CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217645Orig1s000

PRODUCT QUALITY REVIEW(S)

Title:	NDA IQA Template Title Page-EXEC SUMMARY
Document ID:	OPQ-ALL-TEM-0040
Effective Date:	26 Sep 2023 Revision: 00
Total Pages:	4

Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary Addendum

1. Application/Product Information

NDA Number	217645		
Applicant Name	Tris Pharma, Inc.		
Drug Product Name	Clonidine Hydrochloride		
Dosage Form	Suspension, extended release		
Proposed Strength(s)	0.1 mg per mL (equivalent to 0.09 mg of Clonidine base per mL)		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	0.4 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	treatment of attention-deficit/hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications		
Drug Product Description	light beige to tan viscous suspension packaged into 1 oz. white HDPE and 5 oz. amber (b) (4) bottle with oral dosing dispenser and adapter		
Co-packaged product information	oral dosing dispenser and adapter		
Device information	oral dosing dispenser and adapter (co-packaged)		
Storage Temperature/ Conditions	20-25 ºC		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Friedrich Burnett	Donna Christner
	Drug Product/ Labeling	Renish Delvadia	Valerie Amspacher/Julia Pinto

	Manufacturing	Yongming Lu	Jingbo Xiao
	Biopharmaceutics	Jia Leo	Ta-Chen Wu
	Microbiology	Helen Ngai	Kelly Ann Miller
	Other (specify)	N/A	N/A
	RBPM	Teshara Bouie	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The Applicant has provided adequate stability data to support the proposed shelf-life of 24 months when stored at 20°C to 25°C (68°F to 77°F). Excursion permitted between 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

This addendum is provided to discuss the lowering of the acceptable intake (b) (4) from (b) (4) ng/day to (b) (4) ng/day. There is no change in the CMC recommendation as a result of the change in acceptable daily intake for (b) (4).

The CMC recommendation is approval for this application based on reviews by drug substance, drug product, process/ facilities, biopharmaceutics and microbiology.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate

QPA for EA(s): No

5. **Life-Cycle Considerations**
   Established Conditions per ICH Q12: No
   Comments:

   Comparability Protocols (PACMP): No
   Comments:

   Additional Lifecycle Comments:

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting Document 1; eCTD 0001	24 Jul 2023	All, original submission
Supporting Document 4; eCTD 0004	20 Nov 2023	Biopharmaceutics
Supporting Document 5; eCTD 0005	30 Nov 2023	Drug product
Supporting Document 10; eCTD 0010	20 Feb 2024	Drug product
Supporting Document 11; eCTD 0011	5 Apr 2024	Biopharmaceutics

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 5/01/2024 11:11:09AM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

4 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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
05/01/2024 11:36:19 AM

Table of Contents

Title:	NDA IQA Template Title Page-EXEC SUMMARY
Document ID:	OPQ-ALL-TEM-0040
Effective Date:	26 Sep 2023 Revision: 00
Total Pages:	4

Template Revision: 03

Office of Pharmaceutical Quality

New Drug Application (NDA)
Integrated Quality Assessment Template

NDA Executive Summary

1. Application/Product Information

NDA Number	217645		
Applicant Name	Tris Pharma, Inc.		
Drug Product Name	Clonidine Hydrochloride		
Dosage Form	Suspension, extended release		
Proposed Strength(s)	0.1 mg per mL (equivalent to 0.09 mg of Clonidine base per mL)		
NDA Classification	Type 3 - New Dosage Form		
Route of Administration	Oral		
Maximum Daily Dose	0.4 mg		
Rx/OTC Dispensed	Rx		
Proposed Indication	treatment of attention-deficit/hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications		
Drug Product Description	light beige to tan viscous suspension packaged into 1 oz. white HDPE and 5 oz. amber (b) (4) bottle with oral dosing dispenser and adapter		
Co-packaged product information	oral dosing dispenser and adapter		
Device information	oral dosing dispenser and adapter (co-packaged)		
Storage Temperature/ Conditions	20-25 ºC		
Review Team	**Discipline**	**Primary**	**Secondary**
	Drug Substance	Friedrich Burnett	Donna Christner
	Drug Product/ Labeling	Renish Delvadia	Valerie Amspacher/Julia Pinto

	Manufacturing	Yongming Lu	Jingbo Xiao
	Biopharmaceutics	Jia Leo	Ta-Chen Wu
	Microbiology	Helen Ngai	Kelly Ann Miller
	Other (specify)	N/A	N/A
	RBPM	Teshara Bouie	
	ATL	Valerie Amspacher	
Consults	N/A		

2. Final Overall Recommendation - Approval

3. Action Letter Information

a. Expiration Dating: The Applicant has provided adequate stability data to support the proposed shelf-life of 24 months when stored at 20°C to 25°C (68°F to 77°F). Excursion permitted between 15°C to 30°C (59°F to 86°F).

b. Additional Comments for Action

4. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The CMC recommendation is approval for this application based on reviews by drug substance, drug product, process/ facilities, biopharmaceutics and microbiology.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

Drug Substance - Adequate
Drug Product - Adequate
Quality Labeling - Adequate
Manufacturing - Adequate
Biopharmaceutics - Adequate
Microbiology - Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

5. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments:

Comparability Protocols (PACMP): No
Comments:

Additional Lifecycle Comments:

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting Document 1; eCTD 0001	24 Jul 2023	All, original submission
Supporting Document 4; eCTD 0004	20 Nov 2023	Biopharmaceutics
Supporting Document 5; eCTD 0005	30 Nov 2023	Drug product
Supporting Document 10; eCTD 0010	20 Feb 2024	Drug product
Supporting Document 11; eCTD 0011	5 Apr 2024	Biopharmaceutics

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 4/16/2024 08:27:02AM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

CHAPTER IV: LABELING

NDA 217645

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information: Adequate with comments/edits in the OND working labeling document and comments for carton/container at the end of the document.

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	ONYDATM XR	Acceptable
Established name(s)	(clonidine hydrochloride) extended-release oral suspension	Acceptable
Route(s) of administration	oral	Acceptable
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	(b) (4)	Extended-Release Oral Suspension: 0.1 mg clonidine hydrochloride per mL
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

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)	N/A	

1.2.2 Section 3 (DOSAGE FORMS AND STRENGTHS)

Item	Information Provided in the NDA	Assessor's Comments
DOSAGE FORMS AND STRENGTHS section		
(b) (4)		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance		Strength based on"clonidine hydrochloride"; USP exemption applied because currently marketed product has strength based clonidine hydrochloride salt amount.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting	Yes	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate 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	

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	ONYDATM XR	Yes
Dosage form(s) and route(s) of administration	**Extended-release Oral Suspension**	Acceptable
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.		Strength based on"clonidine hydrochloride"; USP exemption applied because currently marketed product has strength based clonidine hydrochloride salt amount. Equivalency statement included. Also, amount of complex and free clonidine hydrochloride is added (see the "Change to" section above).
List names of all inactive ingredients. Use USP/NF names. Avoid Brand names.	Yes	
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Statement of being sterile (if applicable)	N/A	
Pharmacological/ therapeutic class	Yes	
Chemical name, structural formula, molecular weight	Yes	Chemical name is edited to remove (b) (4) and redundancy. See "Change to Section above"

If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	N/A	

Section 11 (DESCRIPTION) Continued

Item	Information Provided in the NDA	Assessor's Comments
For oral prescription drug products, include gluten statement if applicable	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity"	(b) (4)	Delete

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 **See the edited version below**		
(b) (4)		
Available dosage form(s)	oral suspension	Acceptable
Strength(s) in metric system	0.1 mg/mL	Acceptable
Available units (e.g., bottles of 100 tablets)	(b) (4) bottle, (b) (4) bottle	See the edits above
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	light beige to tan viscous suspension	See edits above
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	

For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	

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

Item	Information Provided in the NDA	Assessor's Comments
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g. to protect from light or moisture, to maintain stability, etc.)	(b) (4)	See edits above
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."	N/A	
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Store at 20°-25°C (68°-77°F); excursions permitted to 15°-30°C (59°-86°F) [see USP Controlled Room Temperature].	See edits above
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."		
Include information about child-resistant packaging	The (b) (4) packages are child-resistant	In line with the recommendation in in the Guidance for Industry: Child-Resistant Packaging Statements in Drug Product Labeling (August 2019), the Applicant has provided the following statement in the section 3.2.P.7 of the submission "We verify in this submission that the (b) (4) (closures) meet CPSC's standards under 16 CFR 1700." See the edits above.

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 www.trispharma.com	Acceptable

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guide, Patient Information, Instructions for Use):

(clonidine hydrochloride) extended-release oral suspension – Acceptable

(b) (4)

Change to "Store ONYDA XR at room temperature between 68°F to 77°F (20°C to 25°C).

(b) (4)

Change (b) (4) **to "modified starch"**

(b) (4)

Acceptable

(b) (4)

Acceptable

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(Copy/paste or refer to a representative example of a proposed container)

Item	Information Provided in the NDA	Assessor's Comments about Carton/container Labeling
Proprietary name, established name, and dosage form (font size and prominence	ONYADA XR (clonidine hydrochloride) extended-release oral suspension	Acceptable
Dosage strength	0.1 mg/mL	acceptable
Route of administration	oral	acceptable
If the active ingredient is a salt, include the equivalency statement per FDA Guidance		Strength based on"clonidine hydrochloride"; USP exemption applied because currently marketed product has strength based clonidine hydrochloride salt amount. The Applicant will be asked to add equivalency statement for clonidine base.
Net contents (e.g. tablet count)	120 mL	Acceptable
"Rx only" displayed on the principal display	Yes	Acceptable
NDC number	Yes	Acceptable
Lot number and expiration date	Yes	Acceptable
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes	Acceptable
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use)	N/A	

Other package terms include pharmacy bulk package and imaging bulk package which require “Not for direct infusion” statement.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Bar code	Yes	

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

Assessment of Carton and Container Labeling: ***Adequate with comment***

Any deficiencies should be listed at the end in the “ITEMS FOR ADDITIONAL ASSESSMENT.”

Comment to the sponsor

1. **Add a statement on the caron and bottle labels "Each mL of the extended-release suspension contains 0.1 mg of clonidine hydrochloride equivalent to 0.9 mg of clonidine base."**
2. **Change "clonidine hydrochloride" to "(clonidine hydrochloride)" in the established name on the carton label of 120 mL bottle.**
3. **Include the list of excipients on the carton label if space is available.**

ITEMS FOR ADDITIONAL ASSESSMENT

Overall Assessment and Recommendation:

Adequate with the comment.

1. **Add a statement on the caron and bottle labels "Each mL of the extended-release suspension contains 0.1 mg of clonidine hydrochloride equivalent to 0.9 mg of clonidine base."**
2. **Change "clonidine hydrochloride" to "(clonidine hydrochloride)" in the established name on the carton label of 120 mL bottle.**
3. **Include the list of excipients on the carton label if space is available.**

Primary Labeling Assessor Name and Date: Renishkumar Delvadia, 04/02/2024

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto, 04/02/2024

Renishkumar Delvadia

Digitally signed by Renishkumar Delvadia
Date: 4/15/2024 09:46:31AM
GUID: 5388ee7d000671ff7781f1835a3ff7b9

Julia Pinto

Digitally signed by Julia Pinto
Date: 4/15/2024 12:39:52PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

CHAPTER VI: BIOPHARMACEUTICS

IQA NDA Assessment Guide Reference

NDA Number	NDA-217645-ORIG-1
Assessment Cycle Number	01
Drug Product Name/ Strength	Onyda™ XR (Clonidine Hydrochloride) Extended-Release Oral Suspension 0.1 mg/mL
TRoute of Administration	Oral
Applicant Name	Tris Pharma, Inc.
Therapeutic Classification/ OND Division	Neurologic Disorders /DN1
RLD/RS Number	NDA 022331 Kapvay® (Clonidine Hydrochloride) Extended-Release Tablet
Proposed Indication	Treatment of attention-deficit/hyperactivity disorder (ADHD) as monotherapy and as adjunctive therapy to stimulant medications
Primary Reviewer	Jia Leo, Ph.D.
Secondary Reviewer	Ta-Chen Wu, Ph.D.

Assessment Recommendation: **Adequate**

Assessment Summary:

The Applicant is seeking approval of clonidine HCl extended-release oral suspension 0.1 mg/mL (once nightly) via 505(b)(2) pathway. The listed drug (LD) is Kapvay® (clonidine HCl) Extended-Release Tablet 0.1 mg (twice daily) under NDA 022331. The proposed once-nightly clonidine HCl ER oral suspension offers an advantage over the marketed product by allowing for flexible titration and easier administration for patients who have difficulty swallowing a solid dosage form.

Clonidine HCl ER oral suspension was developed using Tris' patented LiquiXR® technology, which is a combination of ion-exchange chemistry and the science of extended release. (b) (4)

(b) (4)

The key Biopharmaceutics review findings with respect to the proposed dissolution method and acceptance criteria, in vitro alcohol dose-dumping potential, Extended-Release (ER) claim, and formulation bridging are summarized below.

Dissolution Method:

The Applicant evaluated different dissolution media ((b) (4), and 0.6M KH_2PO_4), different medium volumes ((b) (4) and 900 mL), and different paddle speeds ((b) (4), 50, and (b) (4) rpm). The selection of 0.6M KH_2PO_4, 900 mL volume, and 50 rpm paddle speed is acceptable. The Applicant also evaluated the discriminating ability of the proposed method against (b) (4) (b) (4)

The proposed dissolution method is considered discriminating against (b) (4) as indicated by dissimilar dissolution profiles (similarity factor f2 < 50). The proposed dissolution method is acceptable.

Dissolution Acceptance Criteria:

The originally proposed dissolution acceptance criteria ((b) (4) NMT (b) (4)%, 4 hr (b) (4)%, and (b) (4) hr NLT (b) (4)%) were deemed permissive. In response to the Biopharmaceutics Information Request (dated 10/20/2023) in which the Division provided guidance for how to properly set dissolution acceptance criteria for extended-release dosage forms, the Applicant revised the dissolution acceptance criteria to 0.5 hr NMT (b) (4)%, 4 hr (b) (4)%, and (b) (4) hr NLT (b) (4)%. Based on the provided dissolution profile of the pivotal bio-batch, the registration batches, and the stability batches, the revised dissolution acceptance criteria are still considered as permissive. The Applicant was requested to tighten the dissolution acceptance criteria to 0.5 hr NMT (b) (4)%, 4 hr (b) (4) (b) (4)%, and 16 hr NLT (b) (4)% in the IR dated 4/3/2024. In response, the Applicant agreed to accept the recommended acceptance criteria at the 0.5 hr and 4 hr time points but proposed to extend the last time point to 18 hr. The justification provided by the Applicant for the last time point is unacceptable. However, considering the tight AUC and Cmax data in both the single dose and multiple dose studies, after internal discussion, Biopharmaceutics will accept the last time point set at 18 hr.

In Vitro Alcohol Dose Dumping:

The Applicant evaluated the in-vitro alcohol dose dumping potential using the pivotal bio-batch (lot 43111) with sampling up to 2 hours in 0.1N HCl medium containing 0%, 5%, 10%, 20%, and 40% (v/v) alcohol and in QC medium containing 0%, 5%, 10%, and 20% (v/v) alcohol. Due to the observed precipitation with 40% alcohol in QC medium, the in vitro alcohol dose-dumping study was not conducted under QC medium + 40% alcohol condition. Based on the results, the dissolution of the proposed drug product is significantly faster with 40% alcohol in 0.1N HCl and with 20% alcohol in 0.1N HCl and QC medium. The proposed drug product exhibited alcohol-induced dose-dumping potential at 20% alcohol level. The in vitro

assessment of alcohol induced dose-dumping potential is acceptable and the proposed language in the labeling is acceptable.

Extended-Release Claim:
Results of the multiple dose study comparing the proposed drug product, clonidine HCl extended-release oral suspension 0.1 mg/mL (once daily) and the LD, Kapvay® (clonidine HCl) extended-release Tablet 0.1 mg (twice daily) showed that the PK profile of the proposed once daily drug product exhibited greater degree of fluctuation in Cmax,ss and Cmin,ss than that of the RLD. Comparison of the PK parameters showed that the AUCt,ss and Cmax,ss are equivalent between the proposed drug product and the LD, but the Cmin,ss of the proposed drug product is not equivalent to that of the LD. Results of food effect study suggest that the proposed drug product is devoid of significant food effects and food-induced dose-dumping potential. In vitro dissolution profiles indicate an extended-release characteristics as intended. In view of the LD for comparison being an extended-release drug product and the provided information/data package being supportive of extended-release characteristics, the Extended-Release claim can be granted from a Biopharmaceutics perspective and based on 21 CFR 320.25(f).

Formulation bridging:
The proposed commercial formulation and the formulation used in pivotal clinical studies are identical. No in vivo bridging study is needed.

Recommendation:
From a Biopharmaceutics perspective, NDA 217645 for Clonidine Hydrochloride Extended-Release Oral Suspension 0.1 mg/mL is ADEQUATE.

FDA-approved dissolution method and acceptance criteria:

USP Apparatus	Speed (RPMs)	Medium /Temperature	Volume (mL)	Acceptance Criteria
II (Paddle)	50	0.6M KH_2PO_4 solution, pH 4.3/37 °C ± 0.5°C	900	(b) (4) NMT (b) (4) % 4 hr (b) (4) % 18 hr NLT (b) (4) %

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Sequence 001 /Original submission	7/24/2023
Sequence 004/ Response to Biopharmaceutics Information Request	11/21/2023
Sequence 011/ Response to Information Request	4/5/2024

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Concise Description of Outstanding Issues (List bullet points with key information and update as needed): None

B.1 BCS DESIGNATION

Assessment:

No BCS designation was requested. No permeability data for the drug substance were provided. Based on the provided aqueous solubility data and the maximum single dose (0.4 mg), the drug substance (clonidine HCl) is highly soluble per BCS criteria and exhibits pH-dependent solubility.

Solubility:

Table 1. Aqueous solubility of clonidine HCl

Solution	Solubility of Clonidine HCl [mg/ml]
buffer pH 1	87
buffer pH 3	89
buffer pH 5	91
buffer pH 7	101
buffer pH 9	3
buffer pH 11	3

Permeability:

No permeability data for the drug substances were provided.

B.2 DISSOLUTION METHOD AND ACCEPTANCE CRITERIA

Assessment: ***{Adequate}***

The Applicant evaluated different dissolution media ((b) (4), and 0.6M KH_2PO_4), different medium volumes ((b) (4) and 900 mL), and different paddle speeds ((b) (4), 50, and (b) (4) rpm). Based on the provided data, the selection of 0.6M KH_2PO_4, 900 mL volume, and 50 rpm paddle speed is acceptable. The Applicant also evaluated the discriminating ability of the proposed method against (b) (4) (b) (4) (b) (4). As the discriminating ability is evaluated based on target value (b) (4) from the target values or ranges, the proposed dissolution method is considered discriminating against (b) (4) as indicated by f2 < 50. Overall, the proposed dissolution method is acceptable.

The originally proposed dissolution acceptance criteria ((b) (4) NMT (b) (4)%, 4 hr (b) (4)%, and (b) (4) hr NLT (b) (4)%) were deemed permissive. The Applicant was given guidance on

how to set dissolution acceptance criteria for extended-release dosage forms and requested to propose a new set of dissolution acceptance criteria in the IR dated 10/20/2023. In response, the Applicant revised the dissolution acceptance criteria to 0.5 hr NMT (b)(4)%, 4 hr (b)(4)%, and (b)(4) hr NLT (b)(4)%. Based on the provided dissolution profile of the pivotal bio-batch, the registration batches, and the stability batches, the revised dissolution acceptance criteria are still considered as permissive. The Applicant was requested to tighten the dissolution acceptance criteria to 0.5 hr NMT (b)(4)%, 4 hr (b)(4)%, and 16 hr NLT (b)(4)% in the IR dated 4/3/2024. In response, the Applicant agreed to accept the recommended acceptance criteria at the 0.5 hr and 4 hr time points but proposed to extend the last time point to 18 hr. The Applicant states that although all batches tested including the clinical batch, met the NLT (b)(4)% specification at 16 hr, the mean dissolution value at the 16-hr time point is very close to the (b)(4)% limit. The Applicant believes that applying the 16 hr test data to the NLT (b)(4)% limit would often result in some unnecessary S2 and S3 level testing in order to meet the overall acceptance criteria. The justification for the last time point is unacceptable. Based on the provided data, none of the clinical batch, registration batches and stability batches have to go through S2 or S3 testing due to dissolution at 16 hr not able to meet S1 testing criterion. However, considering the tight AUC and Cmax data in both the single dose and multiple dose studies, after internal discussion, Biopharmaceutics will accept the last time point set at 18 hr.

1. Dissolution Method

Table 2. Proposed dissolution method

USP Apparatus	Speed (RPMs)	Medium/Temperature	Volume (mL)
II (Paddle)	50	0.6M KH_2PO_4 solution, pH 4.3/37°C ± 0.5°C	900

1) Selection of dissolution parameters

(b) (4)

(b) (4)

Reviewer's comment on the selection of dissolution parameters:
Based on the dissolution profile data of two finished product batches, the selection of dissolution parameters, including dissolution medium, medium volume, and paddle speed is acceptable.

2) Discriminating ability of the dissolution method
As the dissolution behavior is primarily driven by the coated clonidine (b) (4) the Applicant evaluated the discriminating ability of the dissolution method against the critical material attributes (CMAs), critical formulation variables (CFVs) and critical process parameters (CPPs) that impact the drug release from coated clonidine (b) (4) (**Table 9**). Specifically, the Applicant evaluated the discriminating ability of the proposed method against (b) (4)
(b) (4)

The results (**Table 10**) showed that the dissolution method can detect changes in all tested variable as indicated by dissimilar dissolution profiles (similarity factor f2 < 50). As the discriminating ability is evaluated based on target value (b) (4) the proposed dissolution method is considered discriminating against (b) (4)

Table 9. Variables tested in evaluation of the discriminating ability of the dissolution method

Attribute	Variable	Rationale	Target	Level(s)	Batch No.
Material attribute				(b) (4)	RD1257-037
Formulation					PD0005-150
					PD0005-153
					PD0005-159
Manufacturing					PD0005-144
Manufacturing					PD0005-114
Manufacturing					PD0005-100

Table 10. Dissolution profile data of the reference batch and the variant batches

Batch No.	Attribute	Time (h)	0.5	1	2	3	4	6	8	12	14	16	18	24	F2
		Proposed Specification	(b) (4)												
		Variable	% drug released												
43111	Reference	(b) (4)													-
RD1257-037	Material attribute														-
PD0005-150	Formulation														29
PD0005-153	Formulation														43
PD0005-159	Formulation														36
PD0005-144	Process														45
PD0005-114	Process														26
PD0005-100	Process														33

Notebook Reference: MV1092-033,099,100,101,102,103,104,105; RD1273-025; MV1268-056; RD1350-090; RD1359-068; MV1268 -002; RD1350-061

* f2 value (b) (4) and (b) (4) is 27 (calculated by this reviewer).

2. Dissolution Data and Acceptance Criteria

The originally proposed dissolution acceptance criteria are permissive. This Reviewer provided guidance on how to set dissolution acceptance criteria for extended-release dosage forms and requested to propose a new set of dissolution acceptance criteria in the IR dated 10/20/2023. In response, the Applicant revised the dissolution acceptance criteria as 0.5 hr NMT (b) (4)%, 4 hr (b) (4)%, and (b) (4) hr NLT (b) (4)% (**Table 11**). Based on the provided dissolution profile of the pivotal bio-batch, the registration batches (**Figure 1**)[1] and stability batches[2], the revised dissolution acceptance criteria are still considered as permissive. The Applicant was requested to tighten the dissolution acceptance criteria to 0.5 hr NMT (b) (4)%, 4 hr (b) (4)%, and 16 hr NLT (b) (4)% in the IR dated 4/3/2024. In response, the Applicant agreed to accept the recommended acceptance criteria at the 0.5 hr and 4 hr time points but proposed to extend the last time point to 18 hr (**Table 12**). The Applicant states that although all batches tested including the clinical batch, met the NLT (b) (4)% specification at 16 hr, the mean dissolution value at the 16-hr time point is very close to the (b) (4)% limit. The Applicant believes that applying the 16 hr test data to the NLT (b) (4)% limit would often

[1] \\CDSESUB1\EVSPROD\nda217645\0001\m3\32-body-data\32p-drug-prod\clonidine-hcl-er-os\32p2-pharm-dev\mm-diss-alcohol-dose-dump-study.pdf (page 10 - 16)

[2] \\CDSESUB1\EVSPROD\nda217645\0004\m3\32-body-data\32p-drug-prod\clonidine-hcl-er-os\32p8-stab\sub-batches-18m-diss-profile-data.pdf

result in some unnecessary S2 and S3 level testing in order to meet the overall acceptance criteria.

The justification for the last time point is unacceptable. Based on the provided data, none of the clinical batch, registration batches and stability batches have to go through S2 or S3 testing due to dissolution at 16 hr not able to meet S1 testing criterion. However, considering the tight AUC and Cmax data in both the single dose and multiple dose studies, after internal discussion, Biopharmaceutics will accept the last time point set at 18 hr.

Table 11. Revised dissolution acceptance criteria in 11/21/2023 IR response

Dissolution Specifications			
Original Proposed Specifications		**Newly Proposed Specifications**	
Hour	**Drug Release**	**Hour**	**Drug Release**
(b) (4)	NMT (b) (4)%	*0.5*	*NMT (b) (4)%*
4	(b) (4)% to (b) (4)%	4	*(b) (4)% to (b) (4)%*
(b) (4)	NLT (b) (4)%	(b) (4)	NLT (b) (4)%

Figure 1. Dissolution profile of the pivotal bio-batch (43111), and the registration batches (43112, 43113, 43114, 43115, 43116) (plotted by the reviewer)

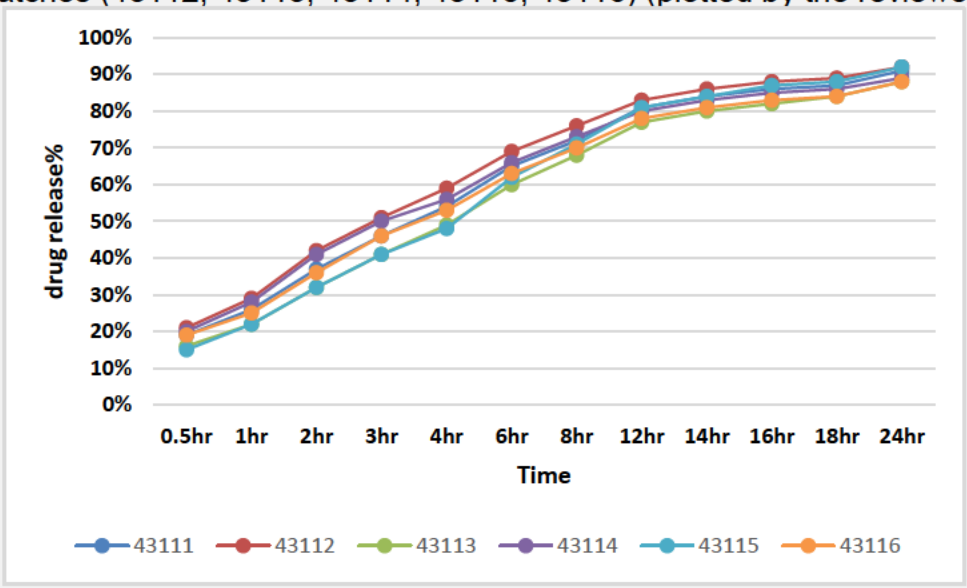


Table 12. Revised dissolution acceptance criteria in 4/6/2024 IR response

Time in hours	Drug Released in %
0.5 hour	NMT (b) (4)%
4 hour	(b) (4)% to (b) (4)%
18 hour	NLT (b) (4)%

B.5 MODIFIED RELEASE ORAL DRUG PRODUCTS – *In-Vitro Alcohol-Induced Dose Dumping*

Assessment: *Adequate*

The Applicant conducted solubility study prior to the in vitro alcohol dose-dumping study to determine the feasibility to perform alcohol dose dumping study in QC medium. According to the Applicant, with 40% alcohol, precipitation was observed in QC medium. Therefore, the in vitro alcohol dose dumping study in QC medium did not include 40% alcohol. The Applicant evaluated the in-vitro alcohol dose-dumping potential using the pivotal bio-batch (lot 43111) with sampling up to 2 hours in 0.1N HCl medium containing 0%, 5%, 10%, 20%, and 40% (v/v) alcohol and in QC medium containing 0%, 5%, 10%, and 20% (v/v) alcohol (**Table 13**). Based on the profile results (**Figure 2 and 3**), the dissolution of the proposed drug product is significantly faster (close to 85% dissolution at 2 hours) with 40% alcohol in 0.1N HCl. There was approximately 2 times increase in drug release with 20% alcohol in both 0.1N HCl and QC medium. The increases in drug release in the presence of 20% could suggest the altering of plasma concentration-time profile during the dosing interval, e.g., higher Cmax and lower Cmin,ss). This is a less concern in the presence of lower concentrations of alcohol at or below 10% v/v. The Applicant included the following language in the drug product labeling:

Alcohol (b) (4)

In an in vitro alcohol-induced dose dumping study, a significantly faster and more variable ONYDA XR drug release was observed in the presence of 20% alcohol, but not with 5% or 10% alcohol, when compared to 0% alcohol.

What should I avoid while taking ONYDA XR?

- Do not drink alcohol or take other medicines that make you sleepy or dizzy while taking ONYDA XR until you talk with your doctor. ONYDA XR taken with alcohol or medicines that cause sleepiness or dizziness may make your sleepiness or dizziness worse.

The Agency typically require complete/full dissolution profile data (the attainment of complete dissolution such as up to 24 hours) for in vitro alcohol dose-dumping studies. However, as the label clearly stated, "Do not drink alcohol…while taking ONYDA XR…", the risk of potential alcohol-induced dose dumping is significantly mitigated. Therefore, we would accept the in vitro alcohol dose-dumping study performed up to 2 hours. The in vitro assessment of alcohol induced dose-dumping potential is acceptable and the proposed language in the labeling is acceptable.

Table 13. Alcohol dose dumping study conditions

Dissolution Test Condition & Acceptance Criteria		
Apparatus		USP Apparatus II (Paddle)
Speed		50 rpm
Media	1	0.1 N HCl with 0%, 5% v/v, 10% v/v, 20% v/v and 40% v/v alcohol
	2	QC Media[1] with 0%, 5% v/v, 10% v/v, and 20% v/v alcohol
Medium Volume	1	496 mL for 0.1 N HCl with 0%, 5% v/v, 10% v/v, 20% v/v and 40% v/v alcohol
	2	896 mL for QC Media[1] with 0%, 5% v/v, 10% v/v, and 20% v/v
Temperature		37°C ± 0.5°C
Finished Product Sample Volume for analysis		4 mL (Well-shaken suspension)
No. of Units		12
Time Interval		15, 30, 45, 60, 75, 90, 105 and 120 minutes
Acceptance Criteria		Report results. For information use only

Figure 2. Dissolution profile of the proposed drug product in 0.1N HCl containing 0%, 5%, 10%, 20% and 40% (v/v) ethanol

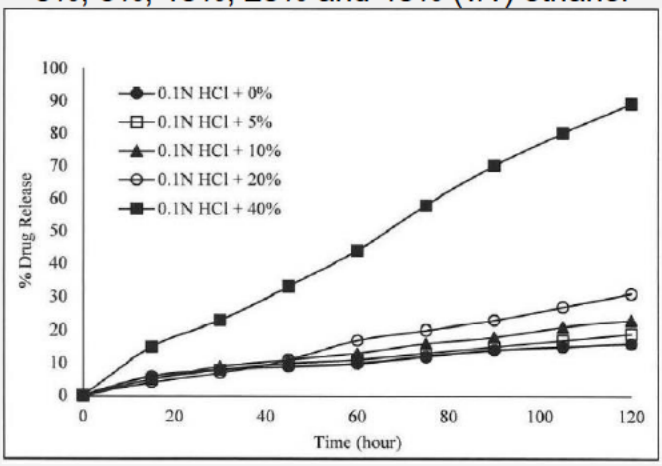
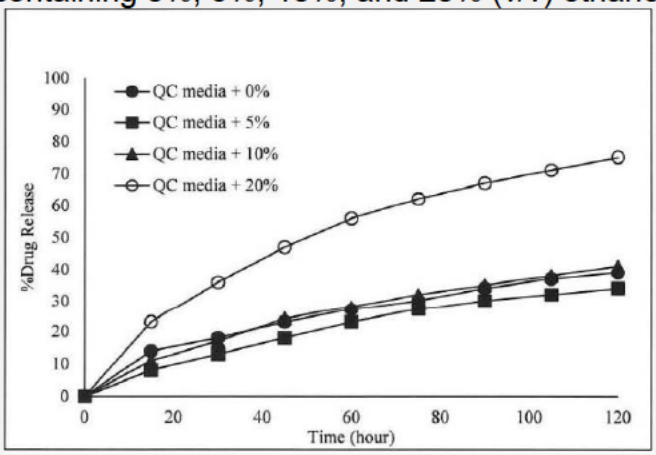


Figure 3. Dissolution profile of the proposed drug product in QC medium containing 0%, 5%, 10%, and 20% (v/v) ethanol



B.11 EXTENDED RELEASE DOSAGE FORMS – *Extended Release Claim*

Assessment: *Adequate*

The Applicant conducted a multiple dose study (2021-5095) in healthy subjects comparing the proposed drug product, clonidine HCl extended-release oral suspension 0.1 mg/mL (once daily) and the LD, Kapvay® (clonidine HCl) extended-release Tablet 0.1 mg (twice daily). The Applicant also evaluated the food effect on the pharmacokinetics (PK) of the proposed drug product in health subjects (study 2021-5094).

As shown in **Figure 4**, the Cmax,ss of the proposed drug product is higher than that of the LD and the Cmin,ss is lower than that of the LD. The PK profile of the proposed once daily drug product exhibited greater degree of fluctuation in Cmax,ss and Cmin,ss than that of the LD. The comparison of the PK parameters (**Table 14**) showed that the AUCt,ss and Cmax,ss are equivalent between the proposed drug product and the LD, but the Cmin,ss of the proposed drug product is not equivalent to that of the LD.

The results of food effect study (**Figure 5** and **Table 15**) showed similar Cmax, AUCt and AUCinf of the proposed drug product under fasted and fed condition. The results suggest that the proposed drug product is devoid of significant food effects and food-induced dose-dumping potential.

In addition, the in vitro dissolution profiles indicate an extended-release characteristics as intended. In view of the LD for comparison being an extended-release drug product and the provided information/data package being supportive of extended-release characteristics, the Extended-Release claim can be granted from a Biopharmaceutics perspective and based on 21 CFR 320.25(f).

Figure 4. Mean PK profile of the proposed drug product (treatment A) and the RLD (treatment B) after multiple dose (5 days) (Study 2021-5095)

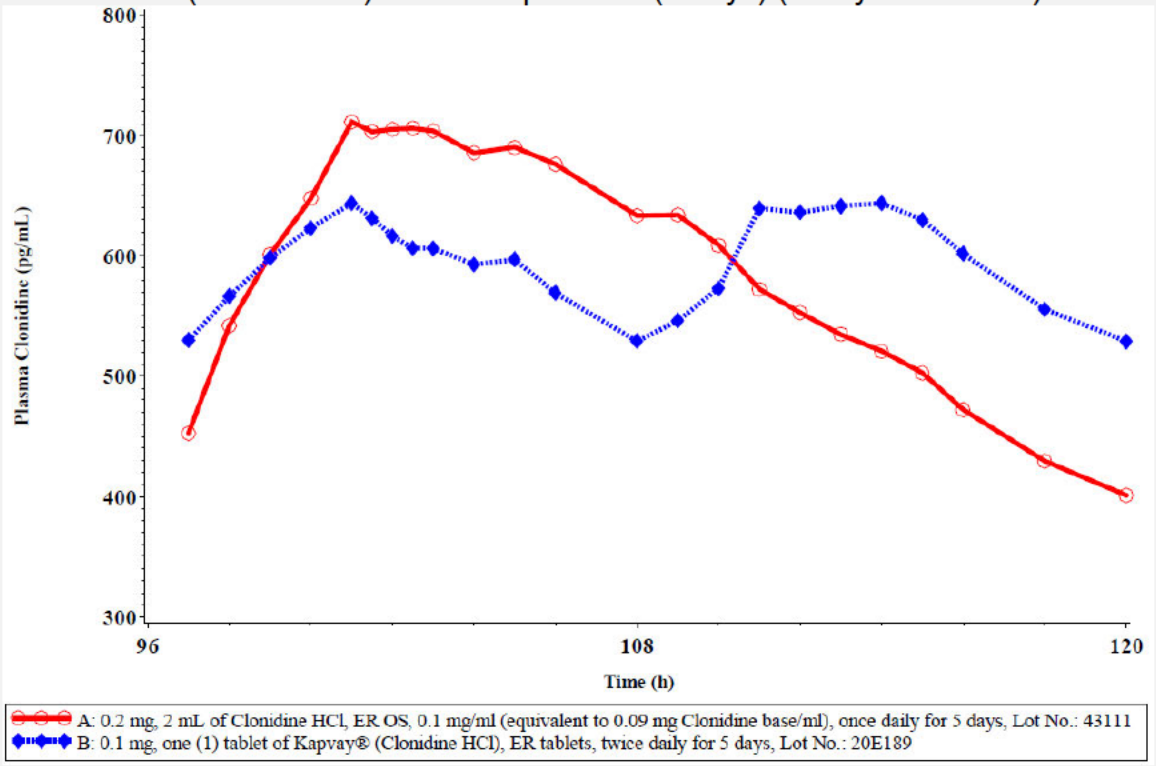


Table 14. PK parameters of the proposed drug product (treatment A) and the LD (treatment B) after multiple dose (5 days) (Study 2021-5095)

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
$AUC_{t,ss}$	A	19	13791.0 (26)	13353.1	A vs B	97.68	93.41 - 102.14	8
*(hr*pg/mL)*	B	19	14120.9 (26)	13670.6				
$C_{max,ss}$	A	19	740.2 (25)	719.7	A vs B	107.90	103.80 - 112.17	7
(pg/mL)	B	19	682.7 (23)	667.0				
$C_{24,ss}$	A	19	401.1 (35)	378.2	A vs B	74.01	69.33 - 79.00	12
(pg/mL)	B	19	528.9 (27)	511.0				

CV, Coefficient of Variation; n, number of subjects; Sbj, Subject; Trt, Treatment.

Treatment A (Test): 0.2 mg (2 mL of Clonidine hydrochloride (HCl), extended release (ER) oral suspension (OS), 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111, (Tris Pharma, Inc., USA) under fasted conditions at 0, 24, 48, 72, and 96 hours

Treatment B (Reference): One (1) tablet of Kapvay® (Clonidine hydrochloride), extended-release tablets, 0.1 mg (equivalent to 0.087 mg of the free base in 0.1 mg tablet) Lot No.: 20E189, (Concordia Pharmaceuticals, USA) under fasted conditions at 0, 12, 24, 36, 48, 60, 72, 84, 96, and 108 hours

Figure 5. Mean PK profile of the proposed drug product under fasted (treatment B) and fed (treatment A) conditions (Study 2021-5094)

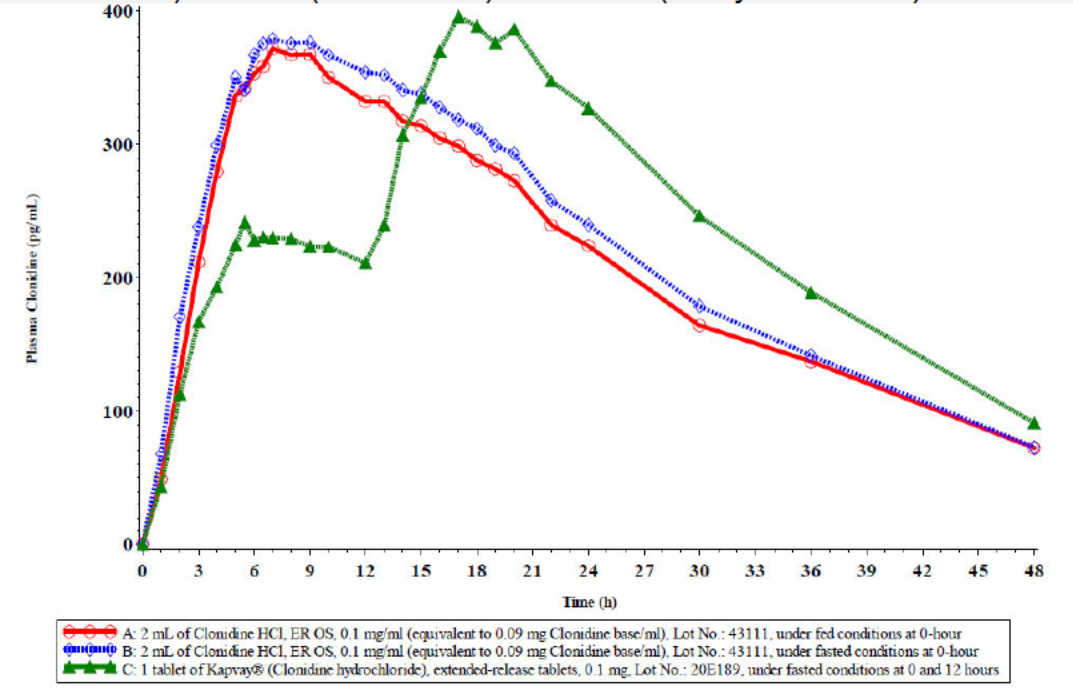


Table 15. PK parameters of the proposed drug product under fasted (treatment B) and fed (treatment A) conditions (Study 2021-5094)

Parameter	*Trt*	*n*	*Arithmetic Mean (CV%)*	*Geometric Mean*	*Contrast*	*Ratio (%)*	*90% Confidence Interval*	*Intra-Sbj CV(%)*
AUC_t	**A**	19	9956.4 (26)	9716.8	**A vs B**	95.27	91.08 - 99.66	8
*(hr*pg/mL)*	**B**	20	10556.3 (27)	10198.9				
AUC_{inf}	**A**	19	11639.0 (29)	11236.5	**A vs B**	96.89	91.80 - 102.26	9
*(hr*pg/mL)*	**B**	20	12107.2 (31)	11597.0				
C_{max}	**A**	19	392.7 (24)	382.4	**A vs B**	96.87	93.26 - 100.61	7
(pg/mL)	**B**	20	404.2 (22)	394.8				

Treatment A (Test)	2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fed conditions at 0-hour
Treatment B (Test)	2 mL of Clonidine HCl, ER OS, 0.1 mg/ml (equivalent to 0.09 mg Clonidine base/ml), Lot No.: 43111 (Tris Pharma, Inc., USA), under fasted conditions at 0-hour

B.12 BRIDGING OF FORMULATIONS

Assessment: *Adequate*

The proposed commercial formulation was used in pivotal clinical studies (**Table 16 and Table 17**). No additional in vivo bridging is needed.

Table 16. Formulations used in clinical studies

Study #	Study Objective	Batch No.	Formulation Name and Type
20-VIN-0304	Formulation confirming pilot study	RD1205-113	Prototype 1 (Similar formulation as the intended commercial)
2021-5094	Pivotal-comparative bioavailability versus listed drug for single dose under fasted conditions and food effect	43111	Intended commercial formulation
2021-5095	Pivotal-comparative bioavailability versus listed drug for multiple dose under fasted conditions	43111	Intended commercial formulation

Table 17. Commercial formulation of the proposed drug product

Components	Quality Standards	Pharmaceutical Function	Strength (label claim) 0.1 mg per mL		
			Qty/unit (mg/mL)	% w/v	% w/w
(b) (4)					

2 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 4/15/2024 08:30:05PM
GUID: 50bdfe8d00003559ede66be3fd299f65

Jia Leo

Digitally signed by Jia Leo
Date: 4/15/2024 05:47:24PM
GUID: 58b87f98014440ef24056beabf77e491

U.S. FOOD & DRUG ADMINISTRATION

CHAPTER VII: MICROBIOLOGY

For more details about the items in this template, please see Chapter VII (Microbiology) of the NDA IQA Guide

Product Information	
NDA Number	217645
Assessment Cycle Number	01
Drug Product Name/ Strength	Clonidine Hydrochloride Extended-Release Oral Suspension / 0.1 mg per mL
Route of Administration	Oral
Applicant Name	Tris Pharma, Inc.
Therapeutic Classification/ OND Division	CDER/OND/ON/DP
Manufacturing Site	Tris Pharma, Inc., 2033 Route 130 South, Suite D, Monmouth Junction, New Jersey (NJ) 08852
Method of Sterilization	N/A. Non-sterile suspension

Assessment Recommendation: **Adequate**

Assessment Summary: The submission **is recommended** for approval on the basis of product quality microbiology.

List Submissions Being Assessed:

Document(s) Assessed	Date Received
Orig-1 (SD 1)	7/24/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A.

Remarks: The internal goal dates are mid-cycle 12/19/2023, QDD 4/2/2024, ODD 4/16/2024.

Concise Description of Outstanding Issues: **None**

Supporting Document:

NDA review (b) (4) .pdf (adequate, dated 11/25/2009). (b) (4) . The review is referenced (b) (4) .

S Drug Substance – non sterile.

Note to reviewer: Per DMF (b) (4), submission dated 12/12/2022, 3.2.S.4.1, *drug-substance.pdf* at (b) (4) The total aerobic microbial count (TAMC) limit is NMT (b) (4) cfu/g, total yeast and mold count (TYMC) limit is NMT (b) (4) cfu/g and bacterial endotoxins limit if NMT (b) (4) EU/mg. Results for drug substance batches 22008310, 22008311, 22008463 were all: TAMC: < (b) (4) cfu/g, TYMC: < (b) (4) cfu/g, endotoxins: < (b) (4) IU/mg (pg. 52/60). The limits are within the USP <1111> acceptance criteria for non-sterile substances and adequate.

P Drug Product

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

- Description of drug product – Clonidine Hydrochloride Extended-Release Oral Suspension (Clonidine HCl ER OS) is manufactured in strength of 0.1 mg per mL, which is equivalent to 0.09 mg of Clonidine base per mL. It is a light beige to tan viscous suspension intended for oral administration. It is supplied as a 7 mL suspension in a (b) (4). bottle as physicians sample pack and as a 120 mL suspension in a (b) (4) bottle. Multiple dose.

- Drug product composition (7/24/2023, 3.2.P.1., *desc-and-comp-of-the-dp.pdf*, pg. 3) – The suspension is formulated with 'Uncoated Clonidine (b) (4),' and 'Coated Clonidine (b) (4),' summarized below.

Component	Quality Standard	Content per mL (mg/mL)	Function
(b) (4)			

(b) (4)

The drug product is formulated with purified water (b) (4) and methyl paraben, propyl paraben (b) (4).

Submission batch size: (b) (4) liters ((b) (4) kg).
Maximum proposed commercial batch size: same, (b) (4) liters ((b) (4) kg)

- Description of container closure system (7/24/2023, 3.2.P.7., *container-closure-narrative-0001.pdf*, pg. 2-4) –

Configuration	Component	Description	Manufacturer
1 fl. Oz. size	Bottle	(b) (4) white HDPE container, Neck finish 24/400	(b) (4)
	Closure	24 mm/ (b) (4) white child resistant closure (b) (4)	
5 fl. Oz size	Bottle	(b) (4) round bottle, neck size: 24/400 mm	
	Closure	24 mm/ (b) (4) white child resistant closure (b) (4)	

Assessment: **Adequate**. The drug product is formulated with purified water and two (b) (4). Components reference USP or NF standards. The drug product composition and container closure are described and adequate.

P.2 PHARMACEUTICAL DEVELOPMENT

(b) (4)

17 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

Helen Ngai

Digitally signed by Helen Ngai
Date: 11/27/2023 09:50:31AM
GUID: 508da70b00028e6d6f228f597b070551

KellyAnn Miller

Digitally signed by KellyAnn Miller
Date: 11/27/2023 09:53:35AM
GUID: 5e1f6620004382592e50464168938fab

Valerie Amspacher

Digitally signed by Valerie Amspacher
Date: 4/16/2024 01:35:17PM
GUID: 5714dbd10078d2d3d9b60a0ceb819fc3

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
04/16/2024 01:41:35 PM