CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

211210Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211210

PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE

TerSera Therapeutics LLC
Two Conway Park
150 N. Field Dr., Suite 195
Lake Forest, IL 60045

ATTENTION: Jay R. Ford
Vice President, Regulatory Affairs

Dear Mr. Ford:

Please refer to your New Drug Application (NDA) dated and received December 21, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Meloxicam Orally Disintegrating Tablets.

We also refer to your correspondence, dated and received August 29, 2018, requesting review of your proposed proprietary name, Qmiiz ODT.

We have completed our review of the proposed proprietary name, Qmiiz ODT and have concluded that it is conditionally acceptable.

If any of the proposed product characteristics as stated in your above submissions are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review. Additionally, if your application receives a complete response, a new request for name review for your proposed name should be submitted when you respond to the application deficiencies.

If you require information on submitting requests for proprietary name review or PDUFA performance goals associated with proprietary name reviews, we refer you to the following:

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)
- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, (https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Taiye Ayoola, Regulatory Project Manager in the Office of New Drugs, at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Danielle Harris, PharmD, BCPS
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS
10/04/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211210

PROPRIETARY NAME ACKNOWLEDGEMENT

TerSera Therapeutics LLC
Two Conway Park
150 N. Field Dr., Suite 195
Lake Forest, IL 60045

ATTENTION: Jay R. Ford
Vice President, Regulatory Affairs

Dear Mr. Ford:

Please refer to your New Drug Application (NDA) dated and received December 21, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Meloxicam Orally Disintegrating Tablets.

We acknowledge receipt of your correspondence, dated and received August 29, 2018, requesting a review of your proposed proprietary name, Qmiiz ODT.

Therefore, the user fee goal date to review your request for proprietary name is November 27, 2018.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (240) 402-4559. For any other information regarding this application, contact Taiye Ayoola, Regulatory Project Manager, in the Office of New Drugs at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Davis Mathew, PharmD, RPh
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DAVIS MATHEW
09/13/2018

MEMORANDUM of TELECONFERENCE

MEETING DATE: August 22, 2018
TIME: 3:00 PM to 4:00 PM
LOCATION: White Oak Building 22, Room 4440
APPLICATION: NDA 211210
DRUG NAME: Meloxicam Orally Disintegrating Tablets, 7.5 mg and 15 mg
TYPE OF MEETING: Applicant Proprietary Name Teleconference

MEETING CHAIR: Otto Townsend, PharmD, Team Leader

FDA ATTENDEES:

Division of Medication Error Prevention and Analysis (DMEPA)
Cameron Johnson, PharmD, Safety Evaluator
Otto Townsend, PharmD, Team Leader
Irene Z. Chan, PharmD, BCPS, Deputy Director

Office of Surveillance and Epidemiology (OSE)
Davis Mathew, PharmD, Safety Regulatory Project Manager

SPONSOR ATTENDEES:
Jay Ford, VP Regulatory Affairs
Heidi Gillmore, Senior VP, Marketing
Edward Donovan, Executive Vice President, General Counsel
Rick Crowley, Executive Vice President, Technical Operations

BACKGROUND:

TerSera Therapeutics submitted a Request for Proprietary Name Review on Friday, May 18, 2018, to review the proposed proprietary name, (b) (4) ODT. The name was found unacceptable and a decision letter was issued to TerSera on August 16, 2018. Within the May 18, 2018 submission, TerSera Therapeutics indicated that their alternate proposed proprietary name was (b) (4) ODT.

MEETING OBJECTIVES:

The purpose of this teleconference is to discuss our preliminary safety concerns with the alternate proposed proprietary name, (b) (4) ODT, with TerSera Therapeutics.

DMEPA CONCERNS WITH THE PROPOSED NAME

We requested this teleconference to notify you that we took a preliminary look at the alternate proposed proprietary name, (b) (4) ODT, that you submitted as part of your previous proprietary name review request.

(b) (4)

We are sharing our preliminary observations, and we want to emphasize that our discussion today in no way constitutes a decision regarding acceptability of the alternate proposed proprietary name. However, given the upcoming action date for your application, we wanted to share this information with you for your consideration as you determine your next steps in pursuing a proprietary name for your product.

REGULATORY OPTIONS

1. If you intend to pursue a proprietary name for your product, we recommend that you submit a proposed proprietary name as soon as possible.

DISCUSSION POINTS:

DMEPA presented their concerns with the alternate name (b) (4) that was submitted by the sponsor. The sponsor was informed that after a preliminary review, DMEPA was concerned (b) (4) (b) (4) In the interest of transparency and in light of the application action date, DMEPA informed the applicant that they wanted to share their preliminary concerns for the Applicant's consideration.

The applicant expressed that they will not be submitting (b) (4) as their alternate name and will move forward with submitting a different proprietary name by the end of next week. The applicant inquired what the review time for the new proprietary name would be and was notified it would be 90 days. However, in this case the applicant was notified DMEPA would strive to expedite their review, based on available resources, to meet the application timeline which would fall prior to the 90 day timeline that is generally allocated for a proprietary name review. In addition, DMEPA

clarified that they review one proposed proprietary name per review request and explained that action on the application is not dependent on the proprietary name review.

ACTION ITEMS

- The applicant indicated they would move forward with two new names which will be submitted via the electronic gateway by the end of next week (August 31, 2018).

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/s/

DAVIS MATHEW
08/24/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211210

PROPRIETARY NAME REQUEST
UNACCEPTABLE

TerSera Therapeutics LLC
Two Conway Park
150 N. Field Dr., Suite 195
Lake Forest, IL 60045

ATTENTION: Jay R. Ford
Vice President, Regulatory Affairs

Dear Mr. Ford:

Please refer to your New Drug Application (NDA) dated and received December 21, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Meloxicam Orally Disintegrating Tablets.

We also refer to your correspondence, dated and received May 18, 2018, requesting review of your proposed proprietary name, (b) (4) ODT.

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

(b) (4)

We note that you have proposed an alternate proprietary name in your submission dated May 18, 2018. In order to initiate the review of the alternate proprietary name, (b) (4) ODT, submit a new complete request for proprietary name review. The review of this alternate name will not be initiated until the new submission is received.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

(b) (4)

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf)

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, (https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm)

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Taiye Ayoola, Regulatory Project Manager in the Office of New Drugs, at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Danielle Harris, PharmD, BCPS
Deputy Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS
08/16/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211210

PROPRIETARY NAME ACKNOWLEDGEMENT

TerSera Therapeutics LLC
Two Conway Park
150 N. Field Dr., Suite 195
Lake Forest, IL 60045

ATTENTION: Jay R. Ford
Vice President, Regulatory Affairs

Dear Mr. Ford:

Please refer to your New Drug Application (NDA) dated and received December 21, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Meloxicam Orally Disintegrating Tablets.

We acknowledge receipt of your correspondence, dated and received May 18, 2018, requesting a review of your proposed proprietary name, (b) (4) ODT.

Therefore, the user fee goal date to review your request for proprietary name is August 16, 2018.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (240) 402-4559. For any other information regarding this application, contact Taiye Ayoola, Regulatory Project Manager, in the Office of New Drugs at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Davis Mathew, PharmD, RPh
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DAVIS MATHEW
05/30/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211210

PROPRIETARY NAME REQUEST
UNACCEPTABLE

TerSera Therapeutics LLC
Two Conway Park
150 N. Field Dr., Suite 195
Lake Forest, IL 60045

ATTENTION: Jay R. Ford
Vice President, Regulatory Affairs

Dear Mr. Ford:

Please refer to your New Drug Application (NDA) dated and received December 21, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Meloxicam Orally Disintegrating Tablet.

We also refer to your correspondence, dated and received January 22, 2018, requesting review of your proposed proprietary name, (b) (4) ODT.

We have completed our review of this proposed proprietary name and have concluded that this name is unacceptable for the following reasons:

(b) (4)

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

(b) (4)

We note that you have not proposed an alternate proprietary name for review. If you intend to have a proprietary name for this product, we recommend that you submit a new request for a proposed proprietary name review.

If you require additional information on developing proprietary names for drugs, proposing alternative proprietary names for consideration, or requesting reconsideration of our decision, we refer you to the following:

- Draft Guidance for Industry Best Practices in Developing Proprietary Names for Drugs, (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf)

- Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)

- PDUFA Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, (https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm446608.htm)

[8] Tu, CM, Taylor, K, and Chai, G. Use of Proprietary Names by Prescribers for Discontinued Brand Drug Products With Existing Generic Equivalents. Drug Information Journal, published online August 21, 2012, available at http://dij.sagepub.com/content/early/2012/08/21/0092861512456282 full.pdf+html
[9] Lesar TS. Prescribing errors involving medication dosage forms. J Gen Intern Med. 2002 Aug;17(8):579-87.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Davis Mathew, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (240) 402-4559. For any other information regarding this application, contact Taiye Ayoola, Regulatory Project Manager in the Office of New Drugs, at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Todd Bridges, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DANIELLE M HARRIS on behalf of TODD D BRIDGES
04/04/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211210

FILING COMMUNICATION -
FILING REVIEW ISSUES IDENTIFIED

TerSera Therapeutics LLC
Two Conway Park
150 N Field Dr.
Suite 195
Lake Forest, IL 60045

Attention: Jay Ford
Vice President, Regulatory Affairs

Dear Mr. Ford:

Please refer to your New Drug Application (NDA) dated and received December 21, 2017, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for meloxicam ODT, 7.5 mg and 15 mg.

We also refer to your amendment dated January 22, 2018.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 21, 2018.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, mid-cycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing requirement/commitment requests by September 28, 2018. This date conforms to the 21st Century Review timeline for your application.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug and contains a paragraph IV certification, this filing communication is the "paragraph IV acknowledgment letter" described in 21 CFR 314.52(b) and the "postmark" is 4 calendar days

after the date on which this letter is signed. Notice of the paragraph IV certification must be sent to the persons described in 21 CFR 314.52(a) no later than 20 days after the date of the postmark on this paragraph IV acknowledgment letter and must contain the information described in 21 CFR 314.52(c).

During our filing review of your application, we identified the following potential review issues:

Clinical

1. You did not submit an Integrated Summary of Effectiveness (ISE). In addition to the Summary of Clinical Efficacy (SCE), submit an ISE in Module 5.3.5.3. If you believe that the SCE in Module 2 otherwise fulfills the regulatory requirements for an ISE, you may submit an ISE in Module 5 that simply references and links back to the SCE.

Clinical Pharmacology

2. It appears you intend to rely on literature data to support labeling claims for your product. However, we are unable to locate the bioanalytical validation/performance data and raw pharmacokinetic (PK) data for the human PK studies you cited and summarized from the literature in your NDA submission. We recommend that you contact the authors to obtain this information. As mentioned to you at the pre-NDA meeting, we expect you to demonstrate due diligence in terms of acquiring such information about these studies. Otherwise, provide adequate justification that the required information is not obtainable and why the results from the literature can still be used to support your proposed product.

Biopharmaceutics

3. Justify the rationale (b) (4)

(b) (4)

(b) (4)

4. (b) (4)

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application.

Please respond to the requests for information listed in the potential review issues described above. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

If your 505(b)(2) application relies on FDA's finding of safety and/or effectiveness for a listed drug, we recommend that the cover letter for amendments to your unapproved 505(b)(2) application either: 1) state that the amendment contains a patent certification (or recertification) or statement required by 21 CFR 314.60(f)(1); or 2) verify that the proposed change described in the amendment is not one of the types of amendments described in 21 CFR 314.60(f)(1), as appropriate.

PRESCRIBING INFORMATION

Your proposed prescribing information (PI) must conform to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57. As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and PLLR Requirements for Prescribing Information websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information in the PI on pregnancy, lactation, and females and males of reproductive potential
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances, and
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

During our preliminary review of your submitted labeling, we have identified the following labeling issues and have the following labeling comments:

Highlights General Format

1. Headings in HL must be presented in the following order:

Heading	Required/Optional
• **Highlights Heading**	Required
• **Highlights Limitation Statement**	Required
• **Product Title**	Required
• **Initial U.S. Approval**	Required
• **Boxed Warning**	Required if a BOXED WARNING is in the FPI
• **Recent Major Changes**	Required for only certain changes to PI*
• **Indications and Usage**	Required
• **Dosage and Administration**	Required
• **Dosage Forms and Strengths**	Required
• **Contraindications**	Required (if no contraindications must state "None.")
• **Warnings and Precautions**	Not required by regulation, but should be present
• **Adverse Reactions**	Required
• **Drug Interactions**	Optional
• **Use in Specific Populations**	Optional
• **Patient Counseling Information Statement**	Required
• **Revision Date**	Required

* RMC only applies to <u>five</u> labeling sections in the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS.

<u>Comment</u>: *Include "Initial U.S. Approval: YYYY" in **bold** font before Boxed Warning*

Highlights Limitation Statement

2. The **bolded** HL Limitation Statement must include the following verbatim statement: "**These highlights do not include all the information needed to use (insert NAME OF DRUG PRODUCT) safely and effectively. See full prescribing information for (insert NAME OF DRUG PRODUCT).**" The name of drug product should appear in UPPER CASE letters.

   <u>Comment</u>: *The HL limitation statement should be in **bold** font*

Product Title in Highlights

3. Product title must be **bolded**.

   <u>Comment</u>: *Revise product title so it is in **bold** font*

Initial U.S. Approval in Highlights

4. Initial U.S. Approval must be **bolded**, and include the verbatim statement "**Initial U.S. Approval:**" followed by the **4-digit year**.

   <u>Comment</u>: *Include "Initial U.S. Approval: YYYY" in **bold** font*

Contraindications in Highlights

5. All contraindications listed in the FPI must also be listed in HL. If there is more than one contraindication, each contraindication should be bulleted. If no contraindications are known, must include the word "None."

   <u>Comment</u>: *Pregnant women starting at 30 weeks of gestation (third trimester) in FPI should also be included in the HL*

Patient Counseling Information Statement in Highlights

6. The Patient Counseling Information statement must include bolded verbatim statements that is most applicable:

   <u>If a product **has (or will have)** FDA-approved patient labeling</u>:

   - **See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**
   - **See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**

   <u>Comment</u>: *Though statement is inserted verbatim, "Medication Guide" should not be in capital letters. Also, remove period after "Guide"*

Revision Date in Highlights

7. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., "**Revised: 8/2015**").
   Comment: *Use **bold font** for **"Revised: M/YYYY"** at the end of the HL*

Contents: Table of Contents (TOC)

8. If a section or subsection required by regulation [21 CFR 201.56(d)(1)] is omitted from the FPI, the numbering in the TOC must not change. The heading "**FULL PRESCRIBING INFORMATION: CONTENTS***" must be followed by an asterisk and the following statement must appear at the end of the TOC: "*Sections or subsections omitted from the full prescribing information are not listed."
   Comment: *Subsections for **Pharmacokinetics** and **Pharmacogenomics** in TOC should be numbered **12.3** and **12.5** respectively, and not 12.2 and 12.3 as currently numbered. Also, ensure that the numbers in the TOC correspond to the numbers in the FPI*

Full Prescribing Information: General Format

9. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1). (Section and subsection headings should be in UPPER CASE and title case, respectively.) If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.
   Comment: *If a section/subsection required by regulation is omitted, the numbering must not change. Therefore, subsections for **Pharmacokinetics** and **Pharmacogenomics** should be numbered **12.3** and **12.5** respectively, and not 12.2 and 12.3 as currently numbered. Also, ensure that the numbers in the FPI correspond to the numbers in the TOC.*

We request that you resubmit labeling (in Microsoft Word format) that addresses these issues by March 26, 2018. The resubmitted labeling will be used for further labeling discussions. Use the SRPI checklist to correct any formatting errors to ensure conformance with the format items in regulations and guidances. The checklist is available at the following link: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf

At the end of labeling discussions, use the SRPI checklist to ensure that the PI conforms with format items in regulations and guidances.

PROMOTIONAL MATERIAL

You may request advisory comments on proposed introductory advertising and promotional labeling. Please submit, in triplicate, a detailed cover letter requesting advisory comments (list each proposed promotional piece in the cover letter along with the material type and material identification code, if applicable), the proposed promotional materials in draft or mock-up form with annotated references, and the proposed package insert (PI), Medication Guide, and patient PI (as applicable). Submit consumer-directed, professional-directed, and television advertisement materials separately and send each submission to:

OPDP Regulatory Project Manager
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion (OPDP)
5901-B Ammendale Road
Beltsville, MD 20705-1266

Alternatively, you may submit a request for advisory comments electronically in eCTD format. For more information about submitting promotional materials in eCTD format, see the draft Guidance for Industry (available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM443702.pdf).

Do not submit launch materials until you have received our proposed revisions to the package insert (PI), and Medication Guide, and you believe the labeling is close to the final version.

For more information regarding OPDP submissions, please see http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm090142.htm. If you have any questions, call OPDP at 301-796-1200.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

We acknowledge receipt of your request for a full disease-specific waiver of pediatric studies for Osteoarthritis and a partial waiver of pediatric studies for Rheumatoid Arthritis. Once we have reviewed your requests, we will notify you if the waiver requests are denied and a pediatric drug development plan is required.

This drug may be appropriately labeled for use in pediatric patients with Juvenile Rheumatoid Arthritis (JRA) Pauciarticular and Polyarticular Course who weigh greater than 60 kg. We will notify you if the current pediatric labeling for that group is not adequate.

If you have any questions, call Taiye Ayoola, PharmD, Regulatory Project Manager, at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Sharon Hertz, MD
Director
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

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/s/

ELLEN W FIELDS on behalf of SHARON H HERTZ
03/01/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

NDA 211210

PROPRIETARY NAME ACKNOWLEDGEMENT

TerSera Therapeutics LLC
Two Conway Park
150 N. Field Dr., Suite 195
Lake Forest, IL 60045

ATTENTION: Jay Ford
Vice President, Regulatory Affairs

Dear Mr. Ford:

Please refer to your New Drug Application (NDA) dated and received December 21, 2017, submitted under section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Meloxicam Orally Disintegrating Tablets.

We acknowledge receipt of your correspondence, dated and received January 22, 2018, requesting a review of your proposed proprietary name, (b) (4) ODT.

If the application is filed, the user fee goal date to review your request for proprietary name is April 22, 2018.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact me at (240) 402-4559. For any other information regarding this application, contact Taiye Ayoola, Regulatory Project Manager, in the Office of New Drugs at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Davis Mathew, PharmD, RPh
Safety Regulatory Project Manager
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

DAVIS MATHEW
01/29/2018

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 104140

MEETING MINUTES

TerSera Therapeutics LLC
Two Conway Park
150 N. Field Dr., Suite 195
Lake Forest, IL 60045

Attention: Richard Crowley
EVP, Operations, Quality Assurance and Regulatory Affairs

Dear Mr. Crowley:

Please refer to your Investigational New Drug Application (IND) submitted under Section 505(i) of the Federal Food, Drug, and Cosmetic Act for Meloxicam Orally Disintegrating Tablets (ODT), 7.5 mg and 15 mg.

We also refer to the teleconference between representatives of your firm and the FDA on July 12, 2017. The purpose of the teleconference was to discuss the content and format of a 505(b)(2) application for marketing approval of meloxicam ODT.

A copy of the official minutes of the teleconference is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (240) 402-8561.

Sincerely,

{See appended electronic signature page}

Taiye Ayoola, PharmD
Regulatory Project Manager
Division of Anesthesia, Analgesia,
and Addiction Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: July 12, 2017, 3:00 p.m. (EDT)
Meeting Location: Teleconference

Application Number: IND 104140
Product Name: Meloxicam ODT, 7.5 mg and 15 mg
Indication: For the relief of the signs and symptoms of osteoarthritis (OA), rheumatoid arthritis (RA), and Pauci-articular or polyarticular course juvenile rheumatoid arthritis (JRA) in patients who weigh ≥ 60 kg

Sponsor/Applicant Name: TerSera Therapeutics LLC

Meeting Chair: Ellen Fields, MD, MPH, Deputy Division Director, DAAAP
Meeting Recorder: Taiye Ayoola, PharmD, Regulatory Project Manager, DAAAP

FDA ATTENDEES

FDA Attendees	Title
Ellen Fields, MD, MPH	Deputy Division Director, DAAAP
Timothy Jiang, MD	Medical Officer, DAAAP
Dan Mellon, PhD	Pharmacology/Toxicology Supervisor, DAAAP
Armaghan Emami, PhD	Pharmacology/Toxicology Reviewer, DAAAP
Yun Xu, PhD	Clinical Pharmacology Team Leader, Office of Clinical Pharmacology (OCP)
Deep Kwatra, PhD	Clinical Pharmacology Reviewer, OCP
Julia Pinto, PhD	Branch Chief, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Ciby Abraham, PhD	Acting Team Leader, ONDP, OPQ
Haritha Mandula, PhD	Acting Biopharmaceutics Assessment Lead, ONDP, OPQ
Kelly Kitchens, PhD	Biopharmaceutics Reviewer, ONDP, OPQ
Lawrence Perez, Ph.D.	CMC Reviewer, DNDAPI, ONDP, OPQ
Taiye Ayoola, PharmD	Regulatory Health Project Manager, DAAAP

SPONSOR ATTENDEES

Sponsor Attendees	Title
Rick Crowley	EVP, Operations, Quality Assurance and Regulatory Affairs, TerSera Therapeutics LLC
Nancy Joseph-Ridge, MD	EVP, Chief Medical Officer, TerSera Therapeutics LLC
Jay Ford	Vice President, Regulatory Affairs, TerSera Therapeutics LLC
Marcy Komocsar, BSN	Executive Director, Clinical and Pharmacovigilance, TerSera Therapeutics LLC
(b) (4)	Consultant to TerSera, (b) (4)
(b) (4)	Clinical Pharmacology Consultant to TerSera, (b) (4) (b) (4)
(b) (4)	Nonclinical Consultant to TerSera, (b) (4)

BACKGROUND

TerSera Therapeutics LLC submitted a request for a Pre-NDA meeting on March 3, 2017, to discuss the content and format of a 505(b)(2) application for marketing approval of meloxicam ODT. The meeting request was granted on March 20, 2017.

TerSera acquired all rights to IND 104140 for meloxicam ODT, 7.5 mg and 15 mg strengths, from the previous owner, Wilmington Pharmaceuticals LLC, on December 14, 2016. The formulation was developed with the disintegration characteristics of an ODT dosage form.

Meloxicam is an anti-inflammatory, analgesic and antipyretic agent. It is an oxicam derivative, which is included in the class of non-steroidal anti-inflammatory drugs (NSAIDs).

TerSera proposes to submit a 505(b)(2) application for marketing approval of meloxicam ODT in 2017. The referenced drug (RD) for the proposed 505(b)(2) application is Mobic (7.5 mg and 15 mg tablets).

The clinical program for meloxicam ODT includes four clinical pharmacology studies, which were designed to establish bioequivalence between meloxicam ODT and branded Mobic tablets. There are no new clinical efficacy or safety studies that have been performed in support of this application. However, TerSera plans to rely on information from the RD as well as recent literature to support the submission.

The questions from the May 17, 2017, meeting package are shown in *italic font*. The Division's preliminary responses are shown in **bold font** and the discussion points are shown in normal font.

The Division sent preliminary comments to the Sponsor on July 11, 2017. Following introductions, the discussion focused on questions 1, 10, 14, 3, 8 and 4 in that specific order.

DISCUSSION

Question 1: To support bioequivalence, TerSera is submitting a summary of Study 10943701 titled "A Study to Evaluate the Relative Bioavailability of a Meloxicam (b) (4) ((b) (4) ODT) Orally Disintegrating 15 mg Tablet compared to Mobic® (meloxicam) 15 mg Tablets in Healthy Volunteers under Fasted Conditions". In addition, TerSera plans to rely on the data in the Mobic package insert demonstrating the pharmacokinetic (PK) linearity between the 7.5 and 15 mg strength doses. Does the Agency agree that bioequivalence has been demonstrated?

FDA Response:
Based on the preliminary PK data you submitted, it appears your product met the bioequivalence criteria with a similar PK profile to Mobic 15 mg strength under fasted condition. However, the final decision on whether the bioequivalence criteria have been met will be decided at the time of NDA review. The adequacy of the data submitted to make such determination will be a review issue. Additionally, we observe that you have conducted a food-effect study with your product. Based on cross-study comparison of your data with the Mobic label, your product has a much longer T_{max} compared to Mobic tablet in the fed state. Therefore, we have concerns regarding the efficacy of your product under the fed condition, especially the onset of action. Further justification will be required to support how the safety and efficacy findings from Mobic can be used to support your product considering these differences in T_{max}. We highly recommend that you conduct a fed BE study between Mobic and your product so the PK profiles under fed conditions can be compared directly within the same study. Refer to the FDA guidance for industry: *Food-Effect Bioavailability and Fed Bioequivalence Studies*, available at, http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126833.pdf for more details.

The final to-be-marketed product must be used in the PK studied to support your NDA application. If not, adequate bridging data or justification must be provided.

Discussion
The Sponsor acknowledged the comments from the Division and stated that their proposed indication is for the relief of the signs and symptoms of OA, RA, and JRA. The Sponsor also stated that, given the chronic nature of the diseases, the once-daily dosing regimen, and the intended therapeutic effect at steady state, they believe that there is no clinical relevance in the delayed $T_{max,}$ especially because the Listed Drug, Mobic, also exhibits a delayed T_{max}. Therefore, the issue of the T_{max} prolongation does not change the strength of the scientific bridge that was established in the pivotal BE study. The Sponsor went further to state that they do not believe that an additional study is required because the therapeutic effect of meloxicam is a function of steady state systemic concentration and not of T_{max}.

The Division acknowledged that the Sponsor's product is being proposed for chronic indications. The Division requested that the Sponsor submit their rationale and provide any additional data at the time of the NDA submission to show that, at steady state and at fed conditions, meloxicam

ODT would have comparable systemic exposure to Mobic. The Division stated that they would review the submitted information and determine its acceptability during the NDA review cycle.

Question 2: The Agency provided Wilmington Pharmaceuticals LLC guidance on receiving a biowaiver for in vivo testing of the 7.5 mg strength, and has confirmed with TerSera its validity in an email dated 06 February 2017. This response outlined the necessary bioavailability and PK information required for the biowaiver, which has been completed. TerSera intends to support a biowaiver request for the 7.5 mg strength with the following data:

- *Bioavailability data on the 15 mg strength;*
- *Demonstration of linear PK between the 7.5 mg and 15 mg strengths, as described in the Mobic package insert;*
- *Compositional proportionality between the 2 strengths; and*

(b) (4)

Will the Agency grant a biowaiver for in vivo testing of the 7.5 mg strength?

FDA Response:
The information you plan to submit to support a biowaiver request for the 7.5 mg strength seems reasonable. The adequacy of the biowaiver request will be determined during the NDA review based on the totality of the information provided.

Discussion
There was no further discussion.

Question 3: Does the Agency agree with the use of literature information as well as information from the RLD to support clinical pharmacology, efficacy and safety?

FDA Response:
Clinical:
You may use literature to support the application, however we disagree with the proposed timeframe for the literature search. The most recent Mobic label update was in response specifically to address the NSAID class cardiovascular Safety Label Change. Therefore, extend the timing of literature search to the time of approval of the Listed Drug.

It is generally acceptable to utilize literature in combination with a relative BE/BA study to bridge the Agency's previous findings of the Listed Drug as a part of your 505(b)(2) NDA application.

Literature articles used to support the NDA must be provided as full articles in the submission. If literature articles are used to support clinical pharmacology findings of your product, the PK study(ies) must be of adequate sample size, and include validated analytical assays the drug and its metabolites. For human PK studies you cite or summarize from literature, provide the bioanalytical validation/performance data and raw PK data in your NDA submission. We recommend you contact the authors to obtain such

information and submit it as a part of your package. Due diligence is required to acquire such information about the studies, otherwise you must provide adequate justification that the required information is not obtainable and why the results from the literature can still be used to support your proposed product. If a proprietary drug name is mentioned in a literature article you plan to use to support the NDA, you must obtain right of reference to that product or list it as a referenced product and provide appropriate patent certification.

Discussion
The Sponsor sought clarification on the date range for the literature search and the relevance of the articles to include. The Sponsor stated that they have performed a search from 2015 to present, and that they have reviewed approximately 1500 abstracts.

The Division advised the Sponsor to perform a literature search from 2000, the year of the initial Mobic approval, to present. The Sponsor should evaluate whether or not there is new information that should be updated for meloxicam in the label for their product, because the last approved meloxicam label did not fully meet the Pregnancy and Lactation Labeling Rule (PLLR). From a nonclinical perspective, the Sponsor should focus on genetic, carcinogenic, reproductive toxicities including new PLLR requirements. From a clinical pharmacology perspective, the Sponsor should not simply focus on pure PK data. Rather, the focus should be on new information related to the drug substance itself, such as hepatic impairment, renal impairment, drug-drug interactions, and metabolism. Clinically, the Sponsor should focus on safety, for example, in relation to special populations.

The Division reiterated that if the Sponsor relies on information in articles which include a brand name product, and that information is necessary for approval of their product, they must include that brand name product as a Listed Drug (LD) for their 505(b)(2) application. Additionally, if the brand name drug is relevant for inclusion in the labeling, then the Sponsor must provide patent certification for the product.

Question 4: Does the Agency agree to waive the requirements for an Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in the NDA?

FDA Response:
No, we disagree. From a safety perspective, the completed four studies must be pooled for analysis as long as the studies are suitable for pooling, and prior safety findings for the listed drug is appropriate to support your product. From an efficacy perspective, you must not only describe the results of your PK studies to establish BE, but also discuss how the Agency's prior findings for the listed drug support the proposed indication.

The sections of ISS and ISE will be satisfied as long as you provide sufficient information in Module 2 which is complete and meets the size limitation, create cross-reference links for Modules 2.7.3 and 2.7.4 from the ISS, and ISE is placed in Module 5.3.5.3.

Discussion

The Sponsor stated that they have limited data on safety and requested that the Division clarify the definition of pooling. The Division responded that the Sponsor can pool just the safety information because efficacy data is not collected in the Phase 1 studies.

Question 5: TerSera proposes to submit CSRs for the 4 clinical pharmacology studies in eCTD format with E3 granularity. TerSera also intends to only submit datasets for the 2 pivotal clinical pharmacology studies (Studies 10943701 and 10943702). These will be included as separate SAS Transport files for each study. Does the Agency agree with this approach?

FDA Response:
This approach is acceptable from a clinical pharmacology prospective. Refer to the FDA guidance for industry: *E3 Structure and Content of Clinical Study Reports*, available at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM336889.pdf for further guidance. Note the PK data submitted in the NDA must be adequate to allow Agency analyses.

Discussion
There was no further discussion.

Question 6: No deaths, serious AEs, discontinuations due to an AE, or other significant AEs were reported during the clinical evaluation of meloxicam ODT. Therefore, no case report forms (CRFs) or patient narratives are planned to be submitted. In addition, TerSera does not intend to submit patient profiles for any study. Does the Agency agree with this approach?

FDA Response:
Since no deaths, serious AEs, discontinuations due to an AE, or other significant AEs were reported during the clinical program, the proposed approach is acceptable from clinical perspective. We may request CRFs if it is deemed to be necessary during the review process.

Discussion
There was no further discussion.

Question 7: Does the Agency have any other recommendations that TerSera should consider regarding the clinical aspects of this application?

FDA Response:
In general, if a product is bioequivalent to the listed drug, no additional clinical efficacy or safety trials will be necessary. However, you must provide clinical justification for the delayed T_{max} with food. For an analgesic, delayed T_{max} could pose concerns for both efficacy and safety, e.g., taking early or additional doses of the medication if pain relief is not achieved.

As a new dosage form, your product triggers PREA. You must have an agreed iPSP before submission of NDA, otherwise, your submission is considered incomplete, which is the grounds for refuse to file. Also see the template language below on iPSP requirement.

Discussion
There was no further discussion.

Question 8: Does the Agency have any comments on the proposed approach for the nonclinical information, specifically:

a. *Inclusion of an abbreviated Module 2.4;*
b. *Proposed dates for the literature search; or*
c. *Omission of Module 2.6?*

FDA Response:
The NDA must be complete per 21 CFR 314.50 and contain all sections of the application, including Modules 2.4 and 2.6. Include a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of your drug product. Although tabulated summaries of the toxicology studies conducted by the innovator are not necessary for Module 2.6, any journal article that impacts the overall safety assessment and considered appropriate to inform labeling should be discussed in 2.4 and summarized in tabular format in 2.6. This search is essential in order to fully comply with the requirements outlined by the Pregnancy Labeling and Lactation Rule (PLLR) requirements.

Your proposal to include a literature search of articles ranging only from January 2015 to January 2017 is not acceptable. The literature search should include references since the approval of the referenced drug product. Include copies of all referenced citations in the NDA submission in Module 4. Journal articles that are not in English must be translated into English.

Discussion
See discussion under Question 3.

Question 9: Does the Agency have any other recommendations that TerSera should consider regarding the nonclinical aspects of this application?

FDA Response:
Refer to the nonclinical comments below to determine if any other nonclinical studies will be warranted for your program.

1. **If the drug substance batch(es) proposed for use in your clinical study are not the same batches as those used in your nonclinical toxicology studies, provide a table in your IND submission that compares the impurity profile across batches. Include justification for why the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed levels in the clinical batches or do not otherwise represent a safety concern.**

2. **For the NDA submission, any impurity or degradation product that exceeds ICH thresholds must be adequately qualified for safety as per ICH Q3A(R2), ICH Q3B(R2) or be demonstrated to be within the specifications of the referenced drug used for approval through the 505(b)(2) pathway. In order to provide adequate qualification:**

    a. **You must complete a minimal genetic toxicology screen (two in vitro genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.**

    b. **In addition, you must conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. For a chronic indication, a study of 90 days should be completed.**

       Refer to
       Guidance for industry: *Q3A(R2) Impurities in New Drug Substances*, available at:
       http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073385.pdf
       and
       Guidance for industry: *Q3B(R2) Impurities in New Drug Products*, available at:
       http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm073389.pdf

    c. **Alternatively, you may be able to justify the safety of a drug product degradant via comparative analytical studies that demonstrate that the levels of the degradant in your drug product are equal to or below the levels found in the referenced drug product. If you elect to pursue this approach, refer to the FDA guidance for industry: *ANDAs: Impurities in Drug Products*, available at,**
       http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072861.pdf.

3. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product, how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds, and if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

4. **The NDA submission must contain adequate information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. Provide justification for the choice of solvents and conditions for the extraction studies (time, temperature,**

etc). The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. Your analytical evaluation threshold (AET) must be established to be able to detect, identify, and quantitate levels of compounds based on these thresholds or you must provide adequate justification that these thresholds are not possible to be met by current analytical methodology. If you cannot meet these thresholds, safety evaluations will be based on the limits of quantitation (LOQ). Your submission must include a detailed discussion of how you established your AET as well as justification for the limits of detection (LOD) and LOQ for the analytical methods used.

Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of your stability studies in order to identify trends in leachable levels over time. The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product.

For all drug products, establish your AET to be able to detect potentially carcinogenic or genotoxic compounds as per ICH M7 qualification thresholds (e.g., not more than 1.5 mcg/day or up to 120 mcg/day pending during of treatment). However, from a general toxicology perspective, for parenteral products, the AET must be able to detect and identify any leachable that is present in the product at 5 mcg/day and higher, unless justified otherwise, to permit an adequate toxicological risk assessment.

For additional guidance on extractables and leachables testing, refer to the following documents:

- **USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**
- **USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**
- **FDA guidance for industry: Container Closure Systems for Packaging Human Drugs and Biologics, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM070551.pdf**

In your assessment, include a table listing all compounds, including the concentration in ppm, the experimental conditions, and the maximum daily exposure to these compounds based on the maximum daily dose of the product. The extractable/leachable data must be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the

extraction studies may be adequate to support the safety assessment during development, evaluate at least three batches of your drug product that have been tested at multiple timepoints over the course of your stability studies, as discussed above, and base the final safety assessment on the maximum predicted levels of leachables identified to determine the safe level of exposure via the label-specified route of administration. The approach for toxicological evaluation of the safety of leachables must be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based.

- **If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.**

- **Published literature to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided to support your assertion that these data are adequate to support the safety of your container closure system.**

- **Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the extractable/leachable compound.**

5. **NOTE: We may refuse to file your application if your NDA submission does not contain adequate safety qualification data for any identified impurity or degradant that exceeds the ICH qualification thresholds, safety justification for a new or novel excipient, or safety characterization of extractables and leachables.**

6. **The nonclinical information in your proposed drug product labeling must include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label must be updated to reflect exposures from your product. If the referenced studies employ a**

different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.

7. **We note that all NDA applications filed after June 30, 2015 must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, you should conduct a thorough review of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at, http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.**

Discussion
There was no further discussion.

Question 10: As the Meloxicam ODT formulation incorporates a "previously- characterized flavoring component at levels which are within that found in the FDA inactive ingredients database," does the Agency agree the use of Orange Flavor (b) (4) *is acceptable?*

FDA Response:
The level of Orange Flavor (b) (4) **used in your product appears to be within the maximum potency levels listed in the FDA Inactive Ingredient Database (IID) for the proposed route. In your NDA, provide justification for how these approved products also provide coverage for the proposed chronic duration of use of your product. We remind you that new excipients must be adequately qualified for safety. Studies must be submitted to the IND in accordance with the guidance for industry: *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*, available at, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079250.pdf. As noted in the guidance, "the phrase *new excipients* means any ingredients that are intentionally added to therapeutic and diagnostic products but which: (1) we believe are not intended to exert therapeutic effects at the intended dosage (although they may act to improve product delivery, e.g., enhancing absorption or controlling release of the drug substance); and (2) are not fully qualified by existing safety data with respect to the currently *proposed level of exposure, duration of exposure, or route of administration*." (emphasis added).**

- **Published literature to support the safety of an excipient rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, (e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, and FEMA evaluations are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports must be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study must be discussed and justification must be provided**

to support your assertion that these data are adequate to support the safety of your drug product formulation.

- **Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your excipient. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the novel excipient.**

- **Safety justifications for oral drug products based on a compound being reported as generally recognized as safe (GRAS) in foods must be accompanied by appropriate reference to the Code of Federal Regulation, a discussion of any GRAS limitations, and an assessment of exposures typically obtained via food compared to the levels that will be obtained via your drug product when dosed up to the maximum daily dose. Maximum daily doses that exceed levels commonly consumed in foods are not supported by CFSAN GRAS determinations.**

Discussion

The Sponsor stated that the orange flavor was selected during development based on the FDA's Inactive Ingredient Database (IID), in which they found the maximum level allowed for an ODT product to be (b) (4) mg. The Sponsor mentioned that the amounts of orange flavor used in meloxicam ODT are (b) (4) mg for the 7.5 mg meloxicam ODT strength and (b) (4) mg for the 15 mg meloxicam ODT strengths. The Sponsor concluded that these numbers are well below the maximum potency levels found in the IID. The Sponsor also elaborated that the manufacturer holds the DMF and that they provided a letter of authorization (LOA). The Sponsor is aware of other approved NDAs in which the same orange flavoring is being used for chronic dosing. The Sponsor therefore believes that there is no need for additional studies to be performed with regards to the orange flavoring.

The Division acknowledged that the orange flavor is listed in the IID but would need to confirm its use in other products used chronically. The Division noted that the IID has some limitations due to the data used to populate the database and the proprietary nature of the ingredients. The Division stated that some limitations of the IID include that relevant information is not provided such as the maximum daily dose, acute or chronic use, and the relative risk benefit for any particular indication. Furthermore, flavorings are complex mixtures which are proprietary blends that typically include various artificial ingredients. The DMFs often list the chemicals as FEMA GRAS which is not an FDA determination of GRAS. The Division advised the Sponsor to use a CFR reference for GRAS instead of the FEMA number. In addition, the Division encouraged the Sponsor to request that the DMF holder list the corresponding CFR reference for GRAS status of any component or the basis of the FEMA designation if the ingredient was not listed as GRAS in the CFR. The Division also stated that we would review the DMF and, if there is confirmation after review that the orange flavoring is being used in comparable chronically administered products, the Sponsor will not be required to perform additional studies.

Question 11: Does the Agency have any comments regarding the proposed drug substance specification?

FDA Response:
Your proposed specification for the drug substance is in agreement with the USP monograph for meloxicam and is reasonable for a 505(b)(2) submission. However, the following should be addressed:

- **In order to support the use of USP<467> (b) (4) for controlling (b) (4) residual solvents, provide information in your application (b) (4) or data to show that there is no carry-over of other solvents used earlier in the process. We remind you that the Agency must also be notified of any change in the manufacturer or in the manufacturing process of the drug substance meloxicam.**

- **The test for Heavy Metals (USP<231>) is being replaced by the test for Elemental Impurities (USP<232> and <233>) on January 1, 2018. The specification should be updated once the Elemental Impurities test becomes implemented.**

- **Ensure that all the tests in the meloxicam monograph in USP40/NF35 are included. For example, the second ID test is not UV, but is based on the retention time of the meloxicam peak in the Assay.**

- **(b) (4) has been identified as a potentially genotoxic impurity. It is unclear if your drug substance and drug product specifications will include monitoring for this impurity based on the information in your briefing package as chemical structures were not provided. Note that genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity must be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7 Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk* for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. This guidance is available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM347725.pdf. Briefly, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. Conduct a hazard assessment to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, propose a control strategy and enact this**

where determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development in order to mitigate risk.

Discussion
There was no further discussion.

Question 12: Does the Agency have any comments regarding the proposed drug product specification?

FDA Response:
The drug product specifications seem reasonable to support a Phase 1 study. However, see our comment regarding the (b) (4) impurity in our response to Question 11 above. Final determination of adequacy of the limits is deferred to the submission review, when the data can be evaluated in its totality.

Discussion
There was no further discussion.

Question 13: Does the Agency agree that the available primary stability data will support the 505(b)(2) NDA application?

FDA Response:
The amount of stability data provided in this package will support a 505(b)2 application. However, additional data is needed to support the 7.5 mg tablet. See our response to Question 14.

Discussion
There was no further discussion.

Question 14: Does the Agency agree that a 36 month expiry period is appropriate, based on the available stability data?

FDA Response:
Thirty-six months of data for three batches of drug product are sufficient data to support the request for a 36-month expiry for the 15 mg tablets. However, twelve months of stability data for at least two batches of the 7.5 mg strength, stored under long term conditions, are required in order to support a commercially viable expiry for the 7.5mg strength.

Discussion
The Sponsor stated that they used the bracketing approach and that three batches of the highest strength (15 mg) and one batch of the lowest strength (7.5 mg) was assessed in the worst case scenario. Based on the Sponsor's assessment that the formulation was identical and that the ingredients between the two formulations were proportional, the Sponsor stated that they believe they can justify that the 7.5 mg stability data is acceptable. The Sponsor continued with a

proposal for a 36-month expiry for the 15 mg strength and an (b) (4)-month expiry for the 7.5 mg strength.

The Division explained that, per the guidance (Q1D), a bracketing approach involves more than two strengths. Therefore, there is insufficient data to set the expiry for the lowest dose. The Division requested at least one additional set of data for the 7.5 mg dosage strength in addition to the batch currently on stability. Six months of accelerated data and12 months of real-time data are required on one additional batch. Additionally, the NDA package must be complete at the time of submission and if all the data submitted are satisfactory, then a 24-month expiry for the 7.5 mg strength would be possible. The additional stability data set could come from clinical or developmental batches.

Question 15: Does the Agency have any comments regarding the NDA contents or content locations based on the TOC that has been provided?

FDA Response:
The proposed TOC of submission is standard, and seems to be acceptable from a clinical perspective.

As noted in the response to Question 8, include Module 2.6.

Discussion
There was no further discussion.

Question 16: Does the Agency have any additional comments or advice that TerSera should consider when preparing the NDA submission?

FDA Response:
Not at this time.

Discussion
There was no further discussion.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints,

and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. You must include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry: *Nonclinical Safety Evaluation of Pediatric Drug Products*, available at,
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079247.pdf.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans* at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM360507.pdf. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email pdit@fda.hhs.gov. For further guidance on pediatric product development, please refer to:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the *PLR Requirements for Prescribing Information* and *Pregnancy and Lactation Labeling Final Rule* websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

The application should include a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive

email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

MANUFACTURING FACILITIES

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft

guidance for industry, *Applications Covered by Section 505(b)(2)* (October 1999), available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at http://www.regulations.gov).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on

published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
4.	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

NARRATIVE SUMMARIES

Narratives summaries of important adverse events (e.g., deaths, events leading to discontinuation, other serious adverse events) should provide the detail necessary to permit an adequate understanding of the nature of the adverse event experienced by the study subject. Narrative summaries should not merely provide, in text format, the data that are already presented in the case report tabulation/forms, as this adds little value. A valuable narrative summary is written like a discharge summary with a complete synthesis of all available clinical

data and an informed discussion of the case, allowing a better understanding of what the patient experienced. The following is a list of components that would be found in a useful narrative summary:

- Patient age and sex
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Pertinent test results (e.g., lab data, ECG data, biopsy data)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

Office of Scientific Investigations (OSI) Requests

The Office of Scientific Investigations (OSI) requests that the following items be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA field investigators who conduct those inspections (Item I and II). This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

The dataset that is requested in Item III below is for use in a clinical site selection model that is being piloted in CDER. Electronic submission of the site level dataset is voluntary and is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
   a. Site number
   b. Principal investigator
   c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
   a. Number of subjects screened at each site
   b. Number of subjects randomized at each site
   c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

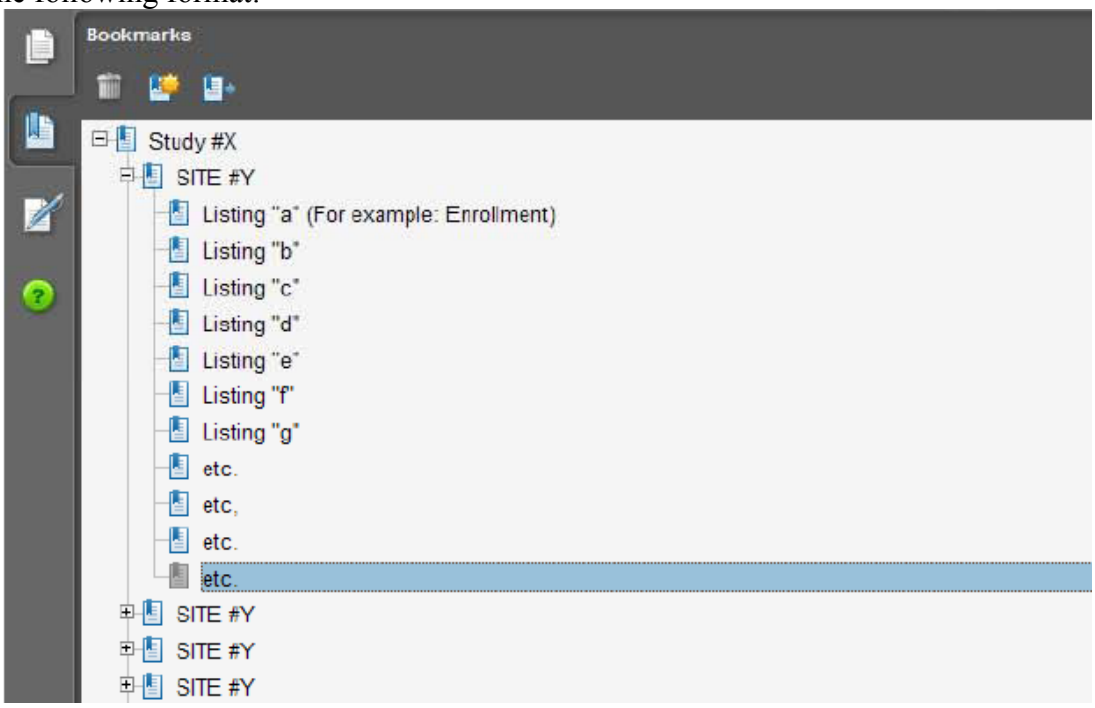
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as "line listings"). For each site, provide line listings for:
   a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
   b. Subject listing for treatment assignment (randomization)
   c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
   d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol

e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
f. By subject listing, of AEs, SAEs, deaths and dates
g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide a dataset, please refer to the draft Guidance for Industry Providing Submissions in Electronic Format – Summary Level Clinical Site Data for CDER's Inspection Planning" (available at the following link http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf) for the structure and format of this data set.

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

A. Data submitted for OSI review belongs in Module 5 of the eCTD. For items I and II in the chart below, the files should be linked into the Study Tagging File (STF) for each study. Leaf titles for this data should be named "BIMO [list study ID, followed by brief description of file being submitted]." In addition, a BIMO STF should be constructed and placed in Module 5.3.5.4, Other Study reports and related information. The study ID for this STF should be "bimo." Files for items I, II and III below should be linked into this BIMO STF, using file tags indicated below. The item III site-level dataset filename should be "clinsite.xpt."

DSI Pre-NDA Request Item[1]	STF File Tag	Used For	Allowable File Formats
I	data-listing-dataset	Data listings, by study	.pdf
I	annotated-crf	Sample annotated case report form, by study	.pdf
II	data-listing-dataset	Data listings, by study (Line listings, by site)	.pdf
III	data-listing-dataset	Site-level datasets, across studies	.xpt
III	data-listing-data-definition	Define file	.pdf

B. In addition, within the directory structure, the item III site-level dataset should be placed in the M5 folder as follows:

C. It is recommended, but not required, that a Reviewer's Guide in PDF format be included. If this Guide is included, it should be included in the BIMO STF. The leaf title should be "BIMO Reviewer Guide." The guide should contain a description of the BIMO elements being submitted with hyperlinks to those elements in Module 5.

References:

[1] Please see the OSI Pre-NDA/BLA Request document for a full description of requested data files

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

For general help with eCTD submissions: ESUB@fda.hhs.gov

ISSUES REQUIRING FURTHER DISCUSSION
There are no issues requiring further discussion.

ACTION ITEMS

1. At the time of NDA submission, the Sponsor will provide justification and any additional data to demonstrate that at, steady state with food, meloxicam ODT will behave similarly and have comparable systemic exposure as Mobic does with food.

2. The Sponsor will perform a literature search since the year of the original approval of the proposed referenced product (2000) to present, and will search for new and relevant information to update all sections of the label, including PLLR.

3. If the Sponsor finds literature upon which they plan to rely that discusses a brand name product, then the Sponsor will either demonstrate that the information on the brand name product is not necessary to approve their product or if it is, then they will include that brand name as a Listed Drug for their 505(b)(2) application.

4. If any brand name drug in the literature is relevant for inclusion in the labeling, then the Sponsor will provide patent certification for that product.

5. The Sponsor will pool the safety data from all Phase 1 studies in the ISS.

6. The Sponsor will make efforts contact the DMF holder to ensure that the ingredients included in the Orange Flavoring are CFR GRAS. For any ingredient in the flavor that is not GRAS as per the CFR, the Sponsor will provided data to support the safety. This may include the basis for a FEMA GRAS designation but not simply a FEMA number.

7. The Sponsor will provide a complete package at the time of NDA submission to include an additional lot of 7.5 mg stability data (12 months real-time data) for review.

ATTACHMENTS AND HANDOUTS
There were no attachments or handouts for the meeting minutes

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TAIYE AYOOLA
08/08/2017