

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

210132Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 114477

MEETING PRELIMINARY COMMENTS

TherapeuticsMD, Inc.
Attention: Valerie Ahmuty
Vice President, Regulatory Affairs
6800 Broken Sound Pkwy, N.W., 3rd Floor
Boca Raton, FL 33487

Dear Ms. Ahmuty:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for oral estradiol/progesterone capsules (TX-001HR).

We also refer to your June 28, 2017, correspondence, received June 28, 2017, requesting a Pre-NDA meeting to discuss submission requirements.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to me, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated minutes.

If you have any questions, call me, at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Kim Shiley, R.N., B.S.N.
Regulatory Health Project Manager
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 28, 2017, 1:30 p.m. – 2:30 p.m.
Meeting Location: 10903 New Hampshire Avenue
White Oak Building 22, Conference Room: 1415
Silver Spring, Maryland 20903

Application Number: IND 114477
Product Name: TX-001HR
Proposed Indication: Treatment of moderate to severe vasomotor symptoms associated with menopause
Sponsor/Applicant Name: TherapeuticsMD, Inc. (TXMD)

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for August 28, 2017, 1:30 p.m. – 2:30 p.m. between TherapeuticsMD, Inc. and the Division of Bone, Reproductive, and Urologic Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting by contacting me. If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact me if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

TX-001HR is a fixed dose combination of estradiol and progesterone proposed for the treatment of women with a uterus with moderate to severe vasomotor symptoms associated with menopause. Estradiol is intended to reduce the frequency and severity of vasomotor symptoms, and progesterone is included for protection of the endometrium. For estradiol, TXMD proposes

to summarize and submit published literature to support the nonclinical safety of TX-001HR and Sections 8 and 13 of the labeling. TXMD intends to rely on FDA's finding of safety for Prometrium (progesterone, USP) [NDA 019781, Virtus Pharmaceuticals LLC] for nonclinical information and to inform Sections 8 and 13 of the labeling. Comparative bioavailability information for TX-001HR vs. Prometrium 200 mg capsules (the current RLD and Reference Standard in the Orange Book for progesterone capsules) was obtained from the three phase 1 comparative BA studies (EPROG-1K-351-12, EPROG-1K-352-12, and EPROG-1K-459-12), and will be provided in the NDA.

QUESTIONS

Chemistry, Manufacturing and Controls (CMC)

Question 1: Drug Product Specifications

Does the Agency have any comments regarding the proposed drug product specifications?

FDA Response:

The tests proposed for inclusion in the drug product specification appear adequate. However, the final determination of the adequacy of the test methods and proposed acceptance criteria will be assessed based on the totality of the information submitted in the NDA.

The selection of the specification time point should be where $Q = \frac{(b)}{(4)}\%$ dissolution occurs. The final determination on the acceptability of the dissolution method and acceptance criterion is a review issue and will be made during the NDA review based on complete dissolution data (individual, mean +/- SD, mean profile, n=12/batch) from the pivotal clinical trial batches and primary (registration) stability batches.

Question 2: Drug Product Stability

Does the Agency agree with the above proposals to: 1) provide 12 months of data from the proposed commercial manufacturer's registration batches; 2) perform regression analysis on those Catalent registration batches to support the proposed commercial shelf life; 3) include summary information for ^{(b) (4)} clinical batches in the NDA, and 4) incorporate the individual ^{(b) (4)} clinical batch data in the NDA by reference to the IND?

FDA Response:

No, we do not completely agree. Your proposal to submit 12 months long-term stability data for three registration batches for each product strength manufactured by Catalent, is acceptable. Accelerated stability data through 6 months should also be provided for these batches.

Submission of regression analyses to support the proposed commercial shelf life is acceptable. Establishment of the shelf life is a review issue and will be assessed based on the totality of the data provided in the NDA.

Final stability data reports for all clinical batches manufactured at [REDACTED] (b) (4) [REDACTED] should be submitted in the NDA. The NDA also should include Certificates of Analyses for all clinical and registration batches manufactured at [REDACTED] (b) (4) and Catalent. Include a tabulation identifying the drug product batches used in each clinical trial.

The stability study reports should include the following information:

- The date the test sample was pulled from the stability chamber
- The date on which the sample test was conducted
- The analytical test method used to generate the data (including revision number)

We have the following additional chemistry, manufacturing and controls (CMC) comments:

- Provide a chronological sequence of changes that have been made to all the analytical test methods for determination of assay, related substances, and dissolution.
 - Include all methods used for testing clinical and registration batches of drug product at release and on stability.
 - List the reasons for the change and indicate if the method was validated and/or verified to be suitable for intended purpose.
 - Demonstrate and provide justification to support that any changes in dissolution methods (dissolution methodology and associated analytical methodology) did not impact the quality of the data.
- Provide a list of failures (out-of-specification) that have been observed during release and stability testing of the drug product along with impact assessment and resolution.

Question 3: Environmental Assessment

Does the Agency agree with our plan for the EA claim of categorical exclusion and that no extraordinary circumstances exist?

FDA Response:

No. Agreement at this time is premature. Your application might be eligible for the exclusion under 21 CFR 25.31(a), if the action does not increase use of the active moiety (see definitions on p. 30 of <https://www.fda.gov/downloads/Drugs/Guidances/ucm070561.pdf>). Otherwise, FDA needs the following information before making a determination about the exclusion under §25.31(b): (1) the expected use amounts and associated expected introduction concentrations (EICs), with supporting calculations; (2) a summary of any applicant-internal data on potential for aquatic effects, including those relevant to FDA's 2016 guidance, Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity, taking into account the substance's EIC, mechanism of action, nonclinical and other toxicity data, plasma-based analysis, "read across" analysis, and any other factors related to environmental risk assessment.

Question 4: Approach to Selection of the Dissolution Media Surfactant Level

Given the rationale and data provided in Section 5.1.5, does the Agency agree with TherapeuticsMD's approach to selecting the surfactant concentration in the dissolution medium?

FDA Response:

No, we do not agree at this time. We note that you evaluated different concentrations of surfactant. Additionally, evaluate surfactants other than SLS and dissolution media with different pH. Include the data supporting the selection of the type and amount of surfactant in your dissolution method development report. The testing conditions used for each test should be clearly specified.

Your dissolution method should demonstrate discriminating ability. In general, the testing conducted to demonstrate the discriminating ability of the selected dissolution method should compare the dissolution profiles of the reference (target) product and the test products that are intentionally manufactured with meaningful variations for the most relevant critical manufacturing variables (i.e., $\pm 10\text{-}20\%$ change to the specification-ranges of these variables). The acceptability of the dissolution method and proposed acceptance criterion will be assessed during review of your submitted NDA.

Biopharmaceutics

Question 5: Proposed Bridging of Formulation Revisions and Sites

Does the Agency have any further comments on the approach to bridge, as outlined above, for the formulation and manufacturing site changes during the development of TX-001HR?

FDA Response:

Your approach to bridge appears reasonable. Provide, in your NDA submission, details about the formulation and manufacturing process changes during development, and changes in dissolution method used to test these formulations. Our final decision on acceptability of your bridging of formulation revisions and manufacturing site changes will be based on the totality of the data provided in the NDA.

Nonclinical

Question 6: Proposed Nonclinical Information

Does the Agency agree that TherapeuticsMD may rely on published literature for estradiol and FDA's finding of safety for Prometrium as the RLD for progesterone, as the complete support for Sections 8 (Use in Specific Populations) and 13 (Nonclinical Toxicology) of the label and the Non-clinical sections of the proposed 505(b)(2) NDA?

FDA Response:

Yes. Your approach appears acceptable. We also refer you to our response to Question 15 regarding submission of 505(b)(2) applications.

Your proposed labeling must comply with the Pregnancy and Lactation Labeling Rule (PLLR). Nonclinical information from the published literature for estradiol and the labeling for Prometrium will be necessary to inform Sections 8 and 13 of your label under the PLLR. We refer you to PRESCRIBING INFORMATION later in this document for additional details.

Clinical Pharmacology

Question 7: Food Effect

Does the Agency have any comments regarding the proposed food effect protocol TXC17-02?

FDA Response:

We note that you submitted a full protocol for proposed Trial TXC17-02 on August 4, 2017, amended on August 14, 2017. The proposed food effect trial design appears reasonable. At this time, we have not identified any clinical safety concerns.

Question 8: Multiple Dose PK Study – Information to Include in the Clinical Pharmacology Section of the Label

Other than the food effect bioavailability study results, does that Agency agree that the results of Study TXC16-01 will fully inform the Clinical Pharmacology section of the proposed label?

FDA Response:

Yes, with qualifications. Your proposal to include the effective half-lives of estradiol and estrone in the labeling of your drug product is acceptable. However, we recommend that you determine the terminal half-lives of estradiol and estrone in your food effect trial (Trial TXC 17-02). Whether the results of Trial TXC16-01 are adequate to support the Clinical Pharmacology section of your labeling will be a review issue.

Question 9: Pharmacokinetics Evaluation of Estrone Sulfate

Does that Agency agree that assessment of estrone sulfate is not required for approval of TX-001HR?

FDA Response:

Yes, we agree.

Question 10: Waiver of In Vivo Bioavailability Requirement for the 0.5 mg/50 mg Strength of TX-001HR

Does the Agency agree that the in vivo bioavailability requirement for the 0.5 mg/50 mg strength of TX-001HR may be waived?

FDA Response:

Yes. Considering the linear pharmacokinetics of progesterone and estradiol within the proposed dose range and proportional similarity of the different strengths, we agree that the bioavailability requirement for the 0.5 mg/50 mg strength of TX-001HR can be waived, provided that the 0.5 mg/50 mg strength meets in vitro test requirements.

Clarify whether the formulation of 0.25 mg/50 mg strength is proportionally similar to that of other strengths.

Question 11: Completeness of the Clinical Pharmacology Program

Does the Agency agree that the Clinical Pharmacology program described herein, which includes the completed studies and the planned food effect study, is complete, and that no further Clinical Pharmacology studies are needed?

FDA Response:

Yes, pending review of your NDA submission. We have not currently identified a need for further Clinical Pharmacology trials.

Clinical Program

Question 12: Completeness of the Clinical Program

Does the Agency agree that these six studies constitute a complete clinical program, and that no other clinical studies should be needed for filing or approval of the NDA?

FDA Response:

Yes. Completed phase 3, 52-week Trial TXC12-05 appears to be adequately designed and conducted to submit your proposed NDA for filing for the indication of treatment of moderate to severe vasomotor symptoms due to menopause. Approvability will be a review issue.

Question 13: Proposal for NDA Summary Sections 2.7.3 and 2.7.4 as Narratives for the Integrated Summaries

Does the Agency agree that Sections 2.7.3 and 2.7.4 may serve as the narratives for the ISE and ISS as described in the FDA guidance, based on the information provided above?

FDA Response:

Yes. We agree that Sections 2.7.3 and 2.7.4 may serve as the narratives for the ISE and ISS.

Study Data Standardization Plan for TX-001HR

Question 14: Clinical Study Data Standardization Plan

Does the Agency agree with the proposed clinical study data standardization plan?

FDA Response:

Yes. We agree with your proposed clinical trial data standardization plan.

Proposed 505(b)(2) NDA

Question 15: Regulatory Pathway for Planned 505(b)(2) NDA

Does the Agency agree with the proposed regulatory pathway outlined for the planned 505(b)(2) NDA for TX-001HR?

FDA Response:

Yes. Your proposal to submit a 505(b)(2) application that relies on published literature for estradiol and FDA's finding of safety and effectiveness for Prometrium Capsules as reflected in the information provided in Table 19 of your meeting package "Information Essential for Approval by Reliance on Published Literature or a Reference Listed Drug", appears acceptable.

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. You also must establish that reliance on studies described in the literature or on other studies is scientifically appropriate.

Refer to the **505(b)(2) Regulatory Pathway** section below for additional information about submitting a 505(b)(2) NDA.

Question 16: Completeness of the Application

Does the Agency agree that the proposed contents of the planned NDA constitute a complete 505(b)(2) new drug application for review?

FDA Response:

The proposed content appears complete for the purpose of submission for filing of your proposed NDA. From a technical standpoint (not content) the proposed documents location for the planned NDA, is acceptable.

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.

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.

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) |
| <i>1. Example: Published literature</i> | <i>Nonclinical toxicology</i> |
| <i>2. Example: NDA XXXXXX “TRADENAME”</i> | <i>Previous finding of effectiveness for indication A</i> |
| <i>3. Example: NDA YYYYYY “TRADENAME”</i> | <i>Previous finding of safety for Carcinogenicity, labeling section B</i> |
| <i>4.</i> | |

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.

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.

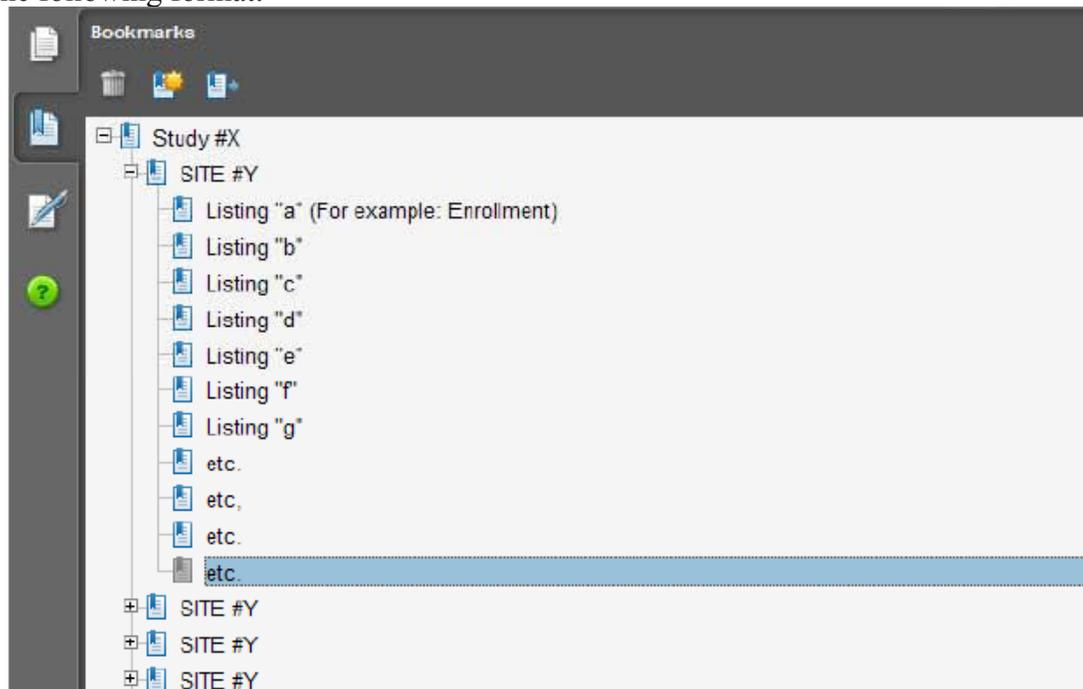
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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.

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

References:

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

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/s/

KIMBERLY A SHILEY
08/25/2017