDA Dissolution Guidance. The selection of 500 mL

Reference ID: 4695893

dissolution medium volume is acceptable. The selection of 0.1 N HCl dissolution medium is also deemed acceptable.

(b) (4)

Reference ID: 4695893

(b) (4)

Discriminating Ability of the Dissolution Method

Despite the Agency's recommendation in the End-of-Phase 2 (EOP2) meeting for IND 130463 (dated 11/14/2017) that the Applicant should evaluate the discriminating ability of the proposed dissolution method, the Applicant has not conducted the recommended study to demonstrate the discriminating ability of the proposed dissolution method in support of the NDA. In the IR dated 8/11/2020, the Applicant was again requested to investigate the discriminating ability of the proposed dissolution method, referring back to the EOP2 meeting minutes for IND 130463 (**Appendix 1**). In response, the Applicant modified the proposed dissolution method to be in line with the dissolution condition described in the 2018 FDA Dissolution Guidance for drug product containing highly soluble drug substance. Referring to the same Guidance, the Applicant justified that as the dissolution condition in the Guidance is adopted, the demonstration of the discriminating ability of the dissolution method is not required.

This Reviewer determines that the Applicant's changed method/test condition and justification acceptable, per the 2018 Guidance for oral drug product containing highly soluble drug substance.

V. Dissolution Acceptance Criterion

Based on the provided dissolution profile data, the proposed dissolution acceptance criterion is **Q =** (b) (4) **in 30 minutes** is deemed acceptable or each drug substance in all strengths of the proposed drug product for batch release and stability testing.

Dissolution Data

The Applicant submitted dissolution profile data up to 45 minutes (n=12) for one full-scale engineering batch on the commercial equipment and one long-term stability batch at the 31 months stability time-point for each of the three strengths of the proposed product using the modified dissolution method (USP Apparatus 2, 50 rpm, 500 mL 0.1 N HCl). **Table 10-13** show the dissolution profile data of commercial engineering batch and the long-term stability batch for the highest strength, 56 mg/12 mg. The mean drug release data of all batches conform to the proposed dissolution acceptance criterion (NLT (b) (4) (Q) at 30 min)

Reference ID: 4695893

up to 31 months. The variability is noticeably higher up to 30 minutes for the long-term stability batches at 31 months.

Table 10 Dissolution of SDX from a commercial engineering batch of SDX/d-MPH capsule (56 mg/12 mg)

	% Label Claim – SDX – Engineering Batch T13320, 56 mg/ 12mg				
	10 min	15 min	20 min	30 min	45 min
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean					
RSD					

Table 11 Dissolution of d-MPH from a commercial engineering batch of SDX/d-MPH capsule (56 mg/12 mg)

	% Label Claim – d-MPH – Engineering Batch T13320, 56 mg/ 12mg				
	10 min	15 min	20 min	30 min	45 min
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean					
RSD					

Reference ID: 4695893

Table 12 Dissolution of SDX from a long-term stability batch of SDX/d-MPH capsule (56 mg/12 mg) at 31 months stability time point

	% Label Claim – SDX – Registration Batch M10425, 56 mg/ 12mg				
	10 min	15 min	20 min	30 min	45 min
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean					
RSD					

Table 13 Dissolution of d-MPH from a long-term stability batch of SDX/d-MPH capsule (56 mg/12 mg) at 31 months stability time point

	% Label Claim – d-MPH – Registration Batch M10425, 56 mg/ 12mg				
	10 min	15 min	20 min	30 min	45 min
1	(b) (4)				
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Mean					
RSD					

In Vitro Alcohol-Induced Dose-Dumping Study

Reviewer's Assessment:

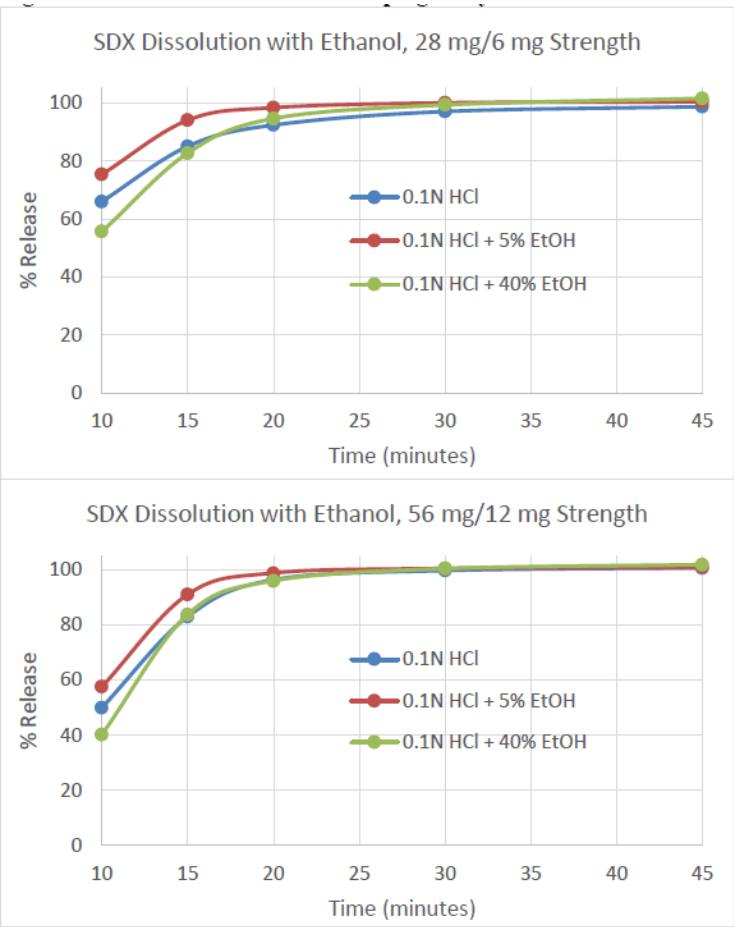
Based on the provided dissolution data for SDX and the calculated f2 values for SDX and d-MPH dissolution, this Reviewer agrees that no in vitro alcohol dose-dumping is observed and slight changes in drug release is unlikely to be clinically meaningful. It is this Reviewer's view that considering the dosage form, drug release characteristics, and location of the reported prodrug conversion, the provide results are acceptable and no additional investigation is necessary.

Reference ID: 4695893

Due to the intrinsic property of the prodrug (SDX) molecule, the proposed product exhibits an extended-release PK profile of the active API, d-MPH. The Applicant was recommended to investigate the in vitro alcohol dose dumping potential of the proposed product in the End-of-Phase 2 (EOP2) meeting on 11/14/2017.

In vitro alcohol dose-dumping potential of SDX/d-MPH capsules was evaluated on the lowest and the highest strengths (28 mg/6 mg and 56 mg/12 mg) with 5% and 40% alcohol (**Figure 1**). Results of similarity factor (f2) calculation (f2 >50) support the similarity in drug release profiles with 0%, 5%, and 40% (v/v) alcohol.

Figure 1 Dissolution of SDX from SDX/d-MPH capsule (28 mg/6 mg ad 56 mg/12 mg) in alcohol dose dumping study



Reference ID: 4695893

Appendix 1
Biopharmaceutics Information Requests (IRs)

IR #1 dated 8/11/2020 and Response received 9/30/2020[1]

1. For the proposed dissolution methods, we note that the provided data and justification do not support the selection [redacted]. No data were submitted in support of the selection of other dissolution parameters (e.g., apparatus, dissolution medium, sinker). In addition, the discriminating ability of the proposed dissolution method has not been investigated. Please refer to the meeting minutes (including Additional Biopharmaceutics Comments) for the End-of-Phase 2 (EOP2) meeting for IND 130463 (dated 11/14/2017) and submit a complete dissolution method development report with all datasets. Note that for the investigation of the discriminating ability of the proposed dissolution method, the change of critical material attributes (CMAs) and critical process parameters (CPPs) should be within a meaningful range, i.e., ± 20% of target value as the Agency recommends.

2. The provided justification for [redacted] your proposed product is not acceptable (refer to comment 1). We recommend that you develop a [redacted] method for [redacted] the proposed drug product.

3. Collect and provide dissolution profile data for all strengths using the updated/optimized dissolution method at current long-term stability time point.

Applicant's Response to IR #1 dated 9/30/2020

The Applicant modified their dissolution method by adopting the recommended dissolution method in 2018 FDA Dissolution Guidance. As a result, the dissolution medium volume is changed to 500 mL for all strengths. And the paddle rotation speed is changed to 50 rpm. Dissolution data for a commercial engineering batch and a registration stability batch at the current long-term stability time point (31 months) using the updated dissolution method were provided for all three strengths.[2]

Also referring to the 2018 FDA Dissolution Guidance, the Applicant states that using the standard dissolution condition in the Guidance eliminated the requirement to show

[1] \\CDSESUB1\evsprod\nda212994\0012\m1\us\111-information-amendment\response-to-information-request-0012.pdf

[2] \\CDSESUB1\evsprod\nda212994\0017\m3\32-body-data\32p-drug-prod\serdexmethylphenidate-chlori-capsule-[redacted]\32p2-pharm-dev\pharmaceutical-development-2.pdf

Reference ID: 4695893

discriminating ability of the method. As a result, no study was conducted to demonstrate the discriminating ability of the proposed dissolution method.

Reference ID: 4695893

Ta-Chen Wu

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

VALERIE R AMSPACHER
11/02/2020 01:28:53 PM