

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210526Orig1s000

PRODUCT QUALITY REVIEW(S)



Memorandum

To: NDA 210526 file through Julia Pinto Branch Chief, Branch 3, DNDPII
From: Valerie Amspacher, SPQA, Branch 3, DNDPII
Date: 4 Nov 21

Subject: Labeling rationale

This memo is a summary of the decision process behind the labeling required for NDA 210526 DYANAVEL XR (amphetamine) extended-release tablets. The motivation is to align the label with USP<7> (which requires the identification of active ingredients) and the misbranding provisions of the FD&C Act, (e)(1)(A) 50 by adding the established name and quantity and the proportion of each active ingredient. A series of meetings included (at different times) David Claffey, Julia Pinto, Martha Heimann, Jibril Abdus-Samad, Rik Lostritto, Andre Raw, Yana Mille.

This NDA is a line extension from NDA 208147 DYANAVEL XR (amphetamine) extended-release oral suspension. The original question was, *"Should the free, uncomplexed salts dextroamphetamine sulfate and amphetamine aspartate present in the drug product be listed separately in the label"*. They were present in the DYANAVEL XR (amphetamine) extended-release oral suspension (NDA 208147) but omitted in the original label.

From an email written by Jibril Abdus-Samad dated 1 Nov 21:

1. Decision was to include within the labeling the active ingredient names and amounts found in the finished DP in labeling to fulfill FDCA.

2. Decision was to keep the current established name. Here are some of the issues considered during the meeting:

a. Length of time that the ER Oral Suspension was on the market (approved 2015). The approved labeling did not contain the active ingredients.

b. Desire to keep the ER Oral Suspension strength expression (2.5 mg/mL expressed as amphetamine base) the same to prevent confusion amongst HCPs and patients.

c. Consideration of including all the active ingredients in a revised established name such as Amphetamine, Amphetamine Aspartate, (b) (4) and Dextroamphetamine Sulfate ER Tablets or even perhaps Amphetamine and Dextroamphetamine ER Tablets while maintaining the current strength expression (2.5 mg/mL expressed as amphetamine base).

d. Consideration of a "Mixed Salts" type of name.

- The final DP contained (b) (4) that are complexed with sodium polystyrene sulfonate were not salts (i.e., amphetamine (b) (4))

- The currently marketed ADDERALL XR (mixed salts of a single-entity amphetamine product) primary strength is expressed in terms of the total amount of mixed amphetamine salts, while DYANAVEL XR's primary strength is expressed as amphetamine base.

e. Consideration of other similar products contained more than one active ingredient in the final DP but only one ingredient represented in the name (e.g. QUILLICHEW ER (methylphenidate HCl ER chewable tablets) contains both Methylphenidate and Methylphenidate HCl.

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
11/04/2021 01:59:47 PM

JULIA C PINTO
11/04/2021 02:29:51 PM

3rd Review Cycle – Integrated Quality Assessment (IQA)

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Microbiology.....	N/A

RECOMMENDATION

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

NDA 210526 Assessment 3

Drug Product Name	DYANAVEL XR (amphetamine) extended-release Tablets
Dosage Form	tablet
Strength	5 mg, 10 mg, 15 mg and 20 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	22 Mar 2021 - Tris Pharma, Inc. 14 Jun 2019 - Emory Partners, LLC 25 Sep 2017 - Tris Pharma, Inc.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 28; eCTD 0027	4 May 21	Process/facilities, drug product, drug substance, biopharmaceutics

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeffrey Medwid	Donna Christner
Drug Product	N/A	N/A
Manufacturing	Teng (Daisy) Xu	Jonathan Swoboda
Microbiology	N/A	N/A
Biopharmaceutics	Ta-Chen Wu	N/A
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	N/A	N/A

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

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

The proposed 36 month expiry period for the drug product is acceptable when stored at 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).

See previous IQA's in DARRTS and Panorama dated 15 Jun 18 and 18 Dec 20.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This NDA resubmission is for DYANAVEL XR (amphetamine) extended release tablets equivalent to 5 mg, 10 mg, 15 mg and 20 mg amphetamine base.

This resubmission (dated 4 May 21) is in response to a Complete Response Letter (CRL) dated 21 Jan 21. This is the third review of this application.

A previous complete response letter was sent 25 July 2018. The sponsor submitted a response to the CRL on 22 Jul 20.

See previous IQA's in DARRTS and Panorama dated 15 Jun 18 and 18 Dec 20.

The proposed 36 month expiry period for the drug product is acceptable when stored under the recommended room-temperature storage conditions 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).

Proposed Indication(s) including Intended Patient Population	Treatment of Attention Deficit Hyper-activity Disorder (ADHD)
Duration of Treatment	chronic
Maximum Daily Dose	20 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The drug substance was adequate in the last review cycle and remains adequate in this review cycle.

The DP includes API mixtures of Amphetamine. There are three APIs, Amphetamine Aspartate (b) (4), Dextroamphetamine Sulfate and Amphetamine (b) (4). The CMC information of the drugs are cross-referenced to DMF (b) (4) (Amphetamine Aspartate (b) (4)), DMF 15307 (Dextroamphetamine Sulfate), and DMF (b) (4) (Amphetamine (b) (4)). All the DMFs are currently Adequate, and thereby the DS part is found satisfactory to support the NDA 210526.

See also previous IQA's in DARRTS and Panorama dated 15 Jun 18 and 18 Dec 20.

Drug Product: Adequate

The drug product was adequate in the previous review cycle and remains adequate in this review cycle. The sponsor submitted updated excipient specifications with minor clerical changes to remain compliant with USP.

The analytical method for the (b) (4) in Polyvinyl Acetate (b) (4) was updated to remain compliant with USP and a method verification was provided. This is all adequate and has no adverse effect on quality.

See also previous IQA's in DARRTS and Panorama dated 15 Jun 18 and 18 Dec 20.

Labeling: Adequate**Manufacturing: Adequate**

Process was determined to be adequate in the first review cycle and remains adequate in this review cycle.

The follow-up inspection was conducted on 05/03/2021-06/08/2021 for drug product manufacturing facility-TRIS PHARMA, INC./FEI: 3004712471 and the final classification is voluntary action indicated (VAI) (CMS Case# 616290). The official action indication (OAI) alert was removed. The subject facility is recommended adequate for the proposed responsibilities of the application based on the acceptable inspection outcome and profile.

See also previous IQA's in DARRTS and Panorama dated 15 Jun 18 and 18 Dec 20.

Biopharmaceutics: Adequate

The Applicant's proposed process improvement to the dissolution method and justifications are deemed acceptable. No change has been made to the agreed/approved in vitro release (IVR) specifications with

four sampling time-points at 1 hour, 3 hours, 3.25 hours, and 8 hours, as shown in the table below. Additionally, validation results met the protocol criteria. From the Biopharmaceutics perspective the submission is adequate.
See also previous IQA's in DARRTS and Panorama dated 15 Jun 18 and 18 Dec 20.

Microbiology (if applicable): Choose an item.

N/A

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)	(b) (4)	3	Jan 2017	by Xu Yichuan
	II			3	Jun 2017	by Jian Yang
	II			3	May 2019	By Dave Skanchy
	II			4		
	IV			4		
	IV			4		
	IV			4		
	IV			4		
	IV			4		
	IV			4		
	IV			4		
	IV			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		
	III			4		

Action codes for

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*

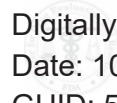
Document	Application Number	Description
IND	129044	
NDA	208147	RLD – Dynavel XR oral suspension
NDA	011522	RLD – Adderall tablets

2. CONSULTS

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



Valerie
Ampacher



Digitally signed by Valerie Ampacher

Date: 10/08/2021 08:54:58AM

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Drug Product.....	24
Environmental.....	N/A
Labeling.....	35
Process/Manufacturing.....	49
Biopharmaceutics.....	57
Microbiology.....	N/A

RECOMMENDATION

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

NDA 210526 Assessment 2

Drug Product Name	DYANAVEL XR (amphetamine) extended-release Tablets
Dosage Form	tablet
Strength	5 mg, 10 mg, 15 mg and 20 mg
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Emory Partners, LLC (previous applicant Tris Pharma, Inc.)
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 21; eCTD 0019	22 Jul 20	Drug product, drug substance, process/facilities, biopharmaceutics

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Jeffrey Medwid	Donna Christner
Drug Product	Stephanie Emory	Julia Pinto
Manufacturing	Teng (Daisy) Xu	Yaodung (Tony) Huang
Microbiology	N/A	N/A
Biopharmaceutics	Ta-Chen Wu	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Stephanie Emory	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommends complete response for this application based on the process/facilities review. Drug substance, drug product and biopharmaceutics all recommend approval.

The proposed 36 month expiry period for the drug product is acceptable when stored under the recommended room-temperature storage conditions 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).

See previous IQA dated 15 Jun 18.

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

This NDA resubmission is for DYANAVEL XR (amphetamine) extended release tablets equivalent to 5 mg, 10 mg, 15 mg and 20 mg amphetamine base.

This resubmission is in response to a Complete Response Letter dated 25 Jul 2018. This is the second review of this application.

The proposed 36 month expiry period for the drug product is acceptable when stored under the recommended room-temperature storage conditions 20°C to 25°C (68°F to 77°F); excursions permitted from 15°C to 30°C (59°F to 86°F).

Proposed Indication(s) including Intended Patient Population	Treatment of Attention Deficit Hyper-activity Disorder (ADHD)
Duration of Treatment	chronic
Maximum Daily Dose	20 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

The DP includes API mixtures of Amphetamine. There are three APIs, Amphetamine Aspartate (b) (4) Dextroamphetamine Sulfate and Amphetamine (b) (4). (b) (4) -

(b) (4)
(b) (4)
(b) (4) thereby the DS part is found satisfactory to support the NDA 210526.

Drug Product: Adequate

The product is an extended-release tablet containing 5, 10, 15, or 20 mg of amphetamine (base equivalent) provided by three salt forms (Amphetamine (b) (4) Dextroamphetamine Sulfate, Amphetamine Aspartate (b) (4) Extended release is achieved (b) (4)

(b) (4)
(b) (4)
(b) (4)
(b) (4) The tablets can be chewed or swallowed without altering the extended-release properties.

No drug product deficiencies were noted during the previous review cycle. The following changes have been made to the application and are the primary focus of this review:

1. Changes to specifications for Triacetin, Amphetamine (b) (4) Dextroamphetamine Sulfate, and Amphetamine Aspartate (b) (4) to align with changes to the USP monographs.
2. Added particle size and (b) (4) testing of drug substances.
3. Additional stability data

The above changes are acceptable. A shelf-life of 36 months is assigned.

Labeling: Adequate

The equivalency statement does not specify the salt forms used as drug substances. In accordance with the USP Salt Policy and related FDA guidance, an appropriate equivalency statement should be determined in consideration of the amphetamine salt forms used and the form(s) present in the finished drug product.

Manufacturing: Inadequate

Withhold recommendation is made in cycle #1 on 05/31/2018 due to the OAI compliance status of drug product manufacturing facility-TRIS PHARMA, INC./FEI: 3004712471. As the surveillance inspection on 03/20/2017 was OAI with WL issued on March 2018. Follow up inspection was conducted on 01/23/2019 and classified OAI and all profiles are to remain with a status of Unacceptable. District File Review (DFR) was sent to check if another follow up inspection would be scheduled before the PDUFA goal date of 01/22/2021. Per DFR response, another follow up inspection is not yet scheduled as of 09/09/2020. The drug product manufacturing facility-TRIS PHARMA, INC./FEI: 3004712471 remains OAI.

Biopharmaceutics: Adequate

In the original NDA review, a three-stage in vitro drug release (IVR) method and acceptance criteria were approved for the routine QC of the finished drug product at batch release and during stability testing. The approved 4-time-points (1 hour, 3 hours, 3.25 hours, 8 hours) acceptance criteria were set based on dissolution profiles generated with (b) (4) sampling timepoints (1 hour, 3 hours, 3 hour 5 minutes, 3 hour 10 minutes, 3 hours 15 minutes, 3 hour 30 minutes, 4 hours, 6 hours, 8 hour (b) (4)).

(b) (4)

From the Biopharmaceutics perspective, resubmission of NDA 210526 for Dyanavel XR (amphetamine) Extended Release Tablets in response to the CR Letter is acceptable.

Microbiology (if applicable): Choose an item.

N/A

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

During a recent inspection of the TRIS PHARMA, INC. (FEI: 3004712471) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

6. Biopharmaceutics Deficiencies

7. Microbiology Deficiencies

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

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

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	II		(b) (4)	3	May 2019	By Dave Skanchy
	II		(b) (4)	4		
	IV		(b) (4)	4		
	IV		(b) (4)	4		
	IV		(b) (4)	4		
	IV		(b) (4)	4		
	IV		(b) (4)	4		
	IV		(b) (4)	4		
	IV		(b) (4)	4		
	IV		(b) (4)	4		
	III		(b) (4)	4		

(b) (4)	III	(b) (4)	4		
	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
IND	129044	
NDA	208147	RLD – Dynavel XR oral suspension
NDA	011522	RLD – Adderall tablets

2. CONSULTS

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



Valerie
Amspacher

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CHAPTER IV: LABELING

1.0 PRESCRIBING INFORMATION (submitted in SD 24)

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	DYANAVEL XR (amphetamine)	Adequate
Established name(s)	extended-release oral suspension, CII	Adequate
Route(s) of administration		Adequate
Controlled substance symbol	DYANAVEL XR (amphetamine) extended-release tablets, for oral use, CII	Adequate
Dosage and Administration Heading in Highlights		
Special instructions	Extended-Release Tablets: May be chewed or swallowed whole	Adequate
	Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine salt compositions and differing pharmacokinetic profiles	Adequate
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	Extended-release tablets: 5 mg (functionally scored), 10 mg, 15 mg, 20 mg	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		Adequate
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	N/A

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

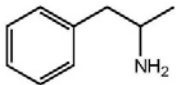
Item	Information Provided in the NDA	Assessor's Comments
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of the reconstituted or diluted product)	DYANAVEL XR tablets may be chewed or swallowed whole	Adequate
	The 5 mg extended-release tablet is functionally scored and may be divided into equal halves for dose adjustments.	Adequate
Other special instructions	Do not substitute for other amphetamine products on a milligram-per-milligram basis, because of different amphetamine salt compositions and differing pharmacokinetic profiles [see Description (11), Clinical Pharmacology (12.3)].	Adequate

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)	DYANAVEL XR (amphetamine) extended-release tablets: • 5 mg: Off-white, speckled, caplet shaped tablet with '5' debossed on one side and functionally scored on the other. • 10 mg: Off-white, speckled, diamond shaped tablet with '10' debossed on one side and plain on the other. • 15 mg: Off-white, speckled, triangle shaped tablet with '15' debossed on one side and plain on the other. • 20 mg: Off-white, speckled, oval shaped tablet with '20' debossed on one side and plain on the other.	Adequate
Strength(s) in metric system		Adequate
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting		Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"		Adequate
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)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	DYANAVEL XR (amphetamine)	Adequate
Dosage form(s) and route(s) of administration	extended-release oral suspension and	Adequate
Pharmacological/therapeutic class	DYANAVEL XR (amphetamine) extended-release tablets are CNS stimulants that contain a 3.2 to 1 ratio of d- to l-amphetamine.	Adequate
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	(b) (4)	The statement does not specify the salt forms used as drug substances. In accordance with the USP Salt Policy and related FDA guidance, an appropriate equivalency statement should be determined in consideration of the amphetamine salt forms used and the form(s) present in the finished drug product.
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	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Statement of being sterile (if applicable)	N/A	N/A

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Chemical name, structural formula, molecular weight	Structural Formula:  <chem>CC(N)Cc1ccccc1</chem> $C_9H_{13}N$ MW 135.21	Provide chemical name
If radioactive, statement of important nuclear characteristics.	N/A	N/A
Other important chemical or physical properties (such as pKa or pH)	DYANAVEL XR extended-release oral suspension and DYANAVEL XR extended-release tablets are intended for oral administration. (b) (4) (b) (4) DYANAVEL XR contains immediate release and extended-release components. (b) (4) (b) (4)	Provide chemical/ physical properties of the drug substances
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Extended-Release Tablets: bubblegum flavor, crospovidone, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl acetate, povidone, silicon dioxide, sodium polystyrene sulfonate, sucralose, talc, triacetin and xanthan gum.	Adequate
For oral prescription drug products, include gluten statement if applicable	N/A	N/A
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	None found	Adequate

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)	DYANAVEL XR (amphetamine) extended-release oral suspension, the concentration is 2.5 mg/mL amphetamine base equivalents and is supplied as light beige to tan viscous suspension with bubblegum flavor in bottles of 464 mL (NDC 27808-102-01).	Adequate
Strength(s) in metric system		Adequate
Available units (e.g., bottles of 100 tablets)		Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	DYANAVEL XR (amphetamine) extended-release tablets are supplied as 5 mg, 10 mg, 15 mg and 20 mg strengths. The 5 mg DYANAVEL XR extended-release tablet is functionally scored (b) (4) and is available as an off-white, speckled, caplet shaped tablet with 5 debossed on one side and scored on the other side, supplied in bottles of 30 (NDC 27808-106-01).	Adequate
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	10 mg DYANAVEL XR extended-release tablet is available as an off-white, speckled, diamond shaped tablet with 10 debossed on one side and plain on the other side, supplied in bottles of 30 (NDC 27808-108-01). 15 mg DYANAVEL XR extended-release tablet is available as an off-white, speckled, triangle shaped tablet with 15 debossed on one side and plain on the other side, supplied in bottles of 30 (NDC 27808-109-01).	Adequate.
Include information about child-resistant packaging	20 mg DYANAVEL XR extended-release tablet is available as an off-white, speckled, oval shaped tablet with 20 debossed on one side and plain on the other side, supplied in bottles of 30 (NDC 27808-110-01).	Specify that the supplied bottles of tablets are child-resistant and contain desiccant.

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

Item	Information Provided in the NDA	Assessor's Comments
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20° to 25°C (68° to 77°F); excursions permitted from 15° to 30°C (59° to 86°F) [see USP Controlled Room Temperature]. DYANAVEL XR oral suspension: The pharmacist should insert the bottle adapter firmly into the neck of the bottle and provide the oral dosing dispenser to the patient when dispensing this product.	Adequate
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	N/A
If the product contains a desiccant, ensure the size and shape differ from the dosage form and desiccant has a warning such as "Do not eat."	From Module 3: The desiccant is a 2-g silica gel canister (b) (4). The dimensions and labeling are unknown.	An IR will be sent to the applicant to confirm the dimensions and labeling of the desiccant canister. This information will not appear in the PI.
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

1.2.5 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	Manufactured by: Tris Pharma, Inc. Monmouth Junction, NJ 08852	Adequate

1.2.6 Structured Product Labeling (submitted in SD 0001)

DYANAVEL XR

amphetamine tablet, chewable, extended release

Product Information

Product Type	HUMAN PRESCRIPTION DRUG	Item Code (Source)	NDC:27808-108
Route of Administration	ORAL	DEA Schedule	CII

Active Ingredient/Active Moiety

Ingredient Name	Basis of Strength	Strength
AMPHETAMINE (UNII: CK833KGX7E) (AMPHETAMINE - UNII:CK833KGX7E)	AMPHETAMINE	5 mg

Inactive Ingredients

Ingredient Name	Strength
CROSPVIDONE (UNII: 2S7830E561)	
GUAR GUM (UNII: E89I1637KE)	
MAGNESIUM STEARATE (UNII: 70097M6I30)	
MANNITOL (UNII: 3OWL53L36A)	
MICROCRYSTALLINE CELLULOSE (UNII: OP1R32D61U)	
POLYVINYL ACETATE (UNII: 32K497ZK2U)	
POVIDONE (UNII: FZ989GH94E)	
SILICON DIOXIDE (UNII: ETJ7Z6XBU4)	
SODIUM POLYSTYRENE SULFONATE (UNII: 1699G8679Z)	
SUCRALOSE (UNII: 96K6UQ3ZD4)	
TALC (UNII: 7SEV7J4R1U)	
TRIACETIN (UNII: XHX3C3X673)	
XANTHAN GUM (UNII: TTV12P4NEE)	

Product Characteristics

Color	WHITE	Score	2 pieces
Shape	OVAL	Size	
Flavor	BUBBLE GUM	Imprint Code	
Contains			

Packaging

#	Item Code	Package Description	Marketing Start Date	Marketing End Date
1	NDC:27808-108-01	30 in 1 BOTTLE, PLASTIC; Type 0: Not a Combination Product	05/31/2018	

Marketing Information

Marketing Category	Application Number or Monograph Citation	Marketing Start Date	Marketing End Date
NDA	NDA210526	05/31/2018	

Assessment of SPL:

(b) (4)

are missing from the inactive ingredients list. Under Product Characteristics, the tablet size and imprint should be listed for each strength. The drug substance manufacturer should be listed as an Establishment.

2.0 PATIENT LABELING

Item	Information Provided in the NDA	Assessor's Comments
Medication Guide		
How should I take DYANAVEL XR?	DYANAVEL XR tablets may be chewed or swallowed whole.	<i>Adequate</i>
How should I store DYANAVEL XR?	- Store DYANAVEL XR at room temperature between 68°F to 77°F (20°C to 25°C). - Store DYANAVEL XR in a safe place, like a locked cabinet. - Dispose of remaining, unused, or expired DYANAVEL XR by a medicine take-back program at authorized collection sites such as retail pharmacies, hospital or clinic pharmacies, and law enforcement locations. If no take-back program or authorized collector is available, mix DYANAVEL XR with an undesirable, nontoxic substance such as dirt, cat litter, or used coffee grounds to make it less appealing to children and pets. Place the mixture in a container such as a sealed plastic bag and throw away DYANAVEL XR in the household trash. Keep DYANAVEL XR and all medicines out of the reach of children.	<i>Add excursion temperature range and reference to USP</i>
What are the ingredients in DYANAVEL XR?	Active ingredient: amphetamine Inactive Ingredients: Extended-release oral suspension: anhydrous citric acid, bubblegum flavor, glycerin, methylparaben, modified (b) (4) starch, polysorbate 80, povidone, polyvinyl acetate, propylparaben, sodium lauryl sulfate, sodium polystyrene sulfonate, sucralose, triacetin and xanthan gum Extended-release tablets: bubblegum flavor, crospovidone, guar gum, magnesium stearate, mannitol, microcrystalline cellulose, polyvinyl acetate, povidone, silicon dioxide, sodium polystyrene sulfonate, sucralose, talc, triacetin and xanthan gum Manufactured by: Tris Pharma, Inc., Monmouth Junction, NJ 08852	<i>Determine if active ingredients should be listed as amphetamine salt forms.</i> (b) (4)

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label (5 mg label shown as example)



Item	Information Provided in the NDA	Assessor's Comments about Container Label
Proprietary name, established name, and dosage form (font size and prominence)	DYANAVEL XR CII (amphetamine) extended-release Tablets	Adequate
Dosage strength	5 mg, 10 mg, 15 mg, or 20 mg	Adequate
Route of administration	Missing	Specify oral use
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	(b) (4)	The statement does not specify the salt forms used as drug substances. In accordance with the USP Salt Policy and related FDA guidance, an appropriate equivalency statement should be determined in consideration of the amphetamine salt forms used and the form(s) present in the finished drug product.
Net contents (e.g. tablet count)	30 Tablets	Adequate
"Rx only" displayed on the principal display	Present	Adequate
NDC number	Present	Adequate
Lot number and expiration date	Present	Adequate

Item	Information Provided in the NDA	Assessor's Comments about Container Label
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Present	Adequate
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	N/A
Other package terms include pharmacy bulk package and imaging bulk package which require "Not for direct infusion" statement.	N/A	N/A
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	N/A
Bar code	Present	Adequate
Name of manufacturer/distributor	Bar code	Present
Medication Guide (if applicable)	N/A	N/A
No text on Ferrule and Cap over seal	No over seal is used	Adequate
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.	None	Adequate. There is no USP monograph for amphetamine extended-release tablets

Assessment of Carton and Container Labeling: Adequate pending resolution of the issues listed above.

ITEMS FOR ADDITIONAL ASSESSMENT

Prescribing Information

Section 11 Description:

1. In accordance with the USP Salt Policy and related FDA guidance, an appropriate equivalency statement should be determined in consideration of the amphetamine salt forms used and the form(s) present in the finished drug product.
2. Provide chemical name for amphetamine
3. Provide chemical/physical properties of the drug substances

Section 16:

4. Specify that the supplied bottles of tablets are child-resistant and contain desiccant.
5. An IR will be sent to the applicant to confirm the dimensions and labeling of the desiccant canister. This information will not appear in the PI.

SPL:

6.  (b) (4)
7. Under Product Characteristics, the tablet size and imprint should be listed for each strength.
8. The drug substance manufacturer should be listed as an Establishment.

MedGuide:

9. Determine if active ingredients should be listed as amphetamine salt forms.
10.  (b) (4)

Container Labels:

11. Specify oral use
12. The statement does not specify the salt forms used as drug substances. In accordance with the USP Salt Policy and related FDA guidance, an appropriate equivalency statement should be determined in consideration of the amphetamine salt forms used and the form(s) present in the finished drug product.



Stephanie
Emory

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Julia
Pinto

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BIOPHARMACEUTICS**NDA:** NDA-210526-ORIG-1-RESUB-21; Class 2 Resubmission**Drug Product Name / Strengths:** Dyanavel XR (Amphetamine) Extended Release
Tablets / 5, 10, 15, 20 mg**Route of Administration:** Oral**Applicant Name:** Emory Partner LLC (Emory), previously Tris Pharma, Inc.**Submission Date:** 07/22/2020**Primary Reviewer:** Ta-Chen Wu, Ph.D.***Background:***

The current resubmission of the NDA 210526 provides a complete response (CR) to deficiencies listed in the CR letter (July 25, 2018) for Dyanavel XR (amphetamine) extended-release tablets. Additionally, the Applicant proposes a 3-year or 36-month expiry period for the drug product stored under the recommended room-temperature storage conditions 20 - 25°C. Among the minor compendial and other changes in the current submission is the Drug Product/Analytical Procedure (Module 3.2.P.5) – dissolution test method (M-108A-DIS3) – for which a change was made to sampling timepoints for drug release during stability testing of the exhibit/registration batches.

Review Summary:

The original 505(b)(2) NDA review was found acceptable and recommended by Dr. Gerlie Gieser for approval from the Biopharmaceutics perspective. A three-stage *in vitro* drug release (IVR) method and the revised acceptance criteria (as tabulated below) were approved for the routine QC of the finished drug product at batch release and during stability testing. The approved 4-time-points acceptance criteria were set based on dissolution profiles generated with 10 sampling timepoints (1 hour, 3 hours, 3 hour 5 minutes, 3 hour 10 minutes, 3 hours 15 minutes, 3 hour 30 minutes, 4 hours, 6 hours, 8 hour (b) (4)).

USP Apparatus	Agitation Speed	Medium Type and Volume (Temperature)	Acceptance criteria
2 (paddle)	50 rpm	500 mL of Stage 1 medium (purified water) for 1 hour, followed by (addition of 200 mL of Stage 2 medium to produce) 700 mL of 0.001N Hydrochloric Acid for next 2 hours, then followed by (addition of 200 mL of Stage 3 medium to produce) 900 mL of pH 6.8 Phosphate Buffer for the remainder of the dissolution testing period; [degassed media] (37 ± 0.5°C)	• NMT (b) (4) at 1 hour • (b) (4) % at 3 hours • (b) (4) % at 3.25 hours • NLT (b) (4) % at 8 hours

The Applicant reported higher dissolution rates for the “3 hours 15 min” time-point for exhibit/registration batch stability samples from 30 months onwards, using the same 10

timepoints collected for 18 and 24 months stability data. The slight overage up to (b) (4) % was reported for dissolution data of Lot TB-165A (5 mg) at 30 and 36 months, Lot TB-170A (10 mg) at 30 months only, and Lot TB-176A (20 mg) at 30 months only. However, the mean dissolution data of all batches at 30 and 36 months conform to the approved acceptance criterion (b) (4) % at 3.25 hours). Consequently, the Applicant proposed a revised sampling scheme to include 9 time-points and remove the (b) (4) time-point for release and stability testing.

The Applicant's counterproposal is deemed acceptable because no change was made to the agreed/approved 4 timepoints and the removal of the last sampling time-point at (b) (4) will unlikely impact the ability of the IVR acceptance criteria to reject the unacceptable drug product batches.

Recommendation:

From the Biopharmaceutics perspective, resubmission of NDA 210526 for Dyanavel XR (amphetamine) Extended Release Tablets in response to the CR Letter is acceptable.



Ta-Chen
Wu

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Valerie
Amspacher

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/s/

VALERIE R AMSPACHER
12/18/2020 10:31:01 AM

Recommendation: Complete Response

NDA 210526

Review #1

Drug Name/Dosage Form	Dyanavel XR (Amphetamine) Extended-Release Tablets
Strength	5 mg, 10 mg, 15 mg and 20 mg
Route of Administration	Oral
Rx/OTC Dispensed	Rx
Applicant	Tris Pharma, Inc.

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
000	09/25/2017	All
0001	11/09/2017	Drug Product
0002	11/22/2017	Biopharmaceutics
0003	12/21/2017	Biopharmaceutics
0005	01/26/2018	Drug Product
0010	03/19/2018	Biopharmaceutics/Process
0011	03/30/2018	Drug Product
0012	04/16/2018	Drug Product
0014	05/29/2018	Biopharmaceutics/Process

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/Drug Substance	Haripada Sarker	Charles Jewell
Drug Product	Rao Kambhampati	Wendy Wilson-Lee
Process	Nathan Davis	Peter Guerrieri
Microbiology		
Facility	Steven Hertz	Ruth Moore
Biopharmaceutics	Gerlie Gieser	Ta-Chen Wu
Regulatory Business Process Manager	Teshara Bouie	
Application Technical Lead	David Claffey	

Quality Review Data Sheet

[IQA Review Guide Reference](#)

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed
(b) (4)	Type II	(b) (4)	(b) (4)	Adequate	See review for details.
	Type II		(b) (4)	Adequate	
	Type II		(b) (4)	Adequate	

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
	NDA 208147 and 11522	Reference products.
	IND 129044	Reference IND.

2. CONSULTS

None.

Executive Summary

I. Recommendations and Conclusion on Approvability

Recommend a **CR action** from a product quality perspective due to the outstanding compliance issues at the Tris Pharma, NJ, drug product manufacturing site. There are no other outstanding product quality issues.

II. Summary of Quality Assessments

A. Product Overview for Dyanavel XR (amphetamine) extended release tablets

The drug product is an extended release oral tablet containing amphetamine in a 3.2:1 enantiomeric ratio. It is designed to be administered in the morning, either chewed or swallowed whole. Marketing of four dosage strengths is proposed (5 mg, 10 mg, 15 mg, and 20 mg). The 5 mg strength has a functional score.

Amphetamine is present as dextroamphetamine sulfate, amphetamine (b) (4) and amphetamine (b) (4).

. This is a (b)(2) application based partially on a near superimposable PK profile to Dyanavel XR oral suspension. This product shares a general design, manufacturing line and most of the major excipients with this reference product. However, the amount of IR and ER components are very different. The oral suspension has (b) (4) IR:ER whereas this product has a (b) (4) IR:ER ratio.

Proposed Indication(s) including Intended Patient Population	Children ages 6 and older for the treatment of Attention Deficit Hyperactivity Disorder (ADHD)
Duration of Treatment	<i>Chronic</i>
Maximum Daily Dose	<i>20 mg</i>
Alternative Methods of Administration	<i>None.</i>

B. Quality Assessment Overview

Dyanavel XR (amphetamine) extended release tablets

The proposed product is an extended-release tablet formulation of amphetamine of four dosage strengths - 5 mg, 10 mg, 15 mg, and 20 mg. The strengths are based on amphetamine base equivalent content. It is designed to be swallowed whole or chewed. This 505(b)(2) NDA relies on the findings of efficacy and safety for two listed drugs - Dyanavel XR (amphetamine) extended release oral suspension (NDA 208147) and Adderall (mixed amphetamine salts) tablets (NDA 11522). It has both immediate and extended release components – a feature shared by many ADHD stimulant extended release products. (b) (4)

(b) (4). The four dosage strengths are compositionally proportional, differing only in tablet weight.

The drug product contains (b) (4) amphetamine components which give a 3.2:1 enantiomeric mixture of dextro to levo amphetamine (b) (4)

(b) (4)

(b) (4).

The reference product Dyanavel XR oral suspension is also manufactured by Tris. The (b) (4)

Drug product components: (b) (4)

(b) (4). The excipients were found acceptable (generally USP/NF). The product will be packaged in 30-count 60 ml white HDPE bottles with 2g desiccant canister with induction liner and PDT closure.

Drug product manufacturing: (b) (4)

(b) (4) The process description and in-process controls were found acceptable.

Drug product release specification: The drug product release specification includes typical tests for an extended release tablet (appearance, ID, CU, assay, microbial limits, isomer ratio, dissolution, impurities).

Long term stability data through 12 months support the proposed (b) (4)-month drug product expiry period. Data supported the functional score on the 5 mg dosage strength.

Biopharmaceutics: (b) (4)

(b) (4) This was replaced with a three-stage method at Agency request. The first stage involves one hour (Apparatus 2, 50 rpm) in purified water with a specified limit of 5%. The next two stages are more typical - 2 hours in dilute acid and the remaining time in pH 6.8 buffer. Note that the (b) (4)

(b) (4) three-stage method was found to be most discriminatory for changes in (b) (4) ratio and (b) (4). Additionally, the original (b) (4) QC method had greater potential for rejecting

batches that were bioequivalent to the target product. Thus, the Biopharmaceutics Review found the final proposed drug product dissolution method and the revised acceptance criteria acceptable. The (b) (4) dissolution method for the (b) (4)

(b) (4) was also found acceptable for this product. Biopharmaceutics accepted the biowaiver request for the strengths <20 mg not evaluated in the pivotal relative BA study. They found that the in vitro studies with 40% alcohol induced dose dumping and that the results support the revised label language. The extended release claim was found to be acceptable based on the superimposable PK profiles compared to the reference Dyanavel XR Oral Suspension product. Dissolution data supported the use of the functional score on the 5 mg strength. Dissolution data of drug product milled for 5 seconds in a coffee grinder showed that its dissolution characteristics were not immediately impacted by mechanical stress.

Drug substance information:

(b) (4)

(b) (4)

Facilities Information: The manufacturing and testing facilities were found to be acceptable by OPF except for the Tris Pharms site for which a withhold recommendation was made due to its current OAI status and March 2018 Warning Letter.

C. Special Product Quality Labeling Recommendations (NDA only)

None.

D. Final Risk Assessment (see Attachment)



David
Claffey

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E. List of Deficiencies for Complete Response**I. Facilities Deficiencies**

- 1) The Tris Pharma manufacturing site has been found to be unacceptable due to compliance deficiencies. These issues will need to be resolved before this application can be approved.

Application Technical Lead Name and Date: David Claffey 14 JUN 2018

BIOPHARMACEUTICS

Product Background:

NDA: 210526; 505(b)(2)

Drug Product Name / Strengths: Dyanavel XR® (Amphetamine) Extended Release Tablets / 5, 10, 15, 20 mg

Route of Administration: Oral

Applicant Name: Tris Pharma, Inc.

Review Recommendation:

From the Biopharmaceutics perspective, NDA 210526 for Dyanavel® XR (amphetamine) Extended Release Tablets is recommended for **APPROVAL**.

Review Summary:

This 505(b)(2) NDA relies for approval on the FDA's findings of efficacy and safety for two Listed Drugs (LDs), i.e., (1) Dyanavel XR® (amphetamine) Extended Release Oral Suspension, 2.5 mg/mL [NDA 208147; Tris Pharma], and (2) Adderall® (mixed amphetamine salts) Tablets [NDA 11522, discontinued; Teva Womens Health]. (b) (4)

This Biopharmaceutics Review focused on the evaluation of the (1) proposed QC *in vitro* drug release (IVR) method and acceptance criteria for the finished drug product, (2) proposed QC *in vitro* drug release method and acceptance criteria for the (b) (4), (3) biowaiver request for the strengths of the proposed drug product not evaluated in the relative BA study conducted to bridge the proposed drug product to Dyanavel XR® Oral Suspension, (4) *in vitro* alcohol induced dose dumping study results, (5) extended release claim, (6) dissolution data to support functional score of the 5 mg strength, (7) dissolution data (b) (4) and (8) formulation bridging.

In Vitro Drug Release Testing of the Finished Product

The currently proposed three-stage *in vitro* drug release method and the revised IVR acceptance criteria (as tabulated below) are approved for the routine QC of all strengths of the finished drug product at batch release and during stability testing.

USP Apparatus	Agitation Speed	Medium Type and Volume (Temperature)	Acceptance criteria*
2 (paddle)	50 rpm	500 mL of Stage 1 medium (purified water) for 1 hour, followed by (addition of 200 mL of Stage 2 medium to produce) 700 mL of 0.001N Hydrochloric Acid for next 2 hours, then followed by (addition of 200 mL of Stage 3 medium to produce) 900 mL of pH 6.8 Phosphate Buffer for the remainder of the dissolution testing period; [degassed media] (37 ± 0.5°C)	• NMT (b) (4) at 1 hour • (b) (4) % at 3 hours • (b) (4) % at 3.25 hours • NLT (b) (4) % at 8 hours

(b) (4)

In Vitro Alcohol-Induced Dose Dumping

A numerical increase in the cumulative *in vitro* drug release of amphetamine from the proposed drug product was observed in 0.1N HCl medium with 40% ethanol but not in acidic medium with 5%, and 20% ethanol.

Extended Release Claim

The proposed drug product can be considered an extended release formulation of amphetamine because (per the Clinical Pharmacology Reviewer) its PK profile is superimposable with that of an already approved Amphetamine extended release product, i.e., Dyanavel® XR Oral Suspension.

Biowaiver Request for the Lower Strengths

The biowaiver request for the 5, 10, and 15 mg strengths of the proposed drug product is acceptable based on evidence of compositional proportionality, same drug release mechanism, similar *in vitro* dissolution profiles to the 20 mg (bio-strength), as well as acceptable relative BA/BE of the biostrength to the Listed Drug.

Functional Score of the Lowest Strength (5 mg)

Manual or mechanical splitting of the 5 mg tablet into equal halves did not impact the *in vitro* dissolution profile of the tablet.

Dissolution of the Ground Tablets

Milling for 5 seconds in a coffee grinder did not significantly impact their *in vitro* dissolution profiles of the tablets.

Formulation Bridging

The proposed commercial drug product has the same (b) (4), manufacturer, (b) (4) and API supplier as the drug product that was evaluated in the pivotal relative bioavailability study.

List of Submissions reviewed:

SDN-1, 9/25/2017 (Original NDA)
SDN-4, 12/21/2017 (Response to Biopharmaceutics Information Request, part 1)
SDN-6, 1/26/2018 (Response to Quality Information Request)
SDN-7, 1/31/2018 (Response to Biopharmaceutics Information Request, part 2)
SDN-11, 3/19/2018 (Response to Quality Information Request)
SDN-14, 4/30/2018 (Response to Biopharmaceutics Information Request)
SDN-15, 5/29/2018 (Response to Biopharmaceutics Information Request)

Concise Description Outstanding Issues Remaining:

None

BCS Designation

The Applicant considers the mixed amphetamine salts as BCS-3 (high solubility/low permeability) drug substances. The two APIs were reported to be soluble to freely soluble in water, and slightly soluble in alcohol.

Reviewer's Assessment: NOT APPLICABLE

BCS-based biowaivers are not applicable for the proposed drug product because in the proposed drug product, the APIs are intended for extended release. The available solubility and dissolution information are provided below for reference purposes only.

Solubility: *High.* Per BCS criteria, the two APIs are highly soluble.

Amphetamine aspartate (b) (4) is soluble in water and slightly soluble in alcohol.
Amphetamine (b) (4) is freely soluble in water (1 part dissolves in 10 parts water); slightly soluble in alcohol (1 part dissolves in 500 parts alcohol);
Dextroamphetamine sulfate Freely soluble in water (1 part dissolves in 10 parts water) and slightly soluble in alcohol (1 part dissolves in 500 parts alcohol).

Permeability: *Data Not Provided*

Dissolution: *Not Rapid (across the physiologic pH range)*

The proposed drug product exhibits rapid to very rapid dissolution in pH 1.2 medium but not in higher pH media and in water, when tested using USP Apparatus 2 (paddle) rotating at 50 rpm and 900 mL media maintained at 37°C ± 0.5°C.

Dissolution Method and Acceptance Criteria – FINISHED DRUG PRODUCT

Per the Applicant, the drug release profile of the proposed drug product is controlled primarily by (b) (4)

(b) (4)

Table 1 compares the parameters of the originally proposed (1-stage) QC IVR method and the 2-stage and 3-stage IVR methods recently developed by the Applicant for the routine QC testing of the proposed drug product.

Table 1. Operating Parameters of *In Vitro* Drug Release Methods Developed for the QC Testing of the Proposed Drug Product

	1-Stage	2-Stage	3-Stage
Apparatus	USP Apparatus II (Paddle)		
Paddle Speed	50 rpm		
Final Media Volume	900 mL (total)		
Medium	(b) (4) 500 mL of Stage 1 medium (purified water) for 1 Hr, followed by (addition of 200 mL of Stage 2 medium to produce) 700 mL of 0.001N Hydrochloric Acid for next 2 Hrs, then followed by (addition of 200 mL of Stage 3 medium to produce) 900 mL of pH 6.8 Phosphate Buffer for the remainder of the dissolution testing period [degassed media]		
Temperature	37°C ± 0.5°C		
Sampling Volume		5 mL	
Sampling Time points for Profile	(b) (4) 1, 3 Hrs, 3 Hr 5 min, 3 Hr 10 min, 3 Hr 15 min, 3 Hr 30 min, 4, 6, 8 and 12 Hrs		

Reviewer's Assessment:***In Vitro Drug Release Method – Three-Stage QC IVR Method Recommended***

Of the three QC IVR methods developed by the Applicant, this Reviewer recommends the 3-stage dissolution method for the routine QC testing of the proposed drug product at batch release and during stability testing for the following reasons:

- (1) [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED] This particular concern was resolved by using the 3-stage IVR method recently developed by the Applicant (see the [Applicant's 1/21/2018 Response to the Biopharmaceutics Information Request dated 11/30/2017](#)).
- (2) In terms of solubility characteristics across the physiologic pH range of the gastrointestinal tract, the proposed drug product contains [REDACTED] (b) (4)
[REDACTED] (b) (4) Amphetamine [REDACTED] (b) (4) complex, [REDACTED] (b) (4)
[REDACTED] (see the [Applicant's 1/26/2018 Response to the Quality Information Request dated 12/22/2017](#)). [REDACTED] (b) (4)
[REDACTED]
[REDACTED]
[REDACTED] The target drug product contains an ER:IR ratio of [REDACTED] TS
- (3) The 1-stage, 2-stage, and 3-stage IVR methods were all discriminating for changes [REDACTED] (b) (4)
[REDACTED] [All three IVR methods are deemed to be biorelevant because they were able to discriminate between prototype formulations of the drug product that were bioequivalent and not bioequivalent to the Listed Drug, i.e. in terms of AUC_{0-5h}, an index for early drug exposure. In terms of AUC_{0-t} and AUC_{0-inf} (indices of total systemic exposure to the drug), the 1-stage method is deemed less optimal because it has greater potential for rejecting batches that are bioequivalent to the target product.] The 3-stage IVR method was demonstrated to offer additional advantages over the originally proposed 1-stage IVR method, as well as the 2-stage IVR method. Unlike the 1-stage IVR method and the 2-stage IVR method, the 3-stage IVR method demonstrated discriminating power for changes in the [REDACTED] (b) (4) rate (Figure 2). Furthermore, the 3-stage IVR method (like the 2-stage method) was observed to possess discriminating power for changes [REDACTED] (b) (4)
[REDACTED] (Figure 3).
- (4) There is a regulatory precedent for the use of a 3-stage *in vitro* drug release method for an amphetamine extended-release drug product. According to the FDA Dissolution Methods Database, a 3-stage IVR method is recommended for the routine QC of Amphetamine Extended Release Capsule, based on the data generated for MYDAYIS®, NDA 022063.

(b) (4)

Analytical Method Validation (3-stage IVR Method)

HPLC with UV detection at 215 nm is used to quantify drug in the dissolution samples. The analytical method was validated for system suitability, linearity, accuracy, range, precision, specificity, solution stability, filter compatibility, robustness (with respect to HPLC parameters), and effect of deaeration procedure. Note that per the Drug Product Reviewer (Dr. Rao Khambhampati) the validation of the analytical method for the three-stage in vitro drug release method is acceptable.

In Vitro Drug Release Acceptance Criteria – REVISED ACCEPTANCE CRITERIA ACCEPTABLE

When using the 3-stage IVR method, the Applicant's initially proposed IVR acceptance criteria were (b) (4)

(b) (4) The Applicant stated that these initially proposed IVR acceptance criteria were based on the method validation data, the bio-batch data, as well as the data generated during feasibility and during development and validation of the new dissolution method.

When using the 3-stage IVR method, the Reviewer's initially recommended acceptance criteria were: 'NMT (b) (4)% at 1 hour', (b) (4)% at 3 hours', '(b) (4)% at 3.25 hours', and 'NLT (b) (4)% at 8 hours'. These IVR acceptance criteria are capable of rejecting unacceptable (e.g., not bioequivalent) drug products similar to those manufactured using an ER:IR ratio of TS and (b) (4) (Figure 1), a (b) (4) (Figure 2), (b) (4) (Figure 3), as well as those with properties similar to ground tablets (Figure 7).

Dissolution on Stability

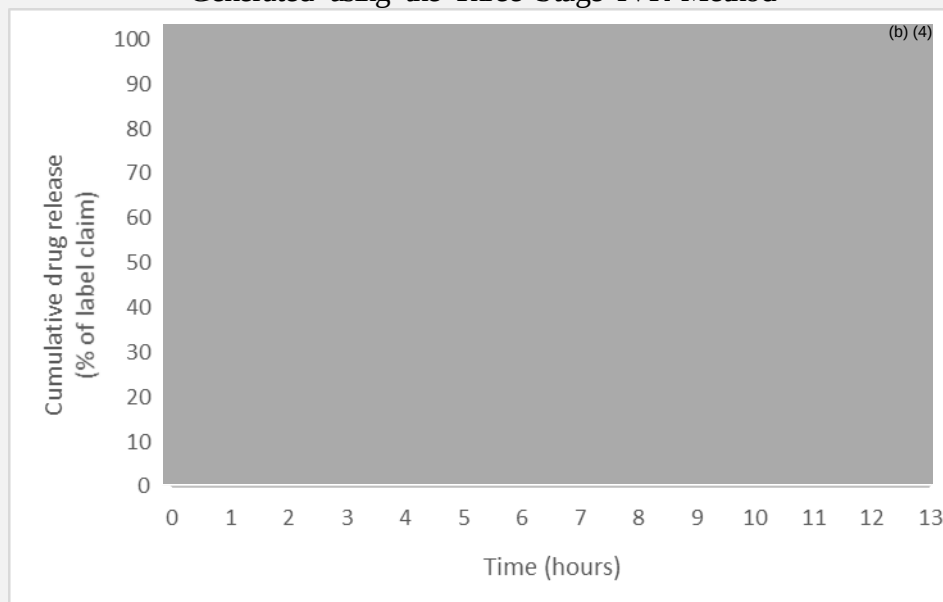
Based on the data provided in the NDA, no trends were observed for *in vitro* drug release during 12 months long-term stability testing of the primary registration stability batches when using the proposed (1-stage) QC IVR method.

Note that based on the IVR data provided for the retained/current samples of the bio-batch/bio-strength at the time of batch release and at Months 3, 12 and 18 months of long-term storage (generated using the 3-stage IVR method; Figure 4), the proposed drug product is expected to conform to this Reviewer's initially recommended acceptance criteria by USP Level 1 Testing (n=6) during its proposed shelf-life (b) (4) months).

In the 5/29/2018 Response to the Biopharmaceutics Information Request dated 5/29/2018 (SDN-15) the Applicant agreed with this Reviewer's recommended acceptance criteria, but counter-proposed (b) (4) % (in lieu of (b) (4) %) for the 3-hour specification time point, based on their review of the in vitro dissolution data of all strengths and the results of their process capability analysis. The Applicant's counterproposal is acceptable because such change does not impact the ability of the IVR acceptance criteria to reject the previously identified unacceptable drug product batches. The Applicant revised the finished product QC specifications to reflect the final FDA recommended IVR acceptance criteria, as shown below

NMT (b) (4) % at 1 hour
(b) (4) % at 3 hours
(b) (4) % at 3.25 hours
NLT (b) (4) % at 8 hours

Figure 4. In Vitro Dissolution Profile of the Retained and the Current Long-Term Stability Samples of the Bio-batch/bio-strength (Lot TB-175A), Generated using the Three-Stage IVR Method



Note: The black markers represent the final *in vitro* drug release tolerance limits.

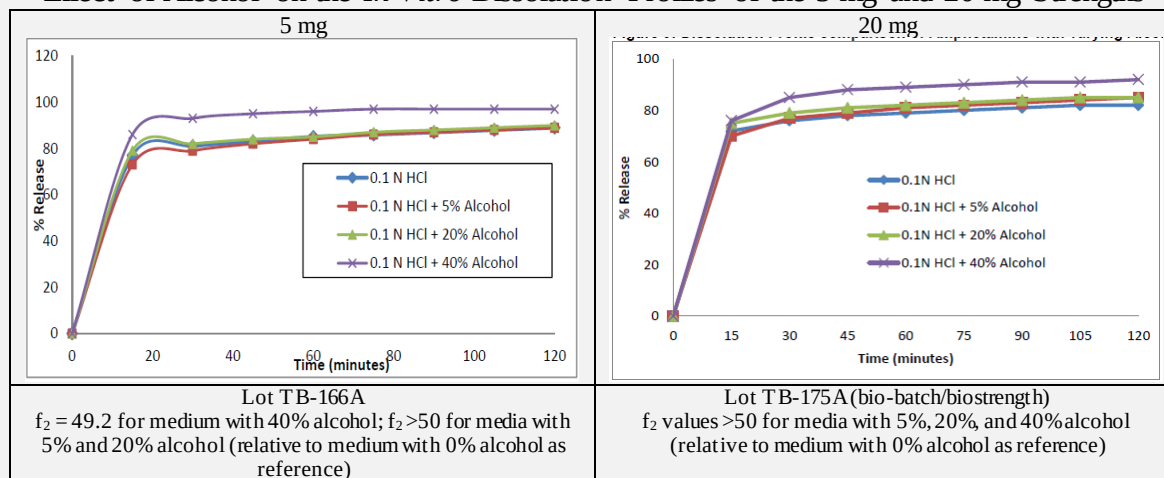
Dissolution Method and Acceptance Criteria – (b) (4)**Reviewer's Assessment:**

(b) (4)

MODIFIED RELEASE ORAL DRUG PRODUCTS–In-Vitro Alcohol Dose Dumping**Reviewer's Assessment: ADEQUATE**

In vitro alcohol induced dose dumping data are available for the lowest strength (5 mg) and the highest strength/biostrength/bio-batch/primary registration stability lot (20 mg, Lot #175A).

Figure 5 shows that for each of these two strengths, there was a numerical increase in the cumulative *in vitro* drug release when 40% ethanol (but not when 5%, and 20% ethanol) was added to 0.1N HCl medium. The labeling of the proposed drug product should reflect the results of this *in vitro* study.

Figure 5.Effect of Alcohol on the *In Vitro* Dissolution Profiles of the 5 mg and 20 mg Strengths

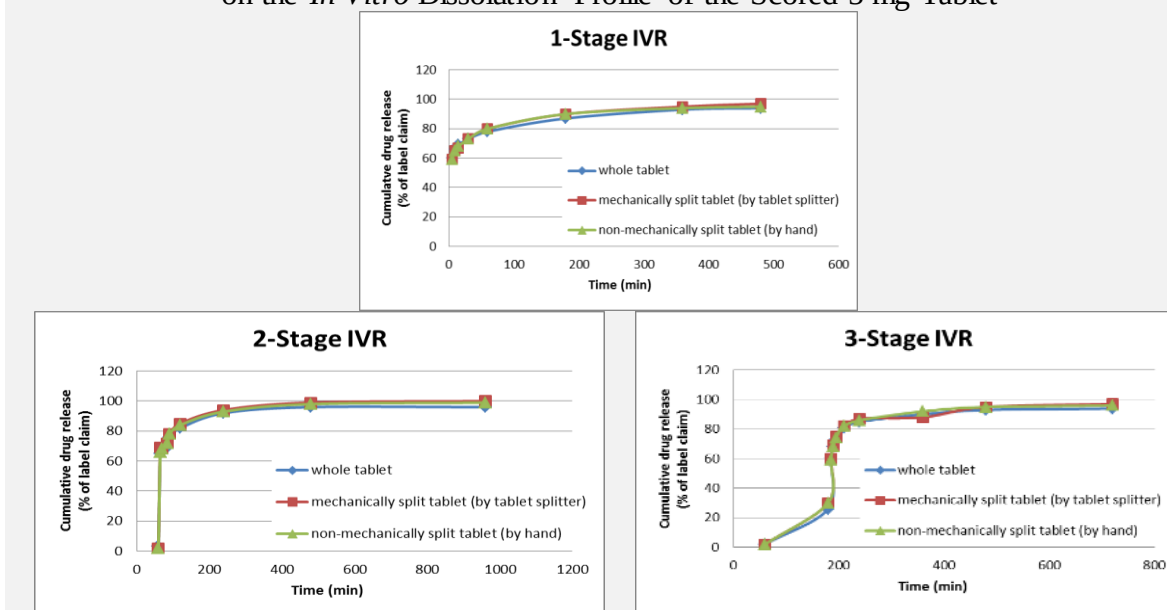
In-Vitro Dissolution of Functionally Scored (5 mg) Tablet: Whole vs Halved

The 5 mg strength is scored to allow for a starting dosage of 2.5 mg daily.

Reviewer's Assessment: ACCEPTABLE

The Applicant evaluated the *in vitro* dissolution profiles of mechanically and non-mechanically split and whole 5 mg tablets in accordance with the FDA Guidance on Tablet Scoring (published in March 2013), using 1-stage, 2-stage, and 3-stage IVR methods. As shown in Figure 6, splitting the 5 mg tablet into equal halves did not appear to impact the *in vitro* dissolution profile of the tablet.

Figure 6. Effect of Mechanical or Non-mechanical Splitting on the *In Vitro* Dissolution Profile of the Scored 5 mg Tablet



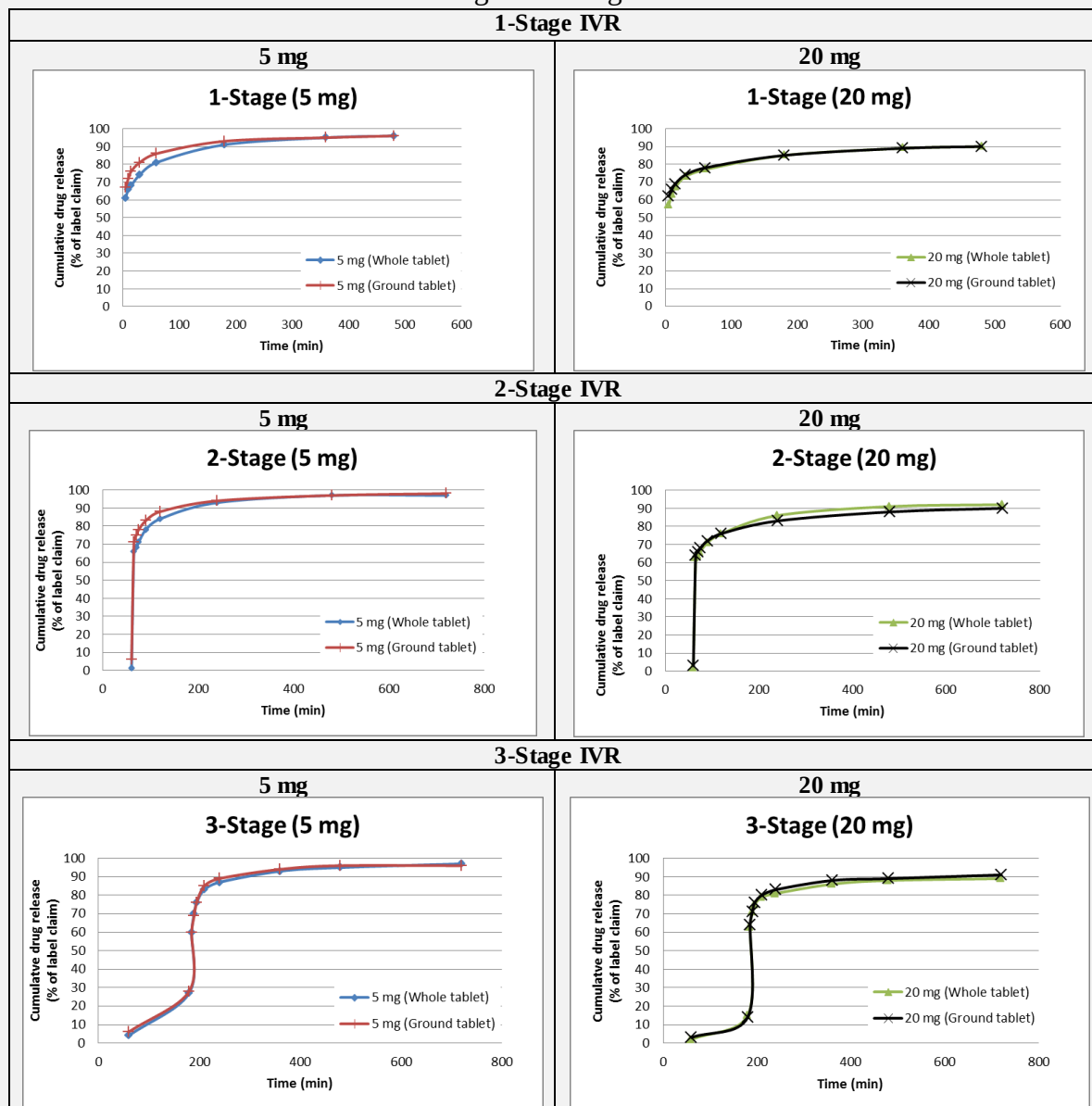
In-Vitro Dissolution of Intact versus Ground Tablets

To demonstrate the integrity of the (b) (4), the Applicant determined the *in vitro* dissolution profiles of 5 mg and 20 mg tablets before and after grinding for 5 seconds in a coffee mill.

Reviewer's Assessment: ACCEPTABLE

Figure 7 compares the *in vitro* drug release profiles of the intact versus the ground tablets (5 mg and 20 mg strengths), generated using the 1-stage, 2-stage and 3-stage QC *in vitro* drug release methods. Under the experimental conditions employed in the grinding study, the *in vitro* drug release rates of the ground tablets were not observed to be significantly different from those of their intact tablet counterparts.

Figure 7. Effect of 5-Second Grinding on *In Vitro* Dissolution Profiles of 5 mg and 20 mg Tablets



*Lots studied: 5 mg (RD0796-078); 20 mg (RD0796-158)

Extended Release Claim

Reviewer's Assessment: ADEQUATE

Single dose PK of the test and reference XR products was determined in Study 2016-4171. Steady-state PK profiles were simulated as confirmed by the Clinical Pharmacology Reviewer (Dr. Huixia Zhang), the PK profiles of the test and the reference XR products are almost superimposable, and an adequate PK bridge is established between the two drug products.

Bridging of Formulations

Formulation bridging data are not needed. The proposed to-be-marketed drug product has the same (b) (4), manufacturer (Tris Pharma), (b) (4) as well as API supplier, as the product that was evaluated in the pivotal relative BA study (Study 2016-4171; Batch # TB-175A) that compared the proposed drug product to the Listed Drug (Dyanavel XR oral suspension). The biostrength is 20 mg.

Note that the pilot relative BA studies used prototype formulations with IR-to-ER ratios different from that in the final to-be-marketed drug product.

Biowaiver Request

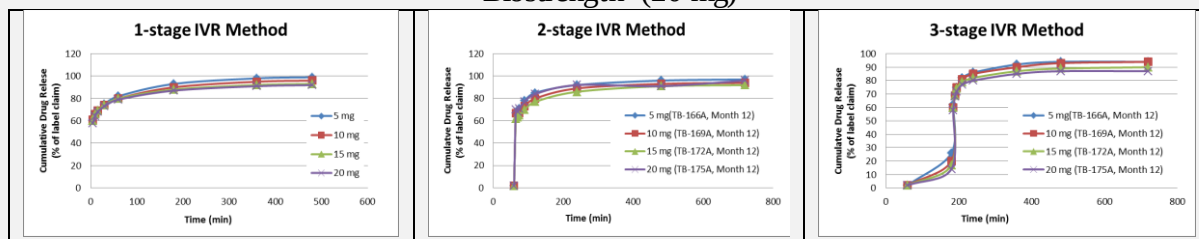
Reviewer's Assessment: ADEQUATE

Pursuant to 21 CFR § 320.22(d)(2), the Applicant requested a waiver to conduct *in vivo* BE studies for the lower strengths (5, 10, and 15 mg) based on compositional proportionality and comparable *in vitro* dissolution profiles to the biostrength (20 mg), and acceptable relative BA data on the bio-strength (20 mg) vs. the Listed Drug (Dyanavel XR® Oral Suspension).

(b) (4), this Reviewer agrees that the 5, 10, and 15 mg strengths are compositionally proportional to the biostrength (20 mg). As shown in Figure 8, the *in vitro* dissolution profiles of the three non-biostrengths are similar to that of the biostrength (with all calculated f_2 values >50 relative to the 20 mg strength), regardless of the QC *in vitro* drug release method used.

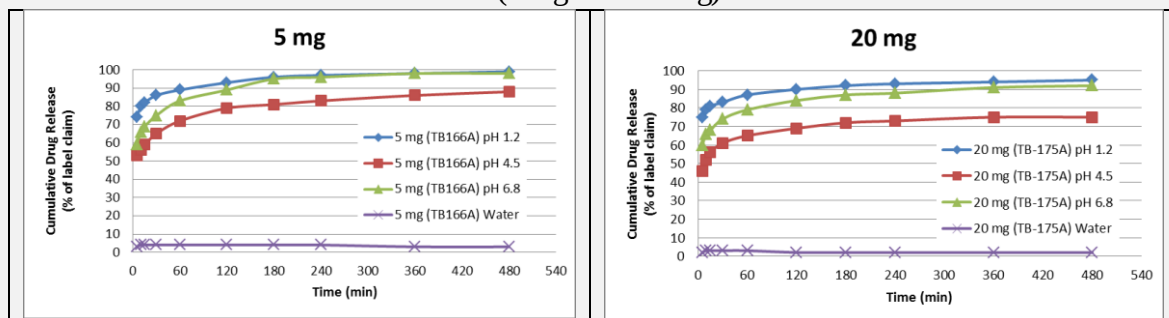
Figure 8.

Comparative *In Vitro* Dissolution Profiles of Non-Biostrengths (5, 10, and 15 mg) vs. Biostrength (20 mg)



Additionally, based on the *in vitro* dissolution profile data provided for the lowest and highest strengths (i.e., 5 mg and 20 mg) in water and in various pH media (as well as in 0.1N HCl with varying concentrations of alcohol), this Reviewer determines that the biowaiver request for the three non-biostrengths can be further supported by evidence of similar *in vitro* drug release profile shapes (b) (4) across strengths via a bracketing approach; see Figure 9. Note that per the approved labeling of Dyanavel XR® Oral Suspension, the recommended dosage range for the Listed Drug is 2.5 to 20 mg daily.

Figure 9. Comparative *In Vitro* Dissolution Profiles of Lowest and Highest Strengths (5 mg and 20 mg)



*USP Apparatus 2 (paddle) rotating at 50rpm, 900 mL of dissolution media; 37 C ± 0.5 C

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date: Gerlie Gieser, Ph.D. (6/5/2018)

Secondary Reviewer Name and Date (and Secondary Summary, as needed): Ta-Chen Wu, Ph.D. (6/5/2018)



Gerlie
Gieser

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Ta-Chen
Wu

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ATTACHMENT I: Final Risk Assessment

A. Final Risk Assessment - NDA

a) Drug Product

Product Property/Impact of change/CQAs	Factors affecting CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations/Comments
Assay, Stability	Drug substance appears relatively stable,	L	(b) (4)	L	
Physical stability of Tablet Hardness, Friability	The tablet may be more fragile than typical oral tablets as it is intended to be chewed. If hardness is too high it could be an issue.	M		L	(b) (4)
Content Uniformity	Tested at release. Will require evaluation (b) (4) _____ _____ _____ _____ _____ _____ Contains a functional score for the lowest strength – will require evaluation. “Dissolution Uniformity” will require evaluation	M		L	
Physical stability (solid state)	(b) (4) should be stable. (b) (4) _____ _____ are susceptible	L		L	

	to degradation. Extended release (b) (4) could be compromised with chewing.		(b) (4)		
Palatability	(b) (4) impact palatability and mouth-feel. Drug load is relatively low and sweeteners and flavors added.	M		L	
Microbial Limits		L		L	
Dissolution		M		L	
Alcohol dose dumping		H		L	



David
Claffey

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NDA 210526 LABELING

[IQA Review Guide Reference](#)

{For NDA Only}

Note: The proposed package insert contains information for the approved oral suspension as well as the proposed oral tablets. This review covers tablets only.

I. Package Insert

1. Highlights of Prescribing Information

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Yes, but needs to be corrected to Dyanavel [®] XR (amphetamine extended-release)
Dosage form, route of administration	Yes
Controlled drug substance symbol (if applicable)	Yes
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Yes

2. Section 2 Dosage and Administration

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Yes

3. Section 3 Dosage Forms and Strengths

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(4))
Available dosage forms	Yes
Strengths: in metric system	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Strength of the free base included but no equivalence statement.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Yes

4. Section 11 Description

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))
Proprietary name and established name	Yes, but needs to be corrected to Dyanavel® XR (amphetamine extended-release)
Dosage form and route of administration	Yes
Active moiety expression of strength with equivalence statement (if applicable)	Expressed for base but no equivalency statements.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Yes
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	Yes
Chemical name, structural formula, molecular weight	Yes for base but no for salts
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	Information regarding (b) (4) was included.

5. Section 16 How Supplied/Storage and Handling

Item	Information Provided in NDA
(Refer to Labeling Review Tool and	21 CFR 201.57(c)(17))
Strength of dosage form	Yes
Available units (e.g., bottles of 100 tablets)	Yes
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Yes
Special handling (e.g., protect from light)	Yes
Storage conditions	Yes
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Yes

Reviewer's Assessment of Package Insert: *Not Adequate*

Prescribing information includes most of the regulatory requirements from the CMC perspective except the following:

- 1) *Throughout the package insert, the name should be changed from (b) (4) to "Dyanavel® XR (amphetamine extended-release)" because XR is USP recommended abbreviation for extended-release.*
- 2) *Description section of the package insert should include the following:*
 - a) *Salt equivalency statements and*
 - b) *Names, structural formulas, and molecular weights of all three active pharmaceutical ingredients.*

II. Labels:**1. Container and Carton Labels**

Bottle labels: Copies of the proposed labels on the 60-cc HDPE bottles containing 30 tablets of 5 mg, 10 mg, 15 mg, or 20 mg strength amphetamine XR extended-release tablets are provided below:

(b) (4)

2. Carton Label

Bottles are not secondary packaged in cartons, therefore, no labels were provided.

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Yes but should be corrected to Dyanavel® XR (amphetamine extended-release)	N/A
Dosage strength	Yes for free base but No for salt equivalency statement	N/A
Net contents	Yes	N/A
“Rx only” displayed prominently on the main panel	Yes	N/A
NDC number (21 CFR 207.35(b)(3)(i))	Yes	N/A
Lot number and expiration date (21 CFR 201.17)	Yes	N/A
Storage conditions	Yes	N/A
Bar code (21CFR 201.25)	Yes	N/A
Name of manufacturer/distributor	Yes	N/A
And others, if space is available	Yes	N/A

Reviewer’s Assessment of Labels: Not Adequate
Labels include most of the regulatory requirements from the CMC perspective except that there is no salt equivalency statement.

List of Deficiencies:

- a) *Throughout the package insert and on container labels, the name should be changed from (b) (4) ” to “Dyanavel® XR (amphetamine extended-release)” because XR is USP recommended abbreviation for extended-release.*
- b) *Salt equivalency statements should be included in the Description section of the package insert and on the container labels.*
- c) *Description section of the package insert should include names, structural formulas, and molecular weights of all three active pharmaceutical ingredients.*

Overall Assessment and Recommendation: *Recommended for corrections as indicated in the List of Deficiencies*

Primary Labeling Reviewer Name and Date: *Rao V. Kambhampati, Ph.D. 6/5/18*

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



Rao
Kambhampati

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Wendy
Wilson- Lee

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