

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**208147Orig1s000**

**CHEMISTRY REVIEW(S)**



*Recommend Approval*

**NDA 208147**  
**Review # 1**  
**Review Date: 18 AUG 2015**

<b>Drug Name/Dosage Form</b>	DYANAVEL XR (amphetamine extended release oral suspension)
<b>Strength</b>	2.5 mg/ml
<b>Route of Administration</b>	Oral
<b>Rx/OTC Dispensed</b>	Rx
<b>Applicant</b>	Tris Pharma Inc.
<b>US agent, if applicable</b>	N/A

<b>SUBMISSION(S) REVIEWED</b>	<b>DOCUMENT DATE</b>
Original Submission (N-000)	12/19/2014
Quality Amendment Response to IR	2/13/2015
Quality Amendment Response to IR	3/16/2015
Quality Amendment Response to IR	4/14/2015
Quality Amendment Response to IR	4/23/2015
Quality Amendment Response to IR	5/11/2015
Response to IR	7/13/2015
Response to IR	8/13/2015
Response to IR	8/14/2015

**Quality Review Team**

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## Quality Review Data Sheet

1. LEGAL BASIS FOR SUBMISSION: 505(b)(2)

2. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	STATUS <sup>1</sup>	DATE REVIEW COMPLETED	COMMENTS
(b) (4)	Type II		(b) (4)	Adequate	Review #14 In DARRTS	LoA provided dt 10/24/13.
	Type II		Adequate	Review #18 In DARRTS	LoA provided, dt 10/24/13	
	Type II		Adequate	Review #13 In DARRTS	LoA provided, dt 10/24/13.	
			N/A			
			N/A			
			N/A			
			N/A			

<sup>1</sup> Adequate, Adequate with Information Request, Deficient, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	116985	Referenced IND
NDA	11522	Listed drug (Adderall Tablets)

3. CONSULTS: N/A

**I. Recommendations**

**A. Recommendation and Conclusion on Approvability**

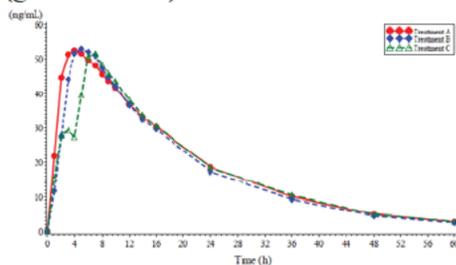
Recommend that this application be approved from a product quality perspective.

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

Recommend post-marketing commitment to develop more discriminatory single-medium dissolution methods for both the drug product and for the extended release (b) (4).

**II. Summary of Quality Assessments**

**Background:** The drug product is single strength (2.5 mg/ml) 16 oz. bulk pharmacy bottle containing amphetamine extended release oral suspension developed to treat Attention Deficit Hyperactivity Disorder (ADHD). The proposed liquid formulation is intended to be more convenient to administer than the currently marketed tablet or capsule amphetamine products. Further, being an extended release formulation it is designed to be administered once daily (in the morning), rather than twice daily for the immediate release amphetamine products. This is a 505(b)(2) application where the listed drug is Adderall Tablets. BE studies were carried out to compare one dose of the proposed product (red and blue, below) with two Adderall tablets taken four hours apart (green below).



(red, fasted; blue fed)

**Design:** The drug product was developed to have both immediate release and extended release components designed in an atypical manner to suit the ADHD patient’s needs. While most extended release products are designed to provide relatively constant drug plasma levels over 24 hours, this product was designed to release ca. 50% of the active within the first hour. This allows the patient the ability to complete necessary tasks in the morning. The remaining half of the drug is released over the morning and afternoon with plasma levels designed to fall in the evening, as higher plasma levels are known to impact the ability to sleep. A 13 hour extended release profile was part of the quality target product profile.

**Product Development:** (b) (4)

(b) (4)

The following table summarizes the (b) (4) commercial formulation:

Table 23. Percentage of Amphetamine (free base equivalent) in the Final Drug Product

Product Component	Percent of amphetamine base in the finished product (%)
(b) (4)	(b) (4)

In summary the amphetamine (free base equivalent) is present in the drug product (b) (4). It should be noted that amphetamine is present in an d:l (b) (4) ratio of 3.2:1. (b) (4)

**Drug product components:** The formulation contains (b) (4) (povidone) and (b) (4) (triacetin), (b) (4) (polysorbate 80), (b) (4) (citric acid), (b) (4) (sucralose), (b) (4) (propyl- and methylparaben), (b) (4) starch and xanthan gum), bubblegum flavor and (b) (4) (glycerin (b) (4)). The excipients were found acceptable (generally USP/NF).

**Packaging and Administration:** The product will be packaged in bulk 16 oz. Amber (b) (4) bottles. The suspension will be filled into smaller bottles at the pharmacy and dispensed to the patient in amber glass bottles with an oral syringe. The product will not be marketed with the smaller bottles or measuring devices – thus they were not part of this application. Regardless, the applicant was asked to provide data to demonstrate that the bulk bottle could be dispensed into smaller typical bottles and that typical measuring devices could reliably deliver between 1 and 8 ml of suspension. These data also established a 40 day in-use period for the opened bulk container and for the dispensed product.

**Drug product manufacturing:** Product development studies (b) (4)

The drug product is manufactured at Tris Pharma. An evaluation of the site found no outstanding concerns which could impact the approvability of the facility and that the finished drug product manufacturing facility and the testing laboratories (b) (4) were acceptable.

**Drug product release specification:** The drug product release specification includes typical tests for an oral suspension (appearance, ID, assay, pH, deliverable volume, microbial limits, preservative levels, (b) (4)). A viscosity test was added to the release and stability specification as changes in viscosity could result in suspension inhomogeneity and under/over dosing. A test for amphetamine ratio was also added to the release specification. Although this ratio is controlled by adding set amounts of various salts to the loading and drug product solutions, the release test will ensure that this critical ratio is as-intended in the final product. The microbiological controls were found acceptable by the microbiological reviewer.

The dissolution test and acceptance criteria underwent considerable discussion with the applicant over the course of this review cycle. Use of a two-stage (acid/neutral) dissolution medium was proposed. The biopharm review team found this approach was not adequately justified as drug dissolution is pH independent. Further, the discriminating ability of the test was not sufficient. The proposed test was found to be adequate on an interim basis and the applicant committed to develop a more discriminating single-medium method as part of a postmarketing commitment. The dissolution acceptance criteria were changed to better distinguish the (b) (4) release at (b) (4) to (b) (4) % release at 15 minutes.

Long term stability data through 12 months support the proposed 24 month drug product expiry period.

**Extended release claim:** The fact that the product releases up to (b) (4) % of the drug at 15 minutes caused the review team to carry out a more in-depth examination of the data supporting the proposed extended release claim. The product was found to clearly meet some of the regulatory requirements (21CFR 320.25(f)) for an extended release claim (e.g. reduced dosing frequency, no dose dumping, consistent PK between units etc.). The

21CFR320.25(F)(iii) requirement for equivalent steady state performance was discussed with the applicant – and in particular the similar but not lower fluctuation index of the proposed product compared to the listed drug. The applicant provided additional justification for the extended release claim during the review cycle. The biopharm team found that the totality of the available data supported the extended release claim. Note also that the product was found to dose dump at 40% alcohol levels – this information will be included in the labeling.

**Drug substance information:** (b) (4)

[Redacted]

[Redacted] . CMC details were referenced to DMFs (b) (4). All were found adequate to support this application. The manufacturing site has undergone three inspections since (b) (4) and was found acceptable (b) (4).

[Redacted]

**A. Summary of Drug Product Intended Use**

<b>Proprietary Name of the Drug Product</b>	Dyanavel XR
<b>Non Proprietary Name of the Drug Product</b>	Amphetamine extended release oral suspension
<b>Non Proprietary Name of the Drug Substance</b>	Amphetamine
<b>Proposed Indication(s) including Intended Patient Population</b>	ADHD
<b>Duration of Treatment</b>	Chronic
<b>Maximum Daily Dose</b>	(b) (4) mg
<b>Alternative Methods of Administration</b>	N/A

**B. Biopharmaceutics Considerations**

1. BCS Classification:

- Drug Substance:
- Drug Product:

**2. Biowaivers/Biostudies**

- Biowaiver Requests
- PK studies
- IVIVC

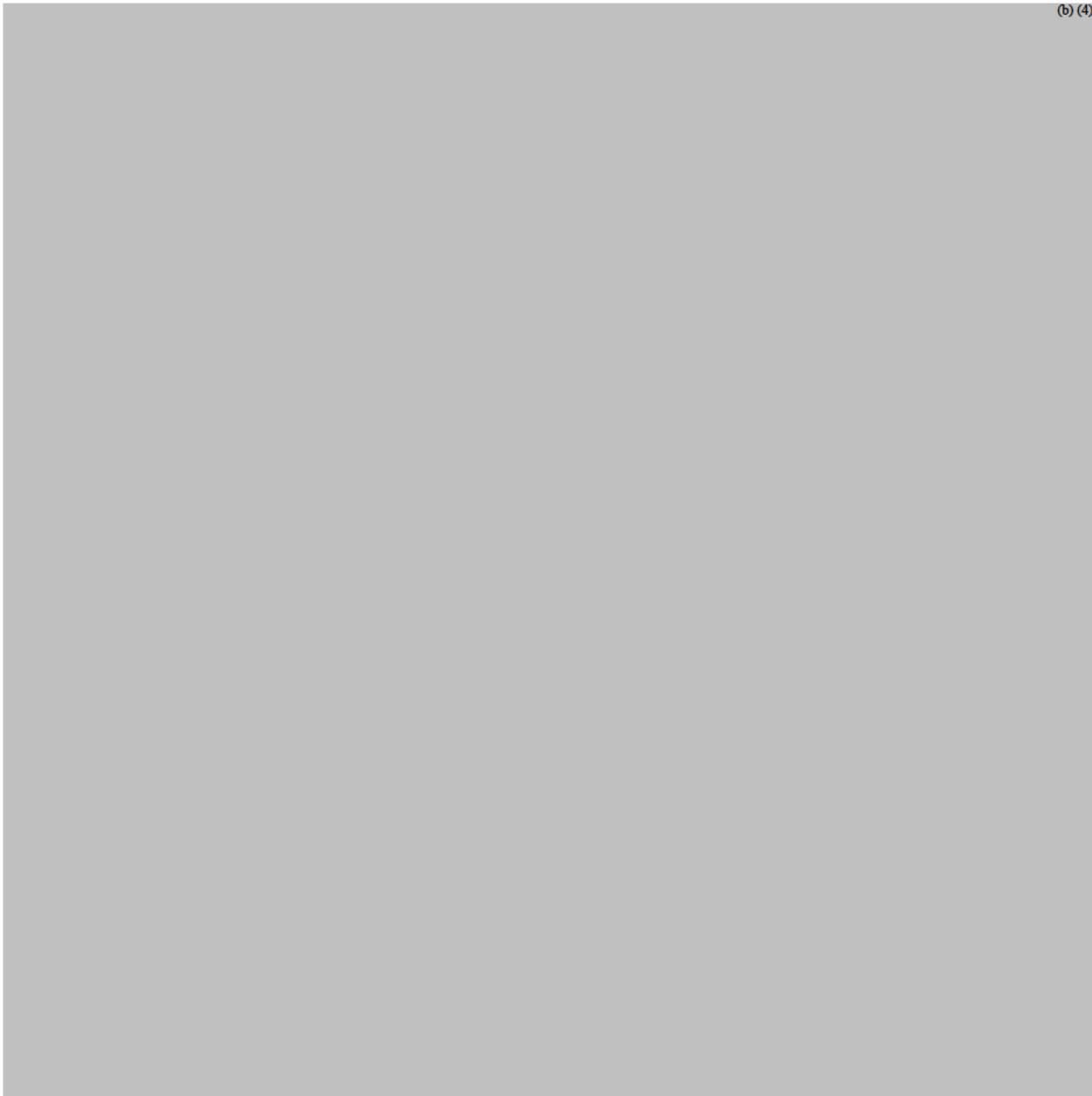
**C. Novel Approaches N/A****D. Any Special Product Quality Labeling Recommendations**

Needs to be shaken well before transferring to smaller bottles and before administration to ensure a homogeneous suspension.

Alcohol dose dumping warning at 40% alcohol.

**E. Process/Facility Quality Summary (see Attachment A)****F. Life Cycle Knowledge Information (see Attachment B)**

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**OVERALL ASSESSMENT AND SIGNATURES: FACILITIES**

**Reviewer's Assessment and Signature:**

Based on the review of the application, inspectional documents and compliance history of the drug substance and drug product manufacturing facilities, and control testing laboratories there are no significant, outstanding risks identified that would prevent the approvability of facilities listed in this application. All facilities listed in the application are acceptable.

**Vipulchandra Dholakia 8/3/2015**

**Vipul Dholakia**  
**S**

Digitally signed by Vipul Dholakia -S  
DN: c=US, o=U.S. Government, ou=HHS,  
ou=FDA, ou=People, cn=Vipul Dholakia -  
S, 0.9.2342.19200300.100.1.1=2000342958  
Date: 2015.08.19 07:35:49 -04'00'

**Supervisor Comments and Concurrence:**

Grace E. McNally -S

Digitally signed by Grace E. McNally -S  
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,  
0.9.2342.19200300.100.1.1=1300042045, cn=Grace E. McNally -S  
Date: 2015.08.19 20:41:49 -04'00'

Note: additional reviewers can be added, as appropriate

## ASSESSMENT OF THE BIOPHARMACEUTICS

### INTRODUCTION

Amphetamine ER Oral Suspension is a formulation manufactured with (b) (4)

(b) (4) has developed the drug product to provide patients with an alternative dosage and strength. The liquid drug product is intended to provide convenience to patients having difficulty swallowing solids and designed to achieve at least 12-hour extended release. The Reference Listed Drug (RLD) is Adderall® Tablets (N011522, Teva Womens).

### BCS CLASSIFICATION

This drug is a BCS class III drug (From global submission-pd-product:  
<http://166.78.14.201/tsrlinc.com/services/bcs/results.cfm>)

(b) (4)

**Biopharm Figure 3** shows the manufacturing process of the amphetamine oral suspension.



**Biopharm Figure 3 Overview of the Manufacturing Process**

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

**33A DISSOLUTION METHOD FOR THE FINAL PRODUCT**

The originally submitted dissolution method and dissolution acceptance criterion are shown below:

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
(b) (4)					

**33A.1 What data are provided to support the adequacy of the proposed dissolution method (e.g. medium, apparatus selection, etc.)?**

*Dissolution Method Development Report*

(b) (4)



(b) (4)



(b) (4)

**33A.2 What is the communication on the dissolution method between the Agency and the Applicant regarding dissolution method for the final product?**

74 day letter communication 1

In the 74 day letter communication, the agency requested the applicant to provide data to justify (b) (4) the dissolution method.

Responses from the Applicant

The responses from the applicant is briefly summarized below:

- (b) (4)
- (b) (4)

74 day letter communication 2

In the 74 day letter communication, the agency also requested the applicant to provide data to demonstrate the discriminating ability of the selected dissolution method. The conducted study should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e.,  $\pm$  10-20% change to the specification-ranges of these variables) for the most relevant critical manufacturing variables. In addition, if available, submit data showing the capability of the selected dissolution method to reject batches that are not bioequivalent.

Responses from the applicant:

(b) (4)

**Reviewer's Assessment:**

- 

(b) (4)

and therefore, the Agency highly recommends the Applicant to develop a dissolution method with a single pH media. The current dissolution method (b) (4) is acceptable on an interim basis provided that the Applicant accept the PMC (post marketing commitment) to develop a single pH medium with appropriate discriminating ability. During a teleconference held on August 3<sup>rd</sup>, 2015, the Applicant accepted the PMC.

- 

(b) (4)

(b) (4)

Therefore, the provided data are not sufficient to support the discriminating ability of the proposed dissolution method.

Information Request dated June 11, 2015

To get more information on how the dissolution method was established including the selection of the dissolution media and the setting of the acceptance criterion, an IR was sent on June 11 to the Applicant, which was shown as follows:

“1. Justify (b) (4) the drug product dissolution method. (b) (4)

(b) (4)

2. (b) (4)

(b) (4)

3. The data you provided are insufficient to support the discriminating ability of your proposed dissolution methods (e.g. release/stability testing (b) (4)

(b) (4)

In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the drug product manufactured under target conditions vs. the drug products that are intentionally manufactured with meaningful variations (i.e., ± 10-20% change to the specification-ranges of these variables) for the most relevant manufacturing variables including critical material attributes (CMAs) and critical process parameters (CPPs). The chosen method should be discriminating and sensitive enough to reject lots that would have less than acceptable clinical performance (e.g. not BE).

Provide the following data:

- a. Dissolution data (in tabular and graphical form) showing the ability of the proposed methods (**both methods**) to discriminate for aberrant batches for the identified CMAs and CPPs.

The responses from the Applicant dated 13 July, 2015

**(1) Responses to request #1:**

The Applicant reiterated the reasons for selecting the (b) (4) ; (b) (4)

(b) (4)

**Reviewer's Assessment:**

- This reviewer does not agree with the selection of the [redacted] (b) (4) proposed dissolution method. Through further communications, the Applicant agreed to develop a dissolution method with single medium as a PMC (see comments in the previous section).

**(2). Responses to request #2:**

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**(3) Responses to request #3**

Refer to question **33C.1**.

**Reviewer's Assessment:**

-  (b) (4)
- The selection of paddle speed  (b) (4) is adequate.

***33A.3 Is the proposed dissolution/release method clinically relevant? What data including but not limited to IVIVC are available to support this claim?***

(b) (4)

(b) (4)

**Reviewer's Assessment:**

- 

(b) (4)

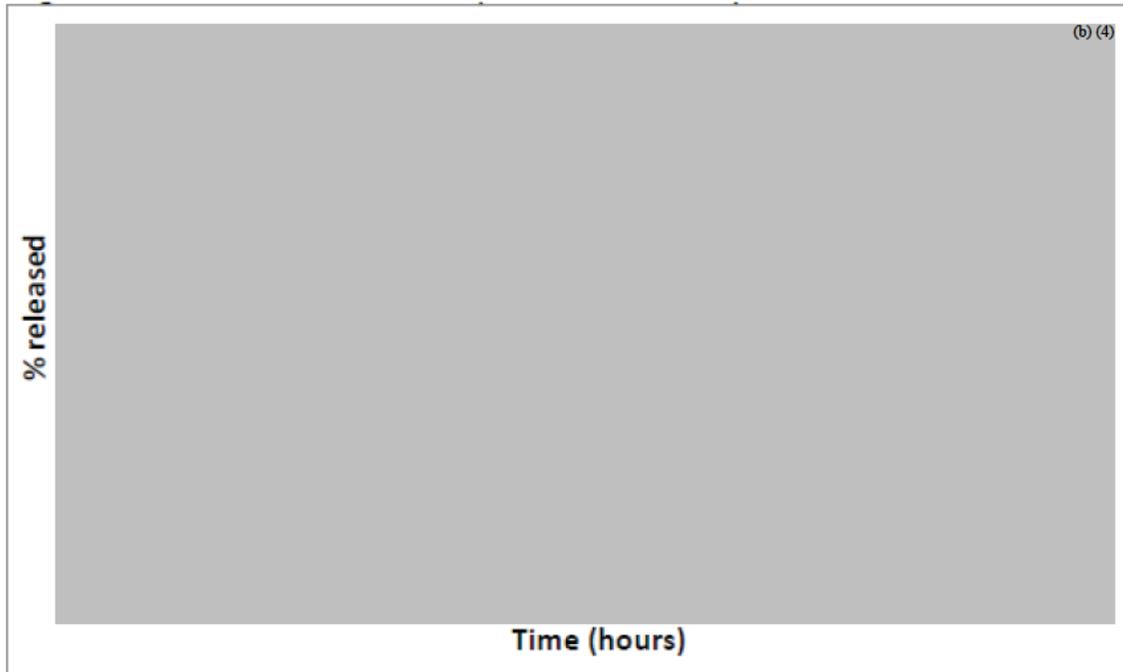
**33B DISSOLUTION ACCEPTANCE CRITERIA**

In the original submission, the following acceptance criteria were proposed:

Acceptance Criteria
Drug amount dissolved (b) (4)

***33B.1 What data are available to support the proposed dissolution acceptance criteria?***

Based on the dissolution study using proposed dissolution method, the dissolution profiles and data for three exhibit batches TB-125B (clinical batch used in the BE study), TB-127A, TB-128A are shown below (**Biopharm Figure 16** and **Table 8**).



**Biopharm Figure 16. Dissolution Profiles (Exhibit Batches)**

**Biopharm Table 8. Dissolution Profile Study Results for TB-125B (50 RPM)**

74 day letter communication

In the 74 day letter communication, the agency recommended that the selection of the dissolution acceptance criteria limits should be based on the mean target (bio-batches) value (b) (4) % and NLT (b) (4) % for the last specification time-point.

Responses from the applicant

The drug product utilizes an ion-exchange resin polymer as a carrier material for the drug substance (b) (4)



Lot to lot variability of greater than 20% and within lot variability about 10% or more were observed in the drug release for the stability samples at different time points and storage conditions, shown in **Biopharm Table 9**.

**Biopharm Table 9** Dissolution data summary for exhibit test batches stored at 25°C/60%RH

Stability Condition	Dissolution Specifications	
		(b) (4)
	<b>TB-125B (bio-batch)</b>	
Initial-Ambient	(b) (4)	
3mo-25°C/60% RH		
6mo-25°C/60% RH		
9mo-25°C/60% RH		
12mo-25°C/60% RH		
	<b>TB-127A</b>	
Initial-Ambient	(b) (4)	
3mo-25°C/60% RH		
6mo-25°C/60% RH		
9mo-25°C/60% RH		
12mo-25°C/60% RH		
	<b>TB-128A</b>	
Initial-Ambient	(b) (4)	
3mo-25°C/60% RH		
6mo-25°C/60% RH		
9mo-25°C/60% RH		
12mo-25°C/60% RH		

<sup>1</sup> n=12

**Reviewer's Assessment:**

(b) (4)

Based on the above considerations, the drug release at time point 15 min was recommended being included in the dissolution specification for the control of amount of (b) (4) drug product (b) (4). Further information request was made (see below).

Request #4 in IR issued on June 11, 2015

In the IR issued by the Agency dated June 11, 2015, further justification of the dissolution acceptance criteria was requested as follows.

“Your proposed dissolution acceptance criteria are not adequate for the following reasons:

(b) (4)

Response to Request

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Lot	Equipment	% Release (b) (4)	Batch Size (b) (4)
RD0500-121	Lab scale (FLM-1)	[REDACTED]	[REDACTED]
RD0500-132			
RD0500-051C	Exhibit Scale (FLM-5)		
RD0500-176			
I13765			
I13766			
I13785			
I13796			
RD0551-080	Commercial Scale (FLM-60)		
RD0551-151			
I15184			
I15185			
I15186			
TS0003-083			

The dissolution specifications for [REDACTED] (b) (4) are proposed below.

Time points	Current Specification	Proposed Specification (b) (4)
[REDACTED]		

**Reviewer’s Assessment:**

The [REDACTED] (b) (4) is the responsibility of the applicant. The acceptance criteria for the [REDACTED] (b) (4) dissolution should assure the product quality to meet the final product specifications.

It is suggested the applicant use the dissolution method to be developed during the dissolution PMC and set the appropriate acceptance criteria accordingly for the [REDACTED] (b) (4) [REDACTED]

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

The to be marketed formulation was used in the pivotal BE study. The final formulation was manufactured at the proposed manufacturing site (Tris Pharma, NJ).

### 34 A. FORMULATION

#### *34A.1. If applicable, how are the formulations used in different phases and/or in different sites are bridged?*

The to-be-marketed formulation Amphetamine ER oral suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B, (Tris Pharma Inc., USA) was used in the pivotal BE study. The final formulation was manufactured at the proposed manufacturing site (Tris Pharma, NJ).

#### **Reviewer's Assessment:**

- The to-be-marketed formulation is the same as those used in the pivotal BE study. Both the to-be-marketed batch and biobatch are manufactured in Tris Pharm, NJ. There are no bridging issues.

### 34 B. Bioavailability (BA)/bioequivalence (BE)

#### *34B.1 What bioavailability (BA)/bioequivalence (BE) data are available for both pre- and post-approval process? Is associated bioanalytical method submitted?*

##### Study 2014-3401

Study 2014-3401 was a Bioavailability study of the test product formulation of amphetamine ER oral suspension under fasted and fed conditions and relative bioavailability of the test product formulation to an equivalent dose of a commercially available reference product under fasted conditions in healthy adult subjects

This BE study is reviewed by Clinical Pharmacology reviewer. Here the results are briefly summarized.

This was an open-label, randomized, three-way cross-over, single-dose pivotal study to evaluate the relative bioavailability of amphetamine ER oral suspension, eq. to 20 mg of amphetamine base per 8 mL, Lot No.: **TB-125B**, (b) (4)

Tris Pharma Inc., USA) vs dextroamphetamine saccharate, amphetamine aspartate, dextroamphetamine sulphate and amphetamine sulfate tablets 15 mg, Lot No: 34016745A (Teva Pharmaceuticals USA) after a single dose in healthy volunteers. Dose are all equivalent to 18.8 mg amphetamine base. The treatment sequences are shown as follows (Biopharm Table 15):

**Biopharm Table 15: Treatment sequence**

Sequence	Treatment		
	Period 1	Period 2	Period 3
ABC	A	B	C

ACB	A	C	B
BAC	B	A	C
BCA	B	C	A
CAB	C	A	B
CBA	C	B	A

**Treatments A and B:** administered an 18.8 mg/7.5 mL dose once using amphetamine ER suspension. A is under fast condition and B is under fed condition.

**Treatment C:** administered a 30 mg dose as two 15 mg (mixed amphetamine salt) tablets, (total dose equivalent to 18.8 mg amphetamine base), at 0 and 4 hours.

In each period 18 samples were collected at: Prior to dosing (0-hour) and 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 12, 14, 16, 24, 36, 48, and 60 hours after drug administration. The 4-hour sample for Treatment C overlaps the 4-hour drug administration.

The following PK parameters were estimated for d-amphetamine and l-amphetamine: AUC<sub>t</sub>, AUC<sub>0-inf</sub>, AUC<sub>0-4</sub>, AUC<sub>4-t</sub>, AUC<sub>0-5</sub>, AUC<sub>5-t</sub>, C<sub>max</sub>, t<sub>max</sub>, t<sub>1/2</sub>, and t<sub>1/2</sub>.

### **Statistical Methods**

Analysis of variance (ANOVA) was performed on log-transformed AUC<sub>t</sub>, AUC<sub>inf</sub> and C<sub>max</sub> parameters, as well as on AUC<sub>0-4</sub>, AUC<sub>4-t</sub>, AUC<sub>0-5</sub>, AUC<sub>5-t</sub> for information purposes only. The significance of the sequence, period, treatment and subject-within-sequence effects were tested.

Using the same statistical model, the least-squares-means, the differences between the treatments least-squares-means and the corresponding standard errors of these differences were estimated for log-transformed AUC<sub>0-4</sub>, AUC<sub>4-t</sub>, AUC<sub>0-5</sub>, AUC<sub>5-t</sub>, AUC<sub>inf</sub> and C<sub>max</sub> parameters. Based on these statistics, the ratios of the geometric means for treatments and the corresponding 90% confidence intervals were calculated.

### **Results**

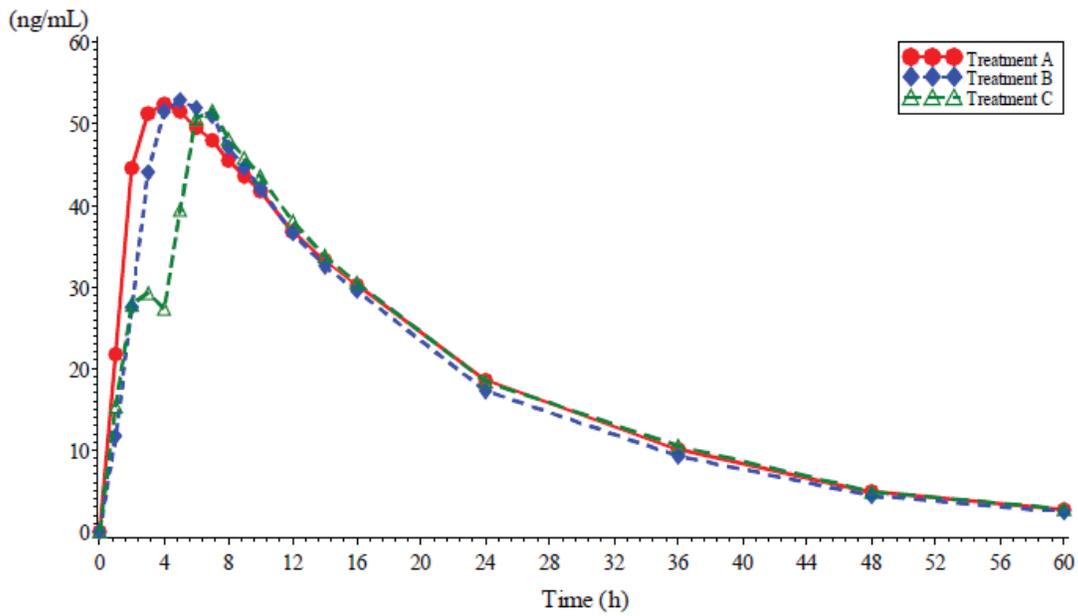
The validation of the bioanalytical analysis is provided in \\cds\sub1\evsprod\NDA208147\0000\m5\53-clin-stud-rep\531-rep-biopharm-stud\5314-bioanalyt-analyt-met\bvp-pmri-1425-13 and demonstrates the robustness of the test. Thirty subjects were enrolled and 29 subjects completed the study. A summary of the pharmacokinetics results is presented in Biopharm **Table 16** and Biopharm **Table 17**, for d-Amphetamine and l-Amphetamine, respectively. The mean plasma concentration time profiles for both formulations were virtually superimposed (**Biopharm Figure 17 to 18**).

### **Biopharm Table 16 Summary of Pharmacokinetic Parameters and Statistical Results of d-Amphetamine**

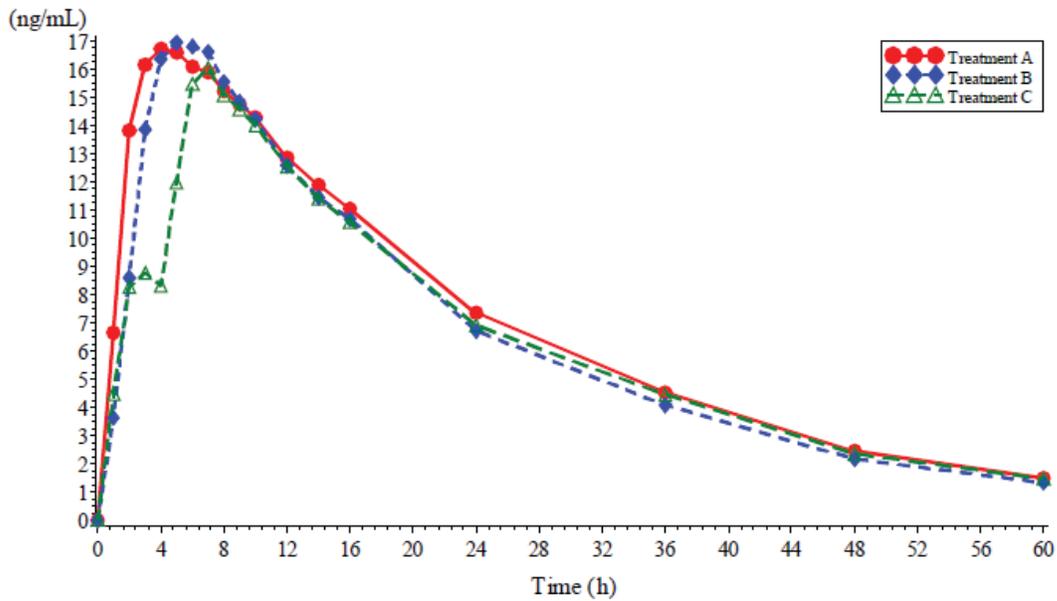
Based on Raw Data								
Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
$C_{max}$ (ng/mL)	A	29	54.128 (19)	53.026	A vs C	102.50	100.15 - 104.91	5
	B	29	55.031 (18)	54.009	B vs A	101.85	99.32 - 104.45	6
	C	29	52.714 (18)	51.732				
$AUC_t$ (ng·h/mL)	A	29	1144.050 (20)	1119.647	A vs C	106.32	102.03 - 110.78	9
	B	29	1080.034 (19)	1059.438	B vs A	94.62	91.17 - 98.21	8
	C	29	1078.946 (22)	1053.113				
$AUC_{inf}$ (ng·h/mL)	A	29	1197.321 (22)	1168.903	A vs C	105.97	101.45 - 110.70	10
	B	29	1125.248 (20)	1102.633	B vs A	94.33	90.68 - 98.12	9
	C	29	1133.257 (24)	1103.036				
		<i>n</i>	<i>Median</i>	<i>Range</i>				
$T_{max}$ (h)	A	29	4.00	2.00- 7.00				
	B	29	5.00	3.00- 8.00				
	C	29	6.02	6.00- 8.00				
<i>Treatment A (Test-1)</i>	<i>FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)</i>							
<i>Treatment B (Test-2)</i>	<i>FED: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)</i>							
<i>Treatment C (Ref)</i>	<i>FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)</i>							

**Biopharm Table 17 Summary of Pharmacokinetic Parameters and Statistical Results of l-Amphetamine**

Based on Raw Data								
Parameter	Trt	n	Arithmetic Mean (CV%)	Geometric Mean	Contrast	Ratio (%)	90% Confidence Interval	Intra-Sbj CV(%)
$C_{max}$ (ng/mL)	A	29	17.286 (19)	16.917	A vs C	106.05	103.56 - 108.59	5
	B	29	17.683 (19)	17.321	B vs A	102.39	99.83 - 105.01	6
	C	29	16.290 (19)	15.952				
$AUC_t$ (ng·h/mL)	A	29	424.835 (20)	414.681	A vs C	111.35	106.22 - 116.73	11
	B	29	395.794 (20)	386.833	B vs A	93.28	89.64 - 97.08	9
	C	29	383.120 (23)	372.403				
$AUC_{inf}$ (ng·h/mL)	A	29	461.544 (23)	448.439	A vs C	110.68	104.97 - 116.70	12
	B	29	425.849 (21)	415.443	B vs A	92.64	88.57 - 96.90	10
	C	29	419.131 (26)	405.169				
		<i>n</i>	<i>Median</i>	<i>Range</i>				
$T_{max}$ (h)	A	29	4.00	2.00- 7.00				
	B	29	5.00	3.00- 8.00				
	C	29	7.00	6.00- 9.00				
<i>Treatment A (Test-1)</i>	<i>FASTING: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)</i>							
<i>Treatment B (Test-2)</i>	<i>FED: Amphetamine ER Oral Suspension, eq. to 20 mg of amphetamine base per 8 mL (CII), Lot No.: TB-125B (Tris Pharma, Inc., USA)</i>							
<i>Treatment C (Ref)</i>	<i>FASTING: DEXTROAMPHETAMINE SACCHARATE, AMPHETAMINE ASPARTATE, DEXTROAMPHETAMINE SULFATE AND AMPHETAMINE SULFATE Tablets 15 mg, Lot No.: 34016745A (Teva Pharmaceuticals USA)</i>							



**Biopharm Figure 17 Arithmetic Mean Plasma Concentration-Time Profiles of d-Amphetamine**



**Biopharm Figure 18 Arithmetic Mean Plasma Concentration-Time Profiles of l-Amphetamine**

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### 34 C. ER DESIGNATION CLAIM

***34C.1 If it is a modified release (MR) oral formulation, how has the MR claim been established?***

#### 74-day communication

In the 74-day letter, FDA requested the applicant to submit data to support the claim.

“The in vitro data provided show that more than (b) (4)% of the drug is dissolved within (b) (4) min which questions the ER claim specially since the proposed dosing regimen is once daily. Data need to be submitted to support the ER claim shown as below.

The drug product’s steady-state performance is comparable (e.g. degree of fluctuation is similar or lower) to a currently marketed noncontrolled release or controlled-release drug product that contains the same active drug ingredient or therapeutic moiety and that is subject to an approved full NDA.

The drug product’s formulation provides consistent pharmacokinetic performance between individual dosage units.

The drug product has a less frequent dosing interval compared to a currently marketed non-controlled release drug product.”

#### Responses from the applicant

a) The extended release claim of the product is supported by the results of a placebo-controlled phase-3 efficacy study (TRI102-ADD-001) where efficacy through 13 hours after a single daily dose administration in pediatric patients with ADHD (n=99) was established.

The extended release profile of the Amphetamine ER Oral Suspension (Test Product) was also confirmed in a single dose pharmacokinetic study against an approved immediate release product Adderall® tablets, NDA 011522 owned by Teva Women’s Health (Reference Product) under fasted conditions in healthy adult and in a simulation of steady-state pharmacokinetics using the measured concentrations from the single-dose relative bioavailability study as the starting point (reported in Steady State Simulation Report).

In the steady state simulation, where the Test Product was modeled to have a dosing regimen of once a day for 8 days (at t=0 h, 18.8 mg amphetamine base per dose) and the Reference Product was modeled to have a dosing regimen of twice a day for 8 days (at

t=0 h and 4 h, 9.4 mg amphetamine base per dose, total dose 18.8 mg amphetamine base), the pharmacokinetic parameters including % fluctuation and C<sub>trough</sub>, were estimated using a non-compartmental approach based on the simulated concentration on day 8.

As reported in the **Biopharm Table 20**, the Applicant provided the simulation of the steady state PK for 8 days and calculated the fluctuation rate of the ER formulation and the Reference product. Based on the results of the steady state simulation, the degree of fluctuation for d- and l-Amphetamine were similar between the Test (ER) and the Reference (IR) products.

**Biopharm Table 20 : Percent Fluctuation of d- and l-Amphetamine for Test and Reference Products at Steady State (n=29)**

	Fluctuation			
	d-Amphetamine		l-	
	Test Product	Reference Product	Test Product	Reference Product
<b>Geometric</b>	99.397	95.834	80.61	77.55
<b>Minimum</b>	58.194	66.144	47.38	53.16
<b>Maximum</b>	133.021	120.468	105.028	99.13

In the responses dated August 13 regarding the ER claim, the Applicant reiterated some of the previously mentioned evidences and also provided some new evidences for the ER claim for amphetamine ER oral suspension, which are summarized below:

- a). Amphetamine ER Oral Suspension allows for a reduction in dosing frequency (once daily) as compared to an immediate release dosage form (2 to 3 times a day).
- b). Similar fluctuation index was obtained between and IR reference and the test ER oral suspension (refer to Biopharm Table 20 and 22 for the fluctuation index comparison).
- c). The fluctuation index for Amphetamine ER Oral Suspension is comparable to that of another approved extended release amphetamine product. Biopharm Table 21 provided the calculation of the fluctuation index for Adderall IR, (b) (4) and the proposed Amphetamine ER oral suspension. (b) (4)

(b) (4)

d). (b) (4)

(b) (4)

**Biopharm Table 21. Percent Fluctuation Comparison for Adderall IR, (b) (4) Amphetamine ER Oral Suspension.**

<b>% Fluctuation</b>			
	<b>Adderall IR</b>	(b) (4)	<b>Amphetamine ER Oral Suspension (Clinical batch)</b>
<b>d-amphetamine</b>			
<b>Geometric Mean</b>	95.834	(b) (4)	99.397
<b>Minimum</b>	66.144	(b) (4)	58.194
<b>Maximum</b>	120.468	(b) (4)	133.021
<b>l-amphetamine</b>			
<b>Geometric Mean</b>	77.556	(b) (4)	80.613
<b>Minimum</b>	53.161	(b) (4)	47.387
<b>Maximum</b>	99.136	(b) (4)	105.028

(b) (4)

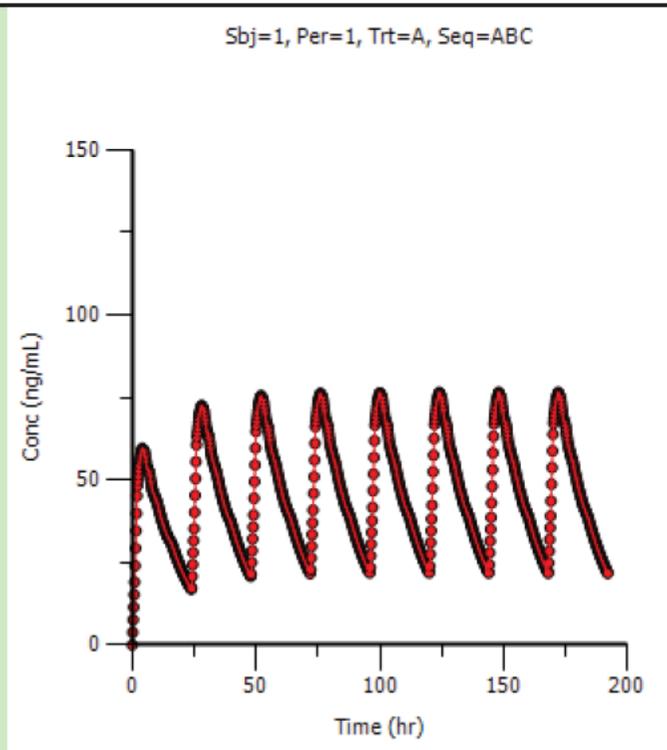
(b) (4)

(b) (4)

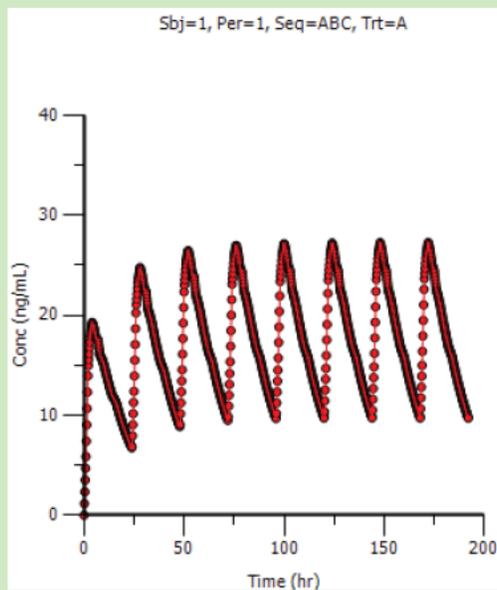


(b) (4)





**Biopharm Figure 23 Simulated steady state PK for d-amphetamine after dosing amphetamine oral ER suspension (18.8 mg) once a day for 8 days.**



**Biopharm Figure 24 Simulated steady state PK for l-amphetamine after dosing amphetamine oral ER suspension (18.8 mg) once a day for 8 days.**

Based on the simulation results, percent fluctuation of d- and l-Amphetamine for Test and Reference Products at Steady State (n=29) are shown in the following Table.

**Biopharm Table 22: Reviewer's analysis: Percent Fluctuation of d- and l-**

**Amphetamine for Test and Reference Products at Steady State (n=29).**

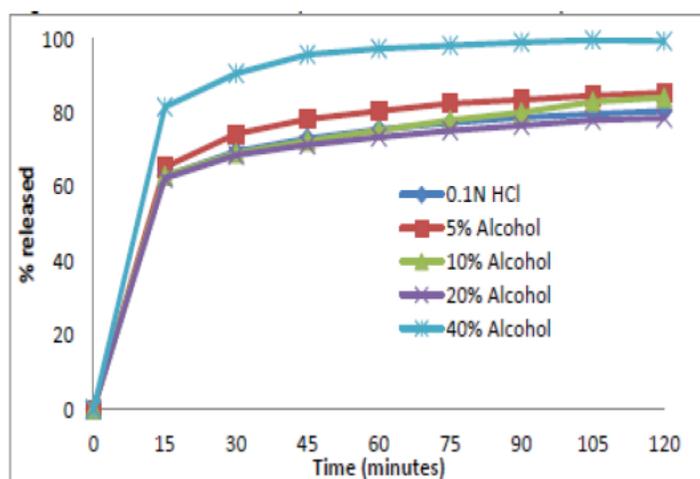
	Fluctuation			
	d-Amphetamine		l-Amphetamine	
	Test	Reference	Test Product	Reference
Geometric Mean	100.71	99.18	82.11	81.50
95% CI	66.68	67.14	53.12	53.15
95% CI	137.75	133.95	113.8	112.4
CV%	20.3	22.53	21.11	24.48

- Based on the data provided by the applicant and the reviewer’s analyses, the fluctuation index is similar between the amphetamine ER suspension and approved immediate release product Adderall® tablets, NDA 011522 owned by Teva Women’s Health (Reference Product). Generally, the fluctuation index for an ER product should be lower than the IR product. The proposed product did not show ER characteristics in this regard. Further, there is a considerable percentage of (b)(4) and in vitro, the drug is released (b)(4)% within 15min, and (b)(4)% within 1 hour indicating more IR rather than ER characteristics. From these aspects, the ER claim for this product is questioned.
- (b)(4)
- Further, the dosing frequency for the proposed product is once a day, less than the dosing frequency of the reference drug product, Adderall® tablets, which meets the requirement for the ER claim stated in CFR 325.25f.
- Also, the variability for the proposed product (CV% is 20.3% for D-amphetamine and 22.53 for L-amphetamine) is comparable to the reference product, Adderall® tablets (CV% is 21.11% for D-amphetamine and 22.53% for L-amphetamine), indicating consistent pharmacokinetic performance between individual dosage units.
- (b)(4)
- Therefore, the review team deems the available data of the proposed product meet the general requirements for ER claim. To help the patients and the physicians use this product and avoid unnecessary medication error, the ER claim can be granted and the nomenclature issues can be handled on a case-by-case bases.

### 34 D. ALCOHOL DOSE DUMPING

#### 34D.1 If it is a modified release (MR) oral formulation, has an in-vitro alcohol dose dumping study submitted?

The potential for dose dumping was evaluated in vitro settings using ethanolic media at different concentrations (0%, 5%, 10%, 20% and 40%). Dose dumping in the presence of 40 % alcohol was observed after 15 min. The f2 test showed significant differences between the dissolution profiles in the presence of 0% alcohol and 40% alcohol (Biopharm Table 23). The results are shown in a file named “dissolution-method-dev-report” (part 5.0).



Biopharm Figure 25 Dissolution profile (at different alcohol conc.)

#### Biopharm Table 23 F2 analysis for alcohol study

Alcohol Concentration	f2 comparison with 0% Alcohol
5%	66
10%	85
20%	83
40%	35

#### **Reviewer’s Assessment:**

Based on the above data, there is a risk of dose dumping in the presence of 40 % alcohol (f2<50 for the dissolution profile comparison with 0% alcohol). The information has been conveyed to the OND clinical team in the mid-cycle meeting and a labeling meeting.

## OVERALL ASSESSMENT AND SIGNATURES: BIOPHARMACUETICS

### Reviewer's Assessment and Signature:

#### 1. The dissolution methodology and acceptance criteria for the final product

The following dissolution method and acceptance criteria are acceptable on an **INTERIM BASIS** for release and stability testing with an agreement on PMC for a new dissolution method development.

USP Apparatus	Spindle Rotation	Medium Volume	Temperature	Medium	Acceptance Criterion
II	50 rpm	750 mL	37°C	750 mL 0.1N HCl for 2 hours followed by additional of 200 mL 0.2M Na <sub>2</sub> HPO <sub>4</sub> to pH 6.0	Drug amount dissolved (b) (4) % at 15min (b) (4) % at 2h NLT (b) (4) % at 4h

#### 2. Post marketing commitment (PMC) for dissolution method development

The Applicant agreed to develop a dissolution method using medium with single pH within one year as a post marketing commitment. The PMC form will be uploaded as a separate file.

#### 3. Alcohol dose dumping

There is a risk of dose dumping in the presence of 40 % alcohol. The information was conveyed to the OND clinical team in the mid-cycle meeting and a labeling meeting. We suggest to state in the product labeling that liquor should be avoided when the proposed product is administered.

#### 4. ER claim

The ER claim is granted based on the submitted data, which generally meet the requirement listed in CFR 325.25f.

Fang Wu, Ph.D.  
Biopharmaceutics Primary Reviewer  
CDER/ONDP/Division of Biopharmaceutics

Fang Wu  
-A

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cn=Fang Wu -A,  
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Date: 2015.08.19 09:23 34 -0400

John Duan, Ph.D.  
Biopharmaceutics Secondary Reviewer  
& Branch Chief  
CDER/ONDP/Division of Biopharmaceutics

John Z.  
Duan -S

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cc. Sandra Suarez, Paul Seo

**Supervisor Comments and Concurrence: Concur. John Z. Duan**

## ASSESSMENT OF MICROBIOLOGY

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

### **Points to consider**

Amphetamine ER Oral suspension is presented as 2.5 mg/mL in a 464 mL amber glass bottle. The product is repackaged into smaller bottles by a pharmacist prior to dispensing to patients. Both the pharmacists' bottle and the patients' bottles are intended for multiple uses.



The drug product is tested for microbial limits at release using a method consistent with USP Chapter <61> (Microbiological Examination of Non-sterile Products: Microbial Enumeration Tests) and <62> (Microbiological Examination of Non-sterile Products: Tests for Specified Microorganisms). The microbial limits acceptance criteria are consistent with USP Chapter <1111> (Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use). Limits listed in Chapter <1111> for products of this type state NMT  $10^2$  total aerobic microbial count, NMT  $10^1$  total combined yeast and mold count, and the absence of *Escherichia coli* and organisms of the *Burkholderia cepacia* complex (BCC) per mL. The microbial enumeration and test for the absence of *E. coli* methods were verified to be appropriate for use with the drug product following procedures consistent with those in USP Chapter <61> and <62>. The applicant performed validation studies demonstrating the adequacy of their test method for detection of BCC. In addition to testing for BCC, the applicant states that

(b) (4)

The drug product will also be tested for microbial enumeration, the absence of *E. coli* and BCC organisms, and antimicrobial effectiveness annually as part of the post-approval stability protocol.

**Reviewer's Assessment:****ADEQUATE**

**The microbial limits specification for Amphetamine ER Oral Suspension is acceptable from a product quality microbiology perspective. Therefore, this submission is recommended for approval from the standpoint of product quality microbiology.**

**2.3.P.6 Reference Standards or Materials**

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

**Point to consider**

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

**Applicant's Response:** This can be adopted from the QbR-QOS and Module 3 provided from the firm.

**Reviewer's Assessment:**

**A APPENDICES**

**A.2 Adventitious Agents Safety Evaluation**

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

**Applicant's Response:** This can be adopted from the QbR-QOS and Module 3 provided from the firm.

**Reviewer's Assessment:**

38. If any of the materials used for the manufacture of the drug substance or drug product are of biological origin or derived from biological sources, what drug substance/drug product processing steps assure microbiological (viral) safety of the component(s) and how are the viral inactivation/clearance capacity of these processes validated?

**Applicant's Response:** This can be adopted from the QbR-QOS and Module 3 provided from the firm.

**Reviewer's Assessment:**

**OVERALL ASSESSMENT AND SIGNATURES: MICROBIOLOGY**

**Reviewer's Assessment and Signature:**

**Erika A. Pfeiler -S** Digitally signed by Erika A. Pfeiler -S  
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**Supervisor Comments and Concurrence:**  
**Stephen E. Langille -S** Digitally signed by Stephen E. Langille -S  
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Note: additional reviewers can be added, as appropriate

## **I. Review of Common Technical Document-Quality (Ctd-Q) Module 1**

### **Labeling & Package Insert**

#### **1. Package Insert**



Item	Information Provided in NDA	Reviewer's Assessment
<b>Product title, Drug name (201.57(a)(2))</b>		
Proprietary name and established name	Proprietary: DYNAVEL XR Established Name: Amphetamine ER Oral Suspension	Adequate. Drug product contains (b) (4) The established name complies with USP <1121>.
Dosage form, route of administration	Dosage: Extended release suspension Route: Oral	Adequate
Controlled drug substance symbol (if applicable)	CII	Both amphetamine and dextroamphetamine belong to <a href="#">schedule II controlled substances</a>
<b>Dosage Forms and Strengths (201.57(a)(8))</b>		
A concise summary of dosage forms and strengths	The drug product is formulated as an oral suspension. Each mL of the suspension provides 2.5 mg of the amphetamine base.	Adequate

**Conclusion: Adequate**

**(b) “Full Prescribing Information” Section**

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

**3. DOSAGE FORMS AND STRENGTHS**

Extended-release oral suspension contains 2.5 mg amphetamine base per mL.

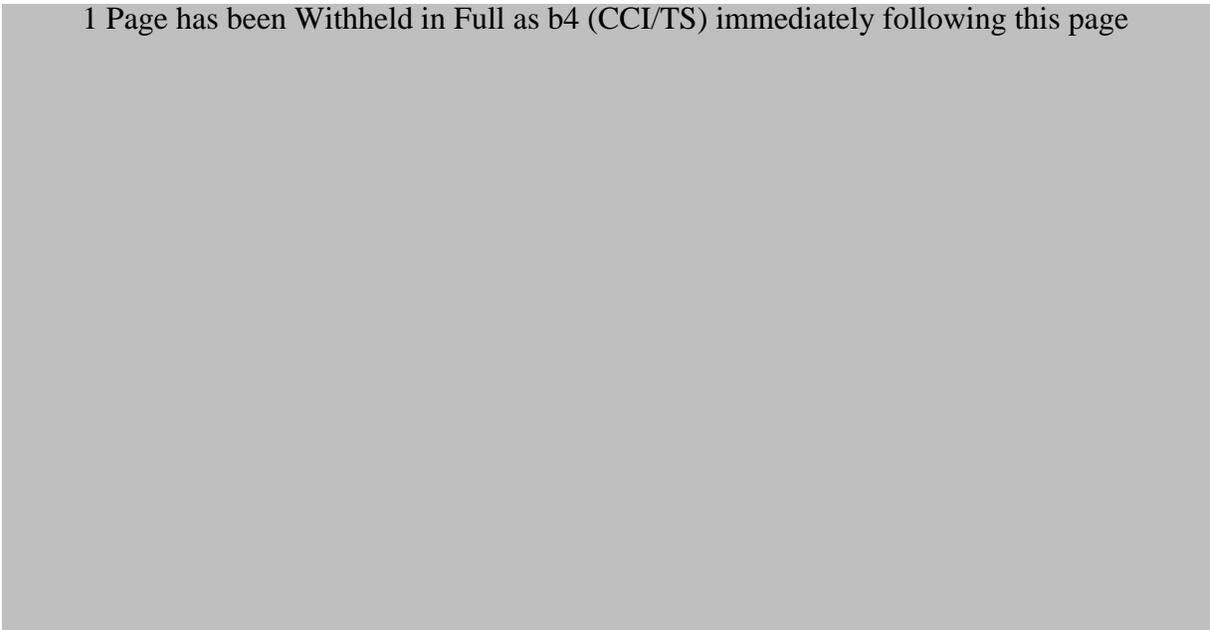
Item	Information Provided in NDA	Reviewer's Assessment
Available dosage forms	Extended release oral suspension	Adequate
Strengths: in metric system	2.5 mg of amphetamine base (3.2:1 ratio of <i>d:l</i> isomers) per mL of suspension	Adequate
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	Extended release oral suspension	Adequate

**Conclusion: Adequate**

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

(b) (4)

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Item	Information Provided in NDA	Reviewer's Assessment
Strength of dosage form	2.5 mg/mL amphetamine	Adequate
Available units (e.g., bottles of 100 tablets)	Bottle of 464 mL	Adequate
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Color/NDC# listed	Adequate
Special handling (e.g., protect from light, do not freeze)	No special handling is required	Adequate
Storage conditions	20° to 25°C (68° to 77°F)	Adequate

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

Item	Information Provided in NDA	Reviewer's Assessment
Manufacturer/distributor name (21 CFR 201.1)	Trispharma is listed as the manufacturer	Adequate

**Conclusion: Adequate**

## **2. Labels**

### **1) Immediate Container Label**



*this was communicated to the label reviewer.*

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))		Adequate
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		Adequate
Net contents (21 CFR 201.51(a))		Adequate
Lot number per 21 CFR 201.18		Adequate
Expiration date per 21 CFR 201.17		Adequate
“Rx only” statement per 21 CFR 201.100(b)(1)		Adequate
Storage (not required)		Adequate
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		Adequate
Bar Code per 21 CFR 201.25(c)(2)**	(b) (4)	Adequate
Name of manufacturer/distributor		Adequate
Others		Adequate

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

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

**Conclusion: Reviewer has communicated with the label reviewer that the container label does not have a barcode. Adequate**

## 2) Cartons

(Attach the proposed carton label here) **Not Applicable**

Item	Comments on the Information Provided in NDA	Conclusions
Proprietary name, established name (font size and prominence (FD&C Act 502(e)(1)(A)(i), FD&C Act 502(e)(1)(B), 21 CFR 201.10(g)(2))		
Strength (21CFR 201.10(d)(1); 21.CFR 201.100(b)(4))		
Net contents (21 CFR 201.51(a))		
Lot number per 21 CFR 201.18		
Expiration date per 21 CFR 201.17		
Name of all inactive ingredients (except for oral drugs); Quantitative ingredient information is required for injectables][ 201.10(a), 21CFR201.100(b)(5)(iii)]		
Sterility Information (if applicable)		
"Rx only" statement per 21 CFR 201.100(b)(1)		
Storage Conditions		
NDC number (per 21 CFR 201.2) (requested, but not required for all labels or labeling), also see 21 CFR 207.35(b)(3)		
Bar Code per 21 CFR 201.25(c)(2)**		
Name of manufacturer/distributor		
"See package insert for dosage information" (21 CFR 201.55)		
"Keep out of reach of children" (optional for Rx, required for OTC)		
Route of Administration (not required for oral, 21 CFR 201.100(b)(3))		

**Conclusion: Drug product will not have a carton and therefore a carton label is not required. Adequate.**

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### III. Administrative

#### A. Application Technical Lead Signature

David J.  
Claffey -S

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Date: 2015.08.18 14:27:47 -04'00'