CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214044Orig1s000

PRODUCT QUALITY REVIEW(S)

Table of Contents

U.S. FOOD & DRUG ADMINISTRATION

RECOMMENDATION

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

NDA 214044
Assessment 1

Drug Product Name	Tramadol Hydrochloride Oral Solution
Dosage Form	Oral solution
Strength	25 mg/5 mL
Route of Administration	oral
Rx/OTC Dispensed	Rx
Applicant	Athena Bioscience, LLC.
US agent, if applicable	N/A

Submission(s) Assessed	Document Date	Discipline(s) Affected
Supporting document 2; eCTD 0001	1 Nov 19	All, original submission
Supporting document 4; eCTD 0004	20 Dec 19	Facilities
Supporting document 7; eCTD 0007	28 Jan 20	Microbiology
Supporting document 8; eCTD 0008	18 Feb 20	Drug product
Supporting document 9; eCTD 0009	17 Mar 20	Process
Supporting document 13; eCTD 0013	13 May 20	Drug product
Supporting document 16; eCTD 0016	16 Jun 20	Drug product
Supporting document 19; eCTD 0019	8 Jul 20	Drug product

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sharon Kelly	Donna Christner
Drug Product	Eric Bow	Julia Pinto
Manufacturing	Ruth Moore	Frank Wackes

Microbiology	Sallie Crenshaw	Christine Craig
Biopharmaceutics	N/A	N/A
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Valerie Amspacher	
Laboratory (OTR)	N/A	N/A
Environmental	Eric Bow	Julia Pinto

EXECUTIVE SUMMARY

I. RECOMMENDATIONS AND CONCLUSION ON APPROVABILITY

CMC recommendation is approval from all disciplines.
The applicant has adequately demonstrated the stability of the drug product over 24 months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature].

II. SUMMARY OF QUALITY ASSESSMENTS

A. Product Overview

Athena Bioscience has developed Qdolo (tramadol HCl) oral solution for the treatment of chronic pain. The reference listed drug is Ultram tablets; the applicant has proposed an oral solution for patients who cannot swallow tablets. The drug product is a clear solution containing 5 mg/mL tramadol HCl USP.
The manufacturing process for this non-sterile oral solution involves (b) (4) and the manufacturing parameters and controls were shown to be adequate to mitigate risks to product CQAs.
The applicant has adequately demonstrated the stability of the drug product over 24 months when stored at 20°C to 25°C (68°F to 77°F); excursions permitted to 15°C to 30°C (59°F to 86°F). [see USP Controlled Room Temperature].

Proposed Indication(s) including Intended Patient Population	An opioid agonist indicated in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate
Duration of Treatment	chronic

Maximum Daily Dose	400 mg/day
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

Drug Substance: Adequate

Reference is made to DMF (b) (4) for Tramadol Hydrochloride USP manufactured by (b) (4) (Letter of Authorization Sept. 24, 2019). The DMF evaluation is currently Adequate (CMC Review #6 inc. SDN #24 and #25). A technical package for the DMF ('open portion' of DMF) was provided to the sponsor. The Tramadol Hydrochloride USP specifications for (b) (4) are in compliance with the current USP monograph. The sponsor has sufficient knowledge of the impurity profile and is able to evaluate the impact on the drug product formulation. The (b) (4) can be an impurity from the (b) (4) use during the (b) (4) manufacturing process. (b) (4) esting for elemental impurities is performed on the drug product. The DMF Holder's certificate of analysis for their lots used by (b) (4) to manufacture the registration batches are comparable to the corresponding certificate of analysis from (b) (4). This comparison demonstrates the analytical method verification as performed by (b) (4) was successful.

(b) (4) tests the API (b) (4) up to the manufacturer's re-test date of (b) (4), then it is disposed.

Drug Product: Adequate

Athena Bioscience has developed Qdolo (tramadol HCl) oral solution for the treatment of chronic pain. The reference listed drug is Ultram tablets; the applicant has proposed an oral solution for patients who cannot swallow tablets. The drug product is a clear solution containing 5 mg/mL tramadol HCl USP.

The drug product contains the following USP/NF excipients: propylene glycol, glycerin, sodium benzoate, sodium citrate, citric acid, sucralose, and purified water. The drug product contains a non-compendial grape flavor.

The applicant has provided release and stability data for three drug product batches, all of which met the set specifications. The container closure system for the drug product is 16 oz rectangular high-density polyethylene bottles, with a child resistant (b) (4) closure. The

components of the container closure system are all GRAS and food-contact compliant.
The drug product has been granted a 24-month expiry based on the provided 24 months of long-term stability data. The drug product will be stored at controlled room temperature.
The proposed product is adequate based on the control strategies, release and stability results.

Labeling: Adequate

Manufacturing: Adequate

The manufacturing process for this non-sterile oral solution involves (b) (4) The process is relatively simple, and the manufacturing parameters and controls were shown to be adequate to mitigate risks to product CQAs. Data was provided to support hold time of up to (b) (4) for the (b) (4) (b) (4) .

No Pre-approval inspections were deemed necessary based on the review of the submission information and assessment of the manufacturing capabilities and inspection history of the facilities. All facilities listed in the application are acceptable to support NDA 214044.

Biopharmaceutics: Choose an item.

N/A

Microbiology (if applicable): Adequate

The drug product is non-sterile and is indicated for multiple uses in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate. The product microbial limits tests and acceptance criteria are acceptable. The microbial limits testing method suitability testing data is acceptable.

C. Risk Assessment

From Initial Risk Identification	Assessment

Attribute/ CQA	Factors that can impact the CQA	Initial Risk Ranking	Risk Mitigation Approach	Final Risk Evaluation	Lifecycle Considerations / Comments
		H, M, or L		Acceptable or Not Acceptable	
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L	Controlled by specification	Acceptable	
Uniformity of Dose – Fill/deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L	Controlled by specification	Acceptable	
pH	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L	Controlled by specification	Acceptable	
Leachables / extractables	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L	Controlled by specification	Acceptable	
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L	Controlled by specification	Acceptable	

Microbial limits	Formulation Raw materials Process parameters Scale/equipments Site	L	Controlled by specification	Acceptable	

QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Assessment Completed	Comments
(b) (4)	II	(b) (4)	(b) (4)	1	1 Apr 19	Last reviewed by Steve Kinsley
	IV		(b) (4)	1	22 Jul 20	Last reviewed by Eric Bow
	III		(b) (4)	4		
	III			4		
	III			4		
	III			4		
	III			4		

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

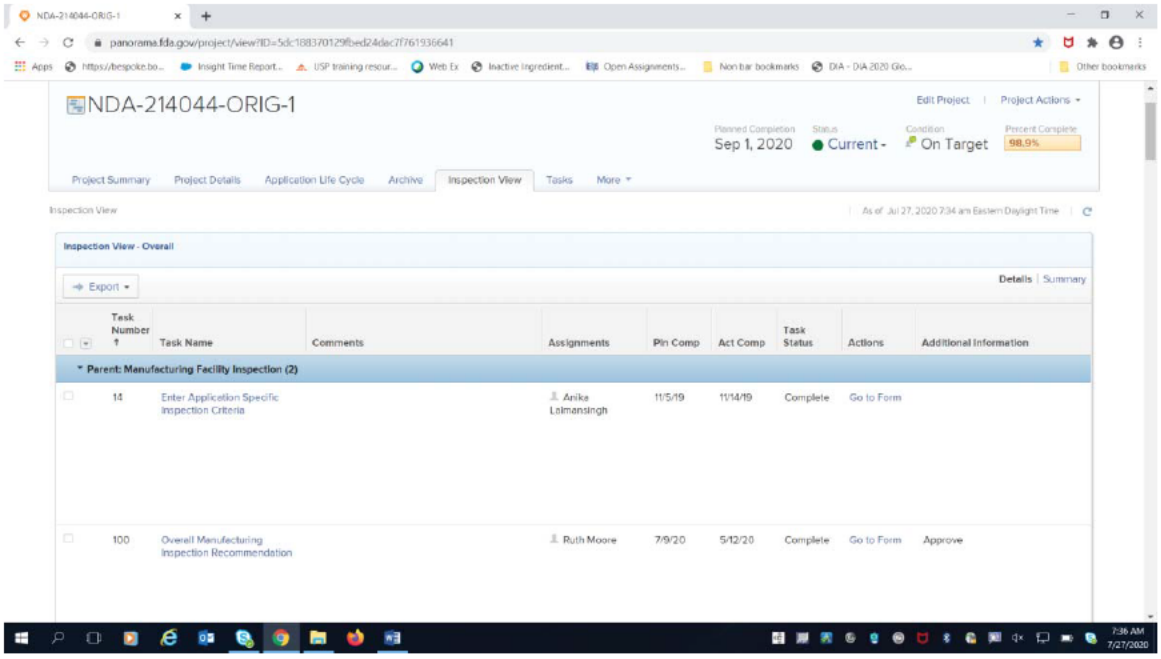
B. OTHER DOCUMENTS: *IND, RLD, RS, Approved NDA*

Document	Application Number	Description
NDA	020281	Ultram
IND	127021	

2. CONSULTS

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

Screenshot of Inspection View in Panorama (taken 27 Jul 20)



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CHAPTER IV: LABELING

IQA NDA Assessment Guide Reference

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION

Item	Information Provided in the NDA	Assessor's Comments
Product Title in Highlights		
Proprietary name	Yes	
Established name(s)	Yes	
Route(s) of administration	Yes	
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system.	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 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		
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	No	Include salt to free base conversion
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	

1.2.3 Section 11 (DESCRIPTION)

Item	Information Provided in the NDA	Assessor's Comments
DESCRIPTION section		
Proprietary and established name(s)	Yes	
Dosage form(s) and route(s) of administration	Yes	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per FDA Guidance.	No	Include salt to free base conversion
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	
If radioactive, statement of important nuclear characteristics.	n/a	
Other important chemical or physical properties (such as pKa or pH)	Yes	

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"	n/a	

1.2.4 Section 16 (HOW SUPPLIED/STORAGE AND HANDLING)

Item	Information Provided in the NDA	Assessor's Comments
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Yes	
Strength(s) in metric system	Yes	
Available units (e.g., bottles of 100 tablets)	Yes	
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	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 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.)	Yes	
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.	Yes	
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of natural rubber latex, state: "Not made with natural rubber latex. Avoid statements such as "latex-free."	n/a	
Include information about child-resistant packaging	No	Include this in the PI

1.2.5 Other Sections of Labeling

n/a

1.2.6 Manufacturing Information After Section 17 (for drug products)

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

2.0 PATIENT LABELING

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

This application is recommended for approval per labeling/labels perspective. The quality-related items in the PI comply with regulatory requirements and are consistent with guidance recommendations, and CDER labeling policies.

3.0 CARTON AND CONTAINER LABELING

3.1 Container Label

(b) (4)

3.2 Carton Labeling

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

n/a

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Proprietary name, established name, and dosage form (font size and prominence	Yes (container)	
Dosage strength	Yes (container)	
Route of administration	Yes (container)	
If the active ingredient is a salt, include the equivalency statement per FDA Guidance	Yes (container)	
Net contents (e.g. tablet count)	Yes (container)	
"Rx only" displayed on the principal display	Yes (container)	
NDC number	Yes (container)	
Lot number and expiration date	Yes (container)	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new BUD.	Yes (container)	
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 (container)	

Item	Information Provided in the NDA	Assessor's Comments about Carton Labeling
Name of manufacturer/distributor	Yes (container)	
Medication Guide (if applicable)	n/a	
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*

This application is recommended for approval per labeling/labels perspective. The quality-related items in the PI comply with regulatory requirements and are consistent with guidance recommendations, and CDER labeling policies.

ITEMS FOR ADDITIONAL ASSESSMENT

Information request 06/12/20

1. We note on the container labeling the established name [redacted] (b) (4) We do not agree. The format for the established name should be "(traMADol hydrochloride) oral solution" on the container labeling.
2. It appears that only labeling for the primary bottle containing the oral solution has been submitted. If the bottle will be packaged in secondary containment, provide the labeling for that carton.

Response 06/16/20

1. *The applicant provided the container labeling in section 3.1 of this review*
2. *The application states that no carton will be used for this drug product.*

Overall Assessment and Recommendation:

Primary Labeling Assessor Name and Date: Eric Bow, 7/8/20

Secondary Assessor Name and Date (and Secondary Summary, as needed): Julia Pinto, 7/8/20

Eric Bow

Digitally signed by Eric Bow
Date: 7/20/2020 01:47:04PM
GUID: 5df160d800320e19970e198e30e1cc2e

Julia Pinto

Digitally signed by Julia Pinto
Date: 7/20/2020 02:19:37PM
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CHAPTER VII: MICROBIOLOGY

Product Information	
NDA Number	N214044
Assessment Cycle Number	MR01
Drug Product Name/ Strength	Tramadol Hydrochloride, 25 mg/5 mL
Route of Administration	oral solution
Applicant Name	Athena Biosciences
Therapeutic Classification/ OND Division	OND/ON/DAAP
Manufacturing Site	(b) (4)
Method of Sterilization	N/A for non-sterile products.

Assessment Recommendation: **Adequate**

Assessment Summary:

Document(s) Assessed	Date Received
Original submission	11/01/2019
IR Response	1/28/2019

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

Remarks: The drug product is non-sterile and is indicated (b) (4) in adults for the management of pain severe enough to require an opioid analgesic and for which alternative treatments are inadequate.

Concise Description of Outstanding Issues: N/A

Supporting Documents: N/A

S DRUG SUBSTANCE

The manufacturing process for the drug substance is not reviewed because the drug substance is non-sterile.

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

Product description: The subject drug product is colorless, grape-flavored oral solution packaged in a white HDPE rectangular bottle with (b) (4) child-resistant white (b) (4) closure with (b) (4). It is a multi-dose,

preserved, oral aqueous product. The strength of the product is 25 mg/5 mL tramadol hydrochloride.

Product composition:

Tramadol Hydrochloride Oral Solution, 25 mg/5 mL			
Ingredient	**Weight (mg per 5 mL)**	**% (w/w)**	**Function**
Tramadol Hydrochloride USP	25.000	(b) (4)	Active ingredient
Propylene Glycol USP	(b) (4)		(b) (4)
Glycerin USP			
Sodium Benzoate NF			
Sodium Citrate Dihydrate USP			
Citric Acid USP (b) (4)			
Sucralose (b) (4)			
Grape Flavor (b) (4)			
Purified Water			
Total Per 5 mL		**100%**	

(Table reproduced from the submission, 3.2.P.1, pg. 1).

Summary Table of the proposed Container Closure System (3.2.P.7, pg. 5):

Component	Description	Manufacturers
Bottle (b) (4)	16 oz rectangular white HDPE bottle (b) (4)	(b) (4)
Closure (b) (4)	(b) (4) white child resistant closure (b) (4) (b) (4)	(b) (4)

Assessment: Adequate

The product description is acceptable.

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

Container/Closure and Package Integrity-N/A for non-sterile products.

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/s/

VALERIE R AMSPACHER
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