CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210583Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Complete Response

NDA 210583

Review #1

Drug Name/Dosage Form	**Meloxicam Injection**
Strength	**30 mg/mL**
Route of Administration	**Intravenous**
Rx/OTC Dispensed	**Rx**
Applicant	**Recro Pharma Inc.**
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Sequence 006	*11/2/2017*	
Sequence 009	*1/10/2018*	
Sequence 010	*1/19/2018*	
Sequence 012	*1/26/2018*	
Sequence 013	*3/5/2018*	
Sequence 014	*3/29/2018*	

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Substance	Fred Burnett	Donna Christner
Drug Product	Chris Hough	Julia Pinto
Process	Karthik Iyer	Haitao Li
Microbiology	Christine Craig	John Arigo
Facility	Rebecca Dombrowski	Derek Smith
Biopharmaceutics	Hansong Chen	Kelly Kitchens
Regulatory Business Process Manager	Steven Kinsley	
Application Technical Lead	Ciby Abraham	
Laboratory (OTR)		
ORA Lead	Caryn McNab	
Environmental		

Quality Review Data Sheet

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCE	STATUS	DATE REVIEW	COMMENTS
(b) (4)	II	(b) (4)			4/1/18	See the Drug Substance review
	V		Active	Adequate	4/1/18	Last reviewed by Reyes, Candau-
	III		Active	Adequate	4/1/18	Last reviewed by Ping, Jiang-Baucom on
	III		Active	Adequate	4/1/18	Last reviewed by JOSEPHINE M JEE on
	V		Active	Adequate	4/1/18	Last reviewed by LAURA W MOUSSA on
	III		Active	Adequate	4/1/18	Last reviewed by Daneli López Pérez on

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
NDA	20938	505 b2 reference

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH	N/A			
Clinical	N/A			
Other	N/A			

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

Based on the recommendation from drug product, CMC recommends a complete response for ANJESO (Meloxicam 30 mg/mL). Drug substance, process, microbiology, and facilities recommend approval.

II. Summary of Quality Assessments

A. Product Overview

ANJESO is an intravenous (IV) form of meloxicam for the management of moderate to severe pain. The proposed commercial dose is 30 mg/mL administered once daily. This form of injectable meloxicam uses a proprietary NanoCrystal® technology originally developed by (b) (4)

N/A	⇦ Total Number of Comparability Protocols (ANDA only)

Proposed Indication(s) including Intended Patient Population	ANJESO is an NSAID indicated in adults for the management of moderate to severe pain.
Duration of Treatment	The recommended dose of ANJESO is 30 mg once daily, administered by intravenous bolus injection over 15 seconds.
Maximum Daily Dose	30 mg
Alternative Methods of Administration	N/A

B. Quality Assessment Overview

ANJESO is a pale yellow, aqueous dispersion containing the active pharmaceutical ingredient meloxicam and the additional components; povidone (b) (4) sodium deoxycholate, sucrose, and water for injection. The drug product formulation is a ready to use 30 mg/mL sterile aqueous dispersion for intravenous (IV) administration. Each vial is filled with a target (b) (4) of product. Using a syringe, 1mL of aqueous dispersion is withdrawn from the vial for dosing. The fill overage is to provide assurance that 1mL can be withdrawn from the vial to deliver 30 mg of drug product for dosing. The drug product is packaged in a 2-mL, USP (b) (4) clear glass vial sealed with a grey (b) (4) rubber stopper with an aluminum over seal/blue

flip-off cap.

The manufacturing of the drug product is (b) (4) (b) (4)

The CMC information for the drug substance meloxicam is manufactured by (b) (4) (b) (4) and is referenced in DMF# (b) (4). A letter of authorization was provided for the DMF and it was last reviewed and found adequate on 11/7/2017 by the drug substance reviewer Dr. Friedrich Burnett for this NDA. Meloxicam drug substance is a pale-yellow powder (b) (4) (b) (4)

During the review, Dr. Julia Pinto identified an issue with the extractables/leachables study. The applicant did not provide an adequate assessment for extractable/leachables of the drug product to recommend approval for this cycle. The two main issues are the lack of leachables testing through the shelf life of the drug product and a lack of correlation of extractables and leachables according to USP <1663> and <1664>. In order to resolve the deficiencies, the applicant must address the following:

Deficiency 1: Insufficient sample size is used to evaluate the presence of the leachables present at greater than 5ug/day.

To resolve this deficiency, commit to increased sampling and to continue to test the identified extractables as leachables for at least 3 batches of drug product through expiry.

Deficiency 2: According to USP <1663> and <1664> there must be a good correlation between the extractables and leachables identified, such that, leachables are not identified that are also not found to be extractables. A lack of correlation may imply that the extractable study was not conducted vigorously enough to extract all possible impurities.

To resolve this deficiency, provide a root-cause analysis for the leachables detected that were not also observed during the extraction study. If the lack of a correlation between the extraction and leachable study, cannot be justified, then commit to monitoring the four unknown impurities identified in the leachable study (and not observed at the corresponding RRT in the extractable study) on at least three batches

of drug product during stability studies. Measure the impurities at each timepoint for the duration of the stability study.

C. Special Product Quality Labeling Recommendations (NDA only)

N/A

D. Final Risk Assessment (see Attachment)

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	**Factors that can impact the CQA**	**Risk Ranking ***	**Risk Mitigation Approach**	**Risk Evaluation**	**Lifecycle Considerations/ Comments****
Assay, stability	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Physical stability (API)	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	N/A	-
Content uniformity	• Formulation • Raw materials • Process parameters • Scale/equipment • Site	L	-	-	-

Microbial Limits	• Formulation • Raw materials • Process parameters • Scale/equipment	H	-	Low	The applicant has provided adequate risk mitigation strategies to prevent microbial contamination
In Vitro Dissolution	• Formulation • Raw materials • Process parameters • Scale/equipment • Site • Exclude major reformulations • Alcohol dose dumping	N/A	-	-	-

*Risk ranking applies to product attribute/CQA

**For example, post marketing commitment, knowledge management post approval, etc.

Ciby Abraham

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MICROBIOLOGY

Product Background:

NDA: 210583

Drug Product Name / Strength: Anjeso (Meloxicam), 30 mg/mL

Route of Administration: Injection solution

Applicant Name: Recro Pharma Inc.

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4);.

Review Recommendation: **Adequate**

Theme (ANDA only): **N/A**

Justification (ANDA only): **N/A**

Review Summary:

List Submissions Being Reviewed: 07/26/2017, 3/29/2018

Highlight Key Outstanding Issues from Last Cycle: NA

Remarks: eCTD submission.

Concise Description Outstanding Issues Remaining: N/A

Supporting Documents: The Type III DMF (b) (4) was reviewed on 6/26/2015 for (b) (4) deemed adequate ((b) (4)mic30.doc). The Type II DMF (b) (4) was reviewed on 3/30/2016 (b) (4) deemed adequate (D (b) (4)M01R01.docx). The Type V DMF (b) (4) was reviewed for (b) (4) the drug product and deemed adequate on 3/29/2012 (DMF (b) (4).doc) and 3/30/2018 (D (b) (4)M01R02.doc).

S Drug Substance

The drug product (b) (4) and the drug substance is not assessed in this review.

P.1 Description of the Composition of the Drug Product

- **Description of drug product** – The drug product is a sterile, pale yellow, aqueous solution for intravenous administration.
- **Drug product composition** – The drug product composition is displayed in the applicant table below (Module 3.2.P.1, Description and Composition of the Drug Product, pg. 2).

Table 1: Composition of 1mL of NCD Meloxicam IV Drug Product

Component	Quality Standard	Function	% Conc.	mg/mL
Meloxicam	USP	Active	(b) (4)	30.0
Sodium Deoxycholate	Non-Compendial			(b) (4)
Povidone (b) (4)	USP			
Sucrose (b) (4)	NF			
Water for Injection (WFI)	USP			
				(b) (4)

- **Description of container closure system** – The primary container closure system includes a 2 mL, USP (b) (4) clear glass vial, sealed with a grey (b) (4) rubber stopper. The container closure component details are displayed in the applicant table below (3.2.P.7, Container Closure System, pg. 1).

Table 1: Component Description

Component	Description	Manufacturer	DMF Number
Vial	2 mL (b) (4) -lear glass vial	(b) (4)	DMF No. 14744
Closure	(b) (4		DMF No. (b) (4) (b) (4)
			DMF No. (b) (4) (b) (4)
Overseal			Not Applicable
			(b) (4)

Adequate

Reviewer's Assessment: The applicant provided an adequate description of the drug

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(b) (4)

[redacted]

Adequate

Reviewer's Assessment: The applicant provided batch records for four batches of drug product.

Comparability Protocols

Not Applicable.

2. REVIEW OF COMMON TECHNICAL DOCUMENT – QUALITY (CTD-Q) MODULE 1

2.A. Package Insert

The drug product is provided as a single-use vial containing 30 mg/ml Meloxicam, and does not require any further dilution.

Post-Approval Commitments:

Not applicable.

List of Deficiencies: **None.**

Primary Microbiology Reviewer Name and Date: Christine M Craig, Ph.D., April 2, 2018

Secondary Reviewer Name and Date (and Secondary Summary, as needed): John W. Metcalfe, April 2, 2018

Ciby Abraham

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