CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211210Orig1s000

PRODUCT QUALITY REVIEW(S)

Recommendation: Approval

NDA 211210

Review 1

Drug Name/Dosage Form	**Meloxicam orally disintegrating tablet**
Strength	**7.5 mg, 15 mg**
Route of Administration	**oral**
Rx/OTC Dispensed	**Rx**
Applicant	**TerSera Therapeutics LLC**
US agent, if applicable	

SUBMISSION(S) REVIEWED	DOCUMENT DATE	DISCIPLINE(S) AFFECTED
Original Submission	12-21-2017	All disciplines
SN0007	16-MAR-2018	Quality
SN0010	11-APR-2018	Quality
SN0012	24-APR-2018	Quality
SN0015	01-JUN-2018	Quality
SN0016	28-JUN-2018	Quality
SN0017	01-AUG-2018	Quality
SN0018	17-AUG-2018	Quality
SN0019	27-AUG-2018	Quality
SN0021	30-AUG-2018	Labeling
SN0023	11-SEP-2018	Labeling
SN0024	12-SEP-2018	Quality
SN0025	19-SEP-2018	Quality
SN0026	20-SEP-2018	Quality

Quality Review Team

DISCIPLINE	PRIMARY REVIEWER	SECONDARY REVIEWER
Drug Master File/ Drug Substance	**Fred Burnett**	**Donna Christner**
Drug Product	**Venkateswara Pavuluri**	**Julia Pinto**
Process and Microbiology	**Rebecca Dombrowski**	**Pei-I**

Facility	**Rebecca Dombrowski**	**Pei-I**
Biopharmaceutics	**Peng (Vincent) Duan**	**Kelly Kitchens**
Regulatory Business Process Manager	**Steven Kinsley**	
Application Technical Lead	**Venkateswara Pavuluri**	
Laboratory (OTR)	N/A	
ORA Lead	**Caryn McNab**	
Environmental	N/A	

Quality Review Data Sheet

IQA Review Guide Reference

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	Type II		(b) (4)	Adequate	30-APR-2018	
	Type III *(if applicable)*			Adequate quality information provided in the NDA		
	Type IV *(if applicable)*			Acceptable, Adequate quality information provided in the NDA was used in another approved NDA		No updates provided to DMF since May 2016, LOA provided in submission
	Other					

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

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
IND	104140	IND linked to the NDA 211210
NDA	020938	RLD, Mobic® NDA

2. CONSULTS

DISCIPLINE	STATUS	RECOMMENDATION	DATE	REVIEWER
Biostatistics	N/A			
Pharmacology/Toxicology	N/A for NDA			
CDRH	N/A			

Clinical	NDA managed by ODEII/OND			
Other				

Executive Summary

IQA Review Guide Reference

I. Recommendations and Conclusion on Approvability

Based on the acceptable OPQ discipline reviews, Trade Name™@ (Meloxicam) Orally Disintegrating Tablets, 7.5 mg and 15 mg are recommended for approval from quality perspective; with assigned shelf-life of 36 months for 15 mg strength and 24 months for 7.5 mg strength when packaged in blister packs of 10's with labeled storage condition: "Store at 20°-25°C (68°-77°F), excursions permitted between 15°C and 30°C (59°-86°F) [See USP Controlled Room Temperature]. Avoid high humidity and excessive heat above 40°C (104°F)."

II. Summary of Quality Assessments

A. Product Overview

The applicant, TerSera Therapeutics LLC is seeking approval for Trade Name™ (Meloxicam) orally disintegrating tablets, 7.5 mg and 15 mg strengths via 505(b)(2) process using Mobic® tablets as reference listed drug to compare the pharmacokinetics of the test product designed to rapidly disintegrate in the mouth and prepared by (b) (4) process. The OPQ discipline reviews for Drug Substance, Drug product, Process including Microbiology, Facilities and Biopharmaceutics are all acceptable with no outstanding request for information.

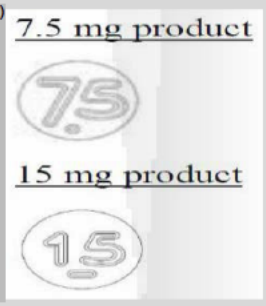
0	⇦ **Total Number of Comparability Protocols (ANDA only)**

Proposed Indication(s) including Intended Patient Population	Relief of the signs and symptoms of osteoarthritis and rheumatoid arthritis and also for the relief of the signs and pauciarticular or polyarticular course symptoms of juvenile rheumatoid arthritis (JRA) in patients weighing greater than or equal to 60 kg.
Duration of Treatment	***Long term (Chronic) use***
Maximum Daily Dose	***15 mg***
Alternative Methods of Administration	***Meloxicam is also available as immediate release Tablets, capsules and suspension for administration by oral route.***

B. Quality Assessment Overview

Tersera Therapeutics LLC is utilizing the 505 (b) 2 regulatory pathway for approval of Trade Name™ (meloxicam) orally disintegrating tablets, 7.5 mg and 15 mg (here after referred as Meloxicam ODT), relying on the reference listed drug (RLD) Meloxicam (b) (4) ODT (NDA 020938). Meloxicam ODT are orange flavored, yellow, circular stable (b) (4) tablets with an identifying logo for each dosage strength; prepared by using (b) (4) technology, intended for disintegration in less than (b) (4) seconds in the mouth, following oral administration with or without liquid drink.

(b) (4)



(b) (4)

Meloxicam drug substance used in the manufacture of Meloxicam ODT is sourced (b) (4) produced in accordance with the Meloxicam USP Monograph. Drug substance information is provided in DMF (b) (4) last reviewed as approvable (b) (4)

The drug product, (b) (4) tablet, is (b) (4) sealed with lidding foil. Meloxicam ODT is packaged into an (b) (4) blister pack of multi-layered (5 layers) laminated blister film and a peelable lidding foil for easy removal of the tablet. The blister packs are subsequently packed into 10, 30, or 90 count cardboard cartons. There are no formulation overages in this drug product. Except for orange flavor which meets supplier /applicant's in-house specification, all other excipients used in manufacturing of the drug product are of compendial grade and are within IID limits for the dosage form / route of administration. Gelatin used in the final formulation composition (b) (4) was provided by the supplier. The specification of not more than (b) (4)% proposed for (b) (4) meloxicam ODT (b) (4) The oposed microbial purity controls, per <1111> of the USP along with testing as specified under <61> and <62> are typical for an oral drug product and are acceptable.

(b) (4)

The disintegration test method and acceptance criterion, along with the dissolution test method and acceptance criterion are acceptable from the Biopharmaceutics review

perspective. Biowaiver request for the 7.5 mg strength is granted per 21 CFR 320.22 (d)(2).

Meloxicam ODT, 7.5mg and 15mg dosage forms were formulated at a (b) (4) Kg scale, while proposed commercial scale is (b) (4) Kg for the 7.5mg and (b) (4) Kg for the 15mg. (b) (4) Applicant committed to complete process validation on three consecutive full-scale batches for each strength, for verifying critical process parameters and in-process controls and establishing appropriate yield limits upon completion of scale up activities and submit the information as part of the executed commercial batch record for Agency review.

A pre-approval inspection of the drug product manufacturing facility, Catalent UK Swindon (b) (4) performed in support of this application during 4/16-20/2018 is acceptable. No significant deficiencies were identified up on review of the application and inspectional histories of the proposed facilities.

The application is recommended for approval from quality perspective.

C. Special Product Quality Labeling Recommendations (NDA only)

Meloxicam ODT is a (b) (4) tablet prepared by using (b) (4) technology, intended for disintegration in less than (b) (4) seconds in the mouth, following oral administration with or without liquid drink. Based on the nature of drug product and how it is made, primary packaging is integral to manufacturing process and thus require special handling during storage and administration of meloxicam ODT.

The following special instructions are included as part of the PI, section 2 Dosage and Administration:

> TRADE NAME™ ODT, administration with liquid is not necessary. TRADE NAME ODT may be taken without regard to timing of meals.
>
> TRADE NAME ODT should be taken as follows:
> - Leave TRADE NAME ODT in the original package until the time of administration.
> - Be sure that hands are dry when handling an orally disintegrating tablet.
> - Open the carton and peel back the foil on the blister. Do not push the tablet through the foil as this could damage the tablet.

- Gently remove the tablet from the blister and place it in the mouth, or onto tongue, immediately after removing from the blister.
- The tablet will disintegrate quickly in saliva and can be easily swallowed with or without drinking liquid.

The following storage statement is included in PI section 16.1 Storage and on Cartons of the Meloxicam ODT:

" Store at 20°-25°C (68°-77°F), excursions permitted between 15°C and 30°C (59°-86°F) [See USP Controlled Room Temperature]. Avoid high humidity and excessive heat above 40°C (104°F)."

D. Final Risk Assessment (see Attachment)

From Initial Risk Identification			Review 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 Stability	• Formulation • Raw materials • Process Parameters • Scale/equipment • Site	L	Drug is highly stable	Acceptable	
Physical Stability (API)	• Formulation • Raw materials • Process Parameters • Scale/equipment • Site	M	(b) (4)	Acceptable	
Content uniformity	• Formulation • Raw materials • Process Parameters • Scale/equipment	H	API specification revised to include acceptance limit for particle size. Applicant to conduct (b) (4) content uniformity testing (b) (4) (b) (4) for the validation batches	Acceptable	Monitor the validation batch in-process data for any outliers with respect to content uniformity of the suspension.
Microbial Limits	• Formulation • Raw materials • Process Parameters • Scale/equipment	H	Adequate controls in place to prevent Microbial growth (b) (4)	Acceptable	

In Vitro Dissolution	• Formulation • Raw materials • Process Parameters • Scale/equipment • Exclude major reformulations • Alcohol dose dumping	M	(b) (4)	L	

@ Trade name proposed by the applicant was pending for approval by DMEPA and DAAAP, at the time of preparing this executive summary for OPQ disciplines.

LABELING

IQA Review Guide Reference

{NDA 211210}

I. Package Insert

1. *Highlights of Prescribing Information*

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	Acceptable generic text, Proprietary name yet to be finalized
Dosage form, route of administration	Orally Disintegrating Tablet (ODT), Oral
Controlled drug substance symbol (if applicable)	Not applicable
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Orally disintegrating tablet: 7.5 mg and 15 mg

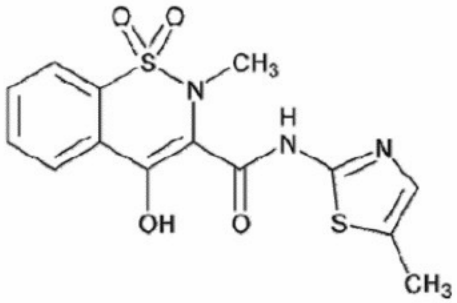
2. *Section 2 Dosage and Administration*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	(b) (4) TRADE NAME ODT, administration with liquid is not necessary. TRADE NAME ODT may be taken without regard to timing of meals. TRADE NAME ODT should be taken as follows: •Leave TRADE NAME ODT in the original package until the time of administration. •Be sure that hands are dry when handling an orally disintegrating tablet. •Open the carton and peel back the foil on the blister. Do not push the tablet through the foil as this could damage the tablet. •Gently remove the tablet from the blister and place it in the mouth, or onto tongue, immediately after removing from the blister. •The tablet will disintegrate quickly in saliva and can be easily swallowed with or without drinking liquid.

3. ***Section 3 Dosage Forms and Strengths***

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	To expand the term ODT to Orally disintegrating tablet
Strengths: in metric system	7.5 mg or 15 mg
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable,
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	orange-flavored, yellow, circular tablets and debossed with an identifying logo, i.e. 7.5 or 15.

4. *Section 11 Description*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	Yet to be finalized
Dosage form and route of administration	To expand the term ODT to Orally disintegrating tablet
Active moiety expression of strength with equivalence statement (if applicable)	Not applicable, base drug used
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	The inactive ingredients in TRADE NAME ODT tablets include gelatin, mannitol, citric acid, aspartame, and orange flavoring.
Statement of being sterile (if applicable)	Not applicable
Pharmacological/ therapeutic class	To add pharmacological class (NSAID) in the first sentence
Chemical name, structural formula, molecular weight	4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide. MW: 351.4 
If radioactive, statement of important nuclear characteristics.	Not a radioactive compound
Other important chemical or physical properties (such as pKa or pH)	No information provided

5. *Section 16 How Supplied/Storage and Handling*

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Not included
Available units (e.g., bottles of 100 tablets)	10-, 30-, or 90 count cardboard cartons
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Not included
Special handling (e.g., protect from light)	Avoid high humidity and excessive heat above 40°C (104°F).
Storage conditions	Store at 20°-25°C (68°-77°F), excursions permitted between 15°C and 30°C (59°-86°F) [See USP Controlled Room Temperature]. Avoid high humidity and excessive heat above 40°C (104°F).
Manufacturer/distributor name (21 CFR 201.1(h)(5))	*Manufactured for:* TerSera Therapeutics LLC Lake Forest, IL 60045 *Manufactured by:* Catalent Health, Inc. Swindon, Wiltshire, SN5 8RU, UK

Reviewer's Assessment of Package Insert: Inadequate

Prescribing Information doesn't comply with regulatory requirements from a CMC perspective. Refer deficiencies listed below.

Deficiencies to be conveyed to applicant:

1. In section 2 Dosage Administration, drug administration instructions should be revised as written below, removing the use of second person pronoun 'you' from the text.

   " (b) (4) TRADE NAME ODT, administration with liquid is not necessary. TRADE NAME ODT may be taken without regard to timing of meals.

   TRADE NAME ODT should be taken as follows:
   - Leave TRADE NAME ODT in the original package until the time of administration.
   - Be sure that hands are dry when handling an orally disintegrating tablet.
   - Open the carton and peel back the foil on the blister. Do not push the tablet through the foil as this could damage the tablet.

- Gently remove the tablet from the blister and place it in the mouth, or onto tongue, immediately after removing from the blister.
- The tablet will disintegrate quickly in saliva and can be easily swallowed with or without drinking liquid."

2. In section 3 Dosage Forms and Strengths, consider including appropriate text describing the logo on each dosage strength or adding the logo itself.
3. In section 11 Description,
   a. Expand the term ODT to orally disintegrating tablet.
   b. Revise the description of drug to include pharmacological category, i.e. *"Meloxicam is a non-steroidal anti-inflammatory drug, chemically designated as 4-hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide."*
   c. Change last sentence in paragraph 4 to read as *"The tablet begins disintegrating in the mouth within seconds, allowing its contents to be subsequently swallowed with or without liquid or chewing."*
4. In section (b) (4)
   a. Text may be simplified as follows *"Meloxicam ODT 7.5 mg and 15 mg tablets are supplied as orange-flavored, yellow, circular tablets debossed with an identifying logo and packaged in aluminum blister packs with a lidding foil, and subsequently packed into 10-, 30-, or 90 count cardboard cartons."*
   b. Include list of NDC numbers with description of each packaging configuration, separately for the two strengths.

II. Labels:

1. ***Container and Carton Labels***

Start of applicant material

(b) (4)

End of applicant material

2. ***Carton Label***

Start of applicant material

(b) (4)

End of applicant material

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	Acceptable font size Trade Name (meloxicam) orally disintegrating tablets.	Acceptable font size Trade Name (meloxicam) orally disintegrating tablets.
Dosage strength	7.5 mg or 15 mg	7.5 mg or 15 mg
Net contents	Not applicable for single blister.	10, 30 OR 90-TABLETS
"Rx only" displayed prominently on the main panel	Acceptable size, but location needs to be changed.	Acceptable size and prominent location.
NDC number (21 CFR 207.35(b)(3)(i))	Present, Example: **NDC 70720-175-10 for 7.5 mg for 10's blister; NDC 70720-175-10 for 15 mg 10's blister.**	Present, example: **NDC 70720-175-10 for 7.5 mg 10's blister carton; NDC 70720-175-10 for 15 mg 10's blister carton.**
Lot number and expiration date (21 CFR 201.17)	Present; Lot: 1234567 Exp.: MMM-YYYY	Present; Lot: 1234567 Exp.: MMM-YYYY
Storage conditions	Not enough space to print on Individual blisters	Tablets should be stored at room temperature, between (b) (4) Keep package dry and away from moisture.
Bar code (21CFR 201.25)	Present	 70720-0175-10
Name of manufacturer/distributor	TerSera Therapeutics LLC	Manufactured for: TerSera Therapeutics LLC Lake Forest, IL 60045 By: Catalent Health, Inc. Swindon, Wiltshire, SN5 8RU, UK Product of Spain
And others, if space is available	None	Dispense enclosed Medication Guide to patient

Reviewer's Assessment of Labels: Inadequate.

Sponsor has presented the same NDA number on 7.5 mg and 15 mg tablet blisters. The storage statement on cartons is not in agrement with the PI section (b) (4)

List of Deficiencies:

5. Same NDC number used on blisters for both 7.5 mg and 15 mg tablets. Provide revised text for 15 mg dose blisters with corrected NDC number.

6. Revise the storage statement on cartons to be in agreement with the statement I in section 16.2 of the prescribing information. i.e. " Store at 20°-25°C (68°-77°F), excursions permitted between 15°C and 30°C (59°-86°F) [See USP Controlled Room Temperature]. Avoid high humidity and excessive heat above 40°C (104°F)."

Overall Assessment and Recommendation: **Inadequate**

1. PI needs revision of the text in sections, 2, 3, 11, and 16.1 as indicated above.

2. NDC number on blister pack (primary packaging) need to be corrected for 15 mg representing correct dosage.

Primary Labeling Reviewer Name and Date:

Venkateswara R. Pavuluri, Ph. D., R. Ph.; 20-SEP-2018

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

Julia C. Pinto, Ph. D.

Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 9/25/2018 11:40:22AM
GUID: 551eb409003b6d46b8d5dfa7699e4742

Julia Pinto

Digitally signed by Julia Pinto
Date: 9/25/2018 02:19:08PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

DRUG PRODUCT

IQA Review Guide Reference

Product Background:

NDA/ANDA (review cycle number): 211210 (1)

Drug Product Name / Strength: Meloxicam, orally disintegrating tablet,7.5 mg, 15 mg

Route of Administration: Oral

Applicant Name: TerSera Therapeutics LLC

Review Recommendation: **Adequate**

Review Summary: Brand Name™ (Meloxicam) orally disintegrating tablets are available in two dosage strengths, 7.5 mg and 15 mg; debossed with either 7.5 or 15 as identifying logo, prepared by freeze-drying process in preformed blisters and sealed with lidding foil, and are further packaged in to 10, 30 or 90 count cartons. Drug substance particles size, quantities of functional excipients, and processing parameters were adequately evaluated during product development stage for assuring control of drug product quality characteristics at release and through the end shelf-life. Except for orange flavor, all other excipients used are compendial grade. All in-house analytical methods used in testing of the drug product were adequately validated for intended use.

Based on available stability data, ***a shelf-life of 36 months for Meloxicam ODT 15 mg*** and a ***tentative shelf-life of 24 months for Meloxicam ODT 7.5 mg*** may be granted, when the drug products are labeled as "Store at 20° -25° C (68° -77° F), with excursions permitted between 15° C and 30° C (59° -86° F) [See USP Controlled Room Temperature]. Avoid high humidity and excessive heat above 40°C (104°F)".

List Submissions being reviewed (table):

Sequence#	Type of Submission	Date of Submission
0001	Original	21-DEC-2017
0007	Response to Information Request (Quality)	16-MAR-2018
0012	Response to Information Request (Quality)	24-APR-2018
0017	Response to Information Request (Quality)	01-AUG-2018
0018	Response to Information Request (Quality)	17-AUG-2018
0019	Response to Information Request (Quality)	27-AUG-2018

0024	Response to Information Request (Quality)	12-SEP-2018

Highlight Key Outstanding Issues from Last Cycle: Not applicable

Concise Description Outstanding Issues Remaining: None

List Number of Comparability Protocols (ANDA only): Not Applicable

21 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

Venkateswara Pavuluri

Digitally signed by Venkateswara Pavuluri
Date: 9/19/2018 11:36:30AM
GUID: 551eb409003b6d46b8d5dfa7699e4742

Julia Pinto

Digitally signed by Julia Pinto
Date: 9/19/2018 12:26:24PM
GUID: 5050dbcb00001294a888a4bdc20a3a58

BIOPHARMACEUTICS

Product Background: The Applicant is seeking approval of Meloxicam Orally Disintegrating Tablets (ODT), 7.5 mg and 15 mg, under the 505(b)(2) regulatory path. The drug product is indicated for once daily administration for the relief of the signs and symptoms of osteoarthritis, rheumatoid arthritis, and pauci-articular or polyarticular course juvenile rheumatoid arthritis.

The NDA relies on:

- In vivo bioequivalence data between the proposed product and the reference product, Mobic (meloxicam) Tablets, approved under NDA 20938;
- The Agency's prior findings of safety and efficacy of meloxicam; and
- Relevant safety and efficacy results from the published literature and the public domain.

NDA: 211210-ORIG-1

Drug Product Name / Strength: Meloxicam Orally Disintegrating Tablets, 7.5 mg and 15 mg

Route of Administration: Oral

Applicant Name: TerSera Therapeutics LLC

Review Recommendation: **Adequate**

(b) (4)

The Biowaiver request for the 7.5 mg strength is granted per 21 CFR 320.22 (d)(2).

From the Biopharmaceutics perspective, NDA 211210 for Meloxicam Orally Disintegrating Tablets is recommended for **approval**.

List Submissions being reviewed:

SN0001: December 21, 2017	Original Submission
SN0007, March 16, 2018	Response to Information Request and Potential Biopharmaceutics Review Issues (March 1, 2018)
SN0012: April 24, 2018	Response to Information Request (April 10, 2018)
SN0015: June 28, 2018	Response to Information Request (May 23, 2018)

Highlight of Key Outstanding Issues from Last Cycle: N/A, this is the first review cycle

Concise Description of Outstanding Issues: N/A

(b) (4)

1 Page has been Withheld in Full as B4 (CCI/TS) immediately following this page

(b) (4)

- The Applicant's proposed disintegration specification is NMT (b) (4) seconds. The disintegration times are provided as follows (the Applicant only reported the 6th and final unit since the disintegration times observed were very quick):

Batch	1024674, 15 mg	1059432, 7.5 mg	1059433, 15 mg	1059435, 15 mg
Disintegration Time (seconds)	(b) (4)	(b) (4)	(b) (4)	(b) (4)

- The Applicant proposed to (b) (4) include disintegration due to the very rapidly disintegrating and dissolving characteristics of the drug product. However, in the absence of meeting the requirements set forth in the ICH Q6A, the Applicant decided to continue testing for dissolution in the finished drug product specification.
- **The disintegration testing and specification are adequate.**

Bridging of Formulations

Reviewer's Assessment: N/A

The clinical batch (batch 1024674) and registration batches (1059433, 1059435, and 1059432) have the same qualitative and quantitative formulation as the to-be-marketed product (see the following tables):

Drug product Development Stage and Formulation Summary (continued)

(b) (4)

Table 3.2.P.1-1 Composition of Meloxicam Orally Disintegrating Tablet

Name of Ingredient	Quantity per 7.5 mg tablet (mg)	Quantity per 15 mg tablet (mg)	Function	Reference to Standards
Active Ingredient				
Meloxicam	7.5	15.0	Active Ingredient	USP
Other Ingredients			(b) (4)	
Gelatin				USP NF
Mannitol				USP
Citric Acid, (b) (4)				USP
Aspartame[1]				USP NF
Orange flavor (b) (4)				In-House
				(b) (4)

[1] Amount of phenylalanine (a component of aspartame) is 0.30 mg for the 7.5 mg dose and 0.59 mg for the 15 mg dose

(b) (4)

Therefore, bridging of formulations is unnecessary.

Biowaiver Request

Reviewer's Assessment: ADEQUATE

The Applicant submitted a biowaiver request for the 7.5 mg strength. The Agency previously communicated the following criteria must be met to support a biowaiver for the 7.5 mg strength (see the response to IND 104140 Advice/Information Request dated May 27, 2010):

- ***The bioavailability of meloxicam and demonstration of bioequivalence of 15 mg meloxicam ODT to Mobic.***

Table 1 **Mean ± SD (% CV) PK Parameters of Meloxicam Across Studies Following Administration of a Single Dose of To-Be-Marketed Meloxicam ODT 15 mg**

Parameter (Unit)	Arithmetic Mean ± SD (% CV) Meloxicam ODT 15 mg (Fasted)		Arithmetic Mean ± SD (% CV) Meloxicam ODT 15 mg (Fed)
	Study 10943701	Study 10943702	Study 10943702
C_{max} (ng/mL)	1493 ± 391 (26)	1277 ± 326 (26)	1165 ± 216 (19)
AUC_{0-t} (ng·h/mL)	46000 ± 11971 (26)	38455 ± 10774 (28)	39202 ± 9703 (25)
$AUC_{0-\infty}$ (ng·h/mL)	53231 ± 15487 (29)	44009 ± 13783 (31)	44657 ± 13666 (31)
T_{max} (h)	4.34 ± 2.71 (62)	3.70 ± 0.567 (15)	13.1 ± 7.68 (59)
λ_z (1/h)	0.0341 ± 0.0111 (33)	0.0357 ± 0.0110 (31)	0.0370 ± 0.0114 (31)
$T_{½}$ (h)	21.8 ± 5.21 (24)	21.6 ± 7.95 (37)	20.4 ± 6.16 (30)

Abbreviations: CV = coefficient of variation; ODT = orally disintegrating tablet; PK = pharmacokinetics; SD = standard deviation
Source: Section 2.7.2.3.2.1

Figure 1 **Linear Plot of the Mean Plasma Concentration over Time Curve for Meloxicam ODT 15 mg (Test) and Mobic® 15 mg Tablets (Reference)**

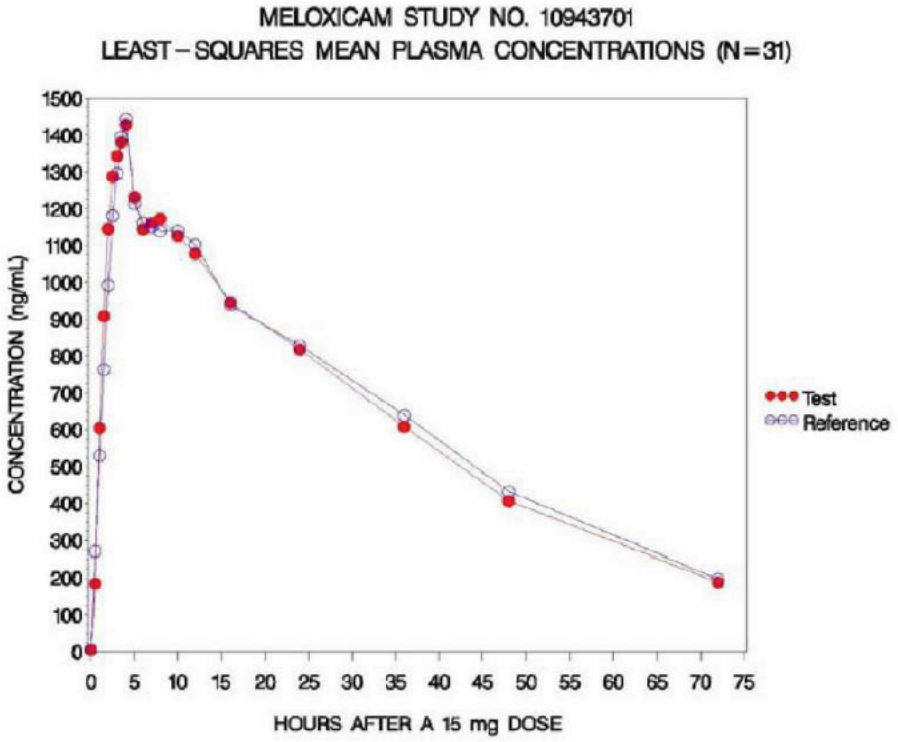


Table 2 Statistical Analysis of Meloxicam PK Parameters: Study 10943701

Parameters (Units)	Geometric Least-squares Means			90% CI	Intra-Subject, %CV
	Test A	Reference B	Ratio (A/B)		
C_{max} (ng/mL)	1447.18	1461.99	0.9899	0.9395, 1.0430	12.1482
AUC_{0-t} (ng·h/mL)	44485.24	45227.92	0.9836	0.9546, 1.0135	6.9449
$AUC_{0-\infty}$ (ng·h/mL)	50001.55	51350.53	0.9737	0.9313, 1.0181	10.1664

Abbreviations: CI = confidence interval; CSR = clinical study report; ODT = orally disintegrating tablet; PK = pharmacokinetics

Test A is a single oral dose of to-be-marketed meloxicam ODT 15 mg

Reference B is a single oral dose of Mobic 15 mg

Note: N = 31 for C_{max} and AUC_{0-t}; N = 30 for $AUC_{0-\infty}$

Source: CSR 10943701 page 29

The Clinical Pharmacology reviewer, Dr. Deep Kwatra, determined the study 10943701 adequately demonstrated bioequivalence between the proposed Meloxcam ODT, 15 mg, and Mobic tablets, 15 mg.

- ***Demonstration of linear PK between the 7.5 mg and 15 mg strengths, as described in the Mobic package insert.***
  The Applicant referenced the Clinical Pharmacology and Biopharmaceutics review of NDA 20938 for Mobic® (meloxicam) Tablets, reviewed by Dr. Veneeta Tandon. Dr. Tandon concluded that meloxicam capsules were dose proportional in the range of 7.5 mg to 30 mg after single doses, and meloxicam capsules were dose proportional in the range of 7.5 mg to 15 mg once a day after multiple doses. In addition, IV bolus doses were dose-proportional in the range of 5 mg to 60 mg. Thus, the Applicant of this current NDA concluded that linear pharmacokinetics has been demonstrated for meloxicam between 7.5 mg and 15 mg.

- ***Compositional proportionality between the 7.5 mg and 15 mg strengths.***
  The 7.5 mg and 15 mg strengths are compositionally proportional (see Table 3.2.P.1-1 in the ***Bridging of Formulations*** section of this review).

(b) (4)

3 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

- The 7.5 mg and 15 mg strength tablets are compositionally proportional. (b) (4) (b) (4) (b) (4) Therefore, the Biopharmaceutics information submitted support the biowaiver request for the 7.5 mg strength.
- The biowaiver for the 7.5 mg strength is granted per 21 CFR 320.22 (d)(2).

Post-Approval Commitments

Reviewer's Assessment: ADEQUATE

- The Applicant indicated their plan to gather data from 15 batches or 2 years of product manufacture and stability, whichever occurs soone (b) (4)
- Using the disintegration test in lieu of dissolution for the drug product will be considered provided the Applicant demonstrates the drug product meets the ICH Q6A requirements.

Primary Biopharmaceutics Reviewers' Names and Date:

Vincent (Peng) Duan, Ph.D. and Kelly M. Kitchens, Ph.D., July 6, 2018

Secondary Reviewer Name and Date:

Okpo Eradiri, Ph.D. July 10, 2018

Appendix: Information Requests

I. Potential Review Issues Identified – communicated to the Applicant on March 1, 2018:

Review Issue #1:

(b) (4)

Summary of Applicant's response submitted on March 16, 2018:

(b) (4)

(b) (4)

Reviewer's assessment of March 16, 2018 response:

The Applicant's response is not acceptable. The following Information Request (IR) was communicated to the Applicant on April 10, 2018:

1) In order to apply disintegration test in lieu of dissolution for an immediate release tablets, you need to meet the following requirements in *ICH Q6A Decision Tree #7*:
    a. High drug solubility at 37 °C throughout the physiological pH range (pH 1.2-6.8);
    b. Dissolution is higher than 80% in 15 min at pH 1.2, pH 4.0, and pH 6.8;
    c. A relationship is established between disintegration and dissolution, and disintegration provides a better discriminatory ability compared to dissolution.

    Submit above data as well as complete disintegration and dissolution data (i.e. individual, mean, %CV, dissolution profiles) to support your proposal of applying disintegration test in lieu of dissolution test as a QC method. Disintegration data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the disintegration acceptance criterion of your product.
2) When disintegration is used as a QC method in lieu of dissolution test, an approved regulatory dissolution method with appropriate dissolution acceptance criterion is still required to support future post-approval changes. Provide the dissolution method development report and complete data as we previously requested in IR# 3 [**Reviewer's note:** this is referencing Review Issue #1].
3) (b) (4)

Applicant's response to IR #1 and #2 submitted on April 24, 2018:

Due to the nature of the drug substance, it is not possible to provide the requested information for points a and b in Question 1. Therefore, at this time, TerSera agrees to continue testing for dissolution in the finished product specification as originally included. Updated Sections 3.2.P.5.1, 3.2.P.5.2, and 3.2.P.5.3, including the test for dissolution are included with this response.

TerSera plans to gather suitable data from 15 batches or 2 years of product manufacture and stability, whichever comes soone (b) (4)

Applicant's response to IR #3 submitted on April 24, 2018:

TerSera agrees to the Food and Drug Administration (FDA) proposal (b) (4)

(b) (4) Section 3.2.P.5.1 has been updated and is included with this submission.

Reviewer's assessment of Applicant's responses to IR #1, #2 and #3:
The Applicant's responses are acceptable.

Applicant's response submitted on June 28, 2018:

(b) (4)

(b) (4)

[redacted]

II. Information Requests – communicated to the Applicant on March 1, 2018:

Information Request #1:

(b) (4)

[redacted]

The Applicant's response is acceptable.

Information Request #2:

(b) (4)

Applicant's response submitted on March 16, 2018:

(b) (4)

The disintegration test is conducted on (b) (4) units in line with pharmacopoeial requirements, however due to the very quick disinteg ation time observed, it is not possible to report the individual unit results. As a result, the disintegration time of the (b) (4) h and final unit is reported.

Reviewer's assessment of response to Information Request #2:

The Applicant's response is acceptable.

Information Request #3:

(b) (4)

Applicant's response submitted on March 16, 2018:

Please refer to TerSera Response to Potential Review Issue #3. TerSera proposes to (b) (4)

Reviewer's assessment of response to Information Request #3:

This response is not acceptable. (b) (4)

Kelly Kitchens

Digitally signed by Kelly Kitchens
Date: 7/10/2018 04:02:52PM
GUID: 508da6fd0002849b46320c175775bdfa

Okponanabofa Eradiri

Digitally signed by Okponanabofa Eradiri
Date: 7/10/2018 05:22:27PM
GUID: 50bdfe8d00003559ede66be3fd299f65