CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208564Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118439

MEETING MINUTES

TherapeuticsMD Inc.
Attention: Valerie Ahmuty
Sr. Director, Regulatory Affairs
6800 Broken Sound Parkway NW
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 TX-004HR (estradiol).

We also refer to the teleconference between representatives of your firm and the FDA on December 15, 2015. The purpose of the meeting was to discuss information required for submission of your New Drug Application (NDA).

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 Kim Shiley, R.N., B.S.N., Regulatory Project Manager at (301) 796-2117.

Sincerely,

{See appended electronic signature page}

Shelley R. Slaughter, M.D., Ph.D.
Clinical Team Leader
Division of Bone, Reproductive, and Urologic Products
Office of Drug Evaluation III
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: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 15, 2015, 12:00 p.m. – 1:00 p.m.
Meeting Location: Teleconference

Application Number: 118439
Product Name: TX-004HR (estradiol)
Proposed Indication: Treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause

Sponsor/Applicant Name: TherapeuticsMD Inc.

Meeting Chair: Shelley R. Slaughter, M.D., Ph.D.
Meeting Recorder: Kim Shiley, R.N.

FDA ATTENDEES

Division of Bone, Reproductive, and Urologic Products
Christine Nguyen, M.D., Deputy Director for Safety
Shelley R. Slaughter, M.D., Ph.D., Clinical Team Leader
Theresa van der Vlugt, M.D., Clinical Reviewer
Nneka McNeal-Jackson, M.D., Clinical Reviewer
Kimberly Hatfield, Ph.D., Pharmacologist
Lynnda Reid, Ph.D., Pharmacology and Toxicology Supervisor
Margaret Kober, R.Ph., M.P.A., Chief, Project Management Staff
Kim Shiley, R.N., B.S.N., Regulatory Health Project Manager

Office of Biostatistics
Kate Dwyer, Ph.D., Reviewer

Office of Clinical Pharmacology:
Chongwoo Yu, Ph.D., Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality:
Mark Seggel, Ph.D., CMC Lead (Acting)

Office of Surveillance and Epidemiology
Danielle Harris

Denise Baugh

Office of Scientific Investigations
Roy Blay, Ph.D., Reviewer

SPONSOR ATTENDEES
Sebastian Mirkin, M.D., Chief Medical Officer
Christine Miller, Pharm.D., Vice President, Regulatory Affairs
Annette Shadiack, Ph.D., Vice President, Early Stage Development
Shelli Graham, Ph.D., Vice President, Medical Affairs
Valerie Ahmuty, Sr. Director, Regulatory Affairs
(b) (4)

1.0 BACKGROUND

TherapeuticsMD is planning to submit a New Drug Application (NDA) in second quarter 2016. The purpose of this meeting is to discuss the completeness of their application for their proposed estradiol product for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. Previous requested meetings include a Type C guidance meeting in May 2014 with discussions pertinent to the Phase 3 clinical study design, clinical and nonclinical development plans, and the regulatory pathway for the proposed NDA. Written advice in lieu of a meeting was issued on July 18, 2014. FDA comments regarding the Phase 3 protocol were addressed by TherapeuticsMD and subsequently submitted as protocol amendments throughout 2014. Additional FDA advice provided in February and August 2015 was addressed by TherapeuticsMD and subsequently submitted as a protocol amendment or submission to the IND application. A CMC End of Phase 2 meeting was held in July 2015.

FDA sent Preliminary Comments to TherapeuticsMD Inc. on December 14, 2015.

2. DISCUSSION

2.1 Chemistry, Manufacturing and Controls

Question 1: Executed Batch Records for Review

TherapeuticsMD proposes to include one set of executed batch records from the manufacture of the fill material, encapsulation, and packaging of the final product for one batch of each strength of the registration batches manufactured at each site, and place them in Module 3.2.R (Regional) of the NDA. Likewise, we plan to place one set of the proposed master batch records for each strength from each site in this section.

Does FDA agree that the number and placement of the executed batch records and the proposed commercial batch records are appropriate?

FDA response:
Yes, the proposals regarding submission of master batch records and executed batch records are acceptable

.

Sponsor accepted FDA response. No discussion.

Question 2: Certificates of Analyses for the Batches

Summary batch analysis data for clinical batches and the registration batches will be provided in section 3.2.P.5.4, Batch Analysis. One of the contract manufacturers, (b) (4), scans their Certificates of Analysis (CoA) to the batch record.

Does the Division agree with the placement of the batch CoAs? Is there any need for provision of the CoAs for the remaining registration batches in light of the summary data for all of the registration batches that will be provided in section 3.2.P.5.4?

FDA response:

Yes, inclusion of (b) (4) Certificates of Analysis (CoA) in the batch records is acceptable. At this time there is no need to submit the remaining CoAs if summary data for all of the batches are provided in 3.2.P.5.4, Batch Analyses. However, the CoAs for all batches should be available upon request during the review of the NDA.

Sponsor accepted FDA response. No discussion.

Question 3: Environmental Assessment

TherapeuticsMD plans to provide an Environmental Assessment (EA) in section 1.12.14 of the NDA for this naturally occurring substance (estradiol (b) (4) is plant based) with a claim of categorical exclusion per 21 CFR 25.31 (would increase the aquatic environmental exposure to estradiol less than 1 ppb as per 21 CFR 25.31(b)), include supporting calculations, and state that to the best of our knowledge that no extraordinary circumstances exist (per 21 CFR 25.15(d)). No Tier 1, 2, or 3 studies are planned. The environmental assessment document and calculations are provided in Appendix A.

TherapeuticsMD is aware of the April 2015 draft guidance "Environmental Assessment: Questions and Answers Regarding Drugs with Estrogenic, Androgenic, or Thyroid Activity," which states that FDA will require an EA if extraordinary circumstances indicate that the quality of the human environment may be significantly affected.

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

FDA response:

Yes. A claim for categorical exclusion per 21 CFR 25.31(b) and statement of no extraordinary circumstances is appropriate for this drug application. In support of the claim, submit the environmental assessment document and calculations in the original NDA submission.

There are errors in your Pre-NDA Meeting Background/ Briefing Materials. Information on page 30 (in multiple paragraphs) of the document incorrectly refers to the Predicted No-Effect Concentration (PNEC) for both estradiol and ethinyl estradiol in units of parts per billion (ppb).

You should refer to the PNECs for estradiol and ethinyl estradiol in parts per trillion (ppt) or alternatively as 0.1 x 10^{-3} ppb, etc.

Additionally, inclusion in the NDA of a risk quotient, i.e., ratio of the Environmental Introduction Concentration (EIC)/PNEC, for both estradiol and ethinyl estradiol would be useful.

Sponsor accepted FDA response. No discussion.

2.2 Nonclinical

Question 4: Nonclinical Studies

A 28-day, repeat-dose, vaginal irritation study in rabbits (study number (b) (4) /1013/G/T077, entitled "28 Day Repeated Dose Toxicity Study of (b) (4) in New Zealand White Female Rabbits by Vaginal Route" of the capsule fill material was performed in response to an Advice/Information Request from the Agency dated 08 July 2013, to evaluate the local tolerance of the inactive ingredient (b) (4) In the 18 July 2014 Written Response to our Type C meeting Question 5 on the adequacy of the preclinical program to support the NDA, the Division indicated that the formulation would be considered adequately assessed to support the NDA from a preclinical perspective, pending review of the final report.

The report was submitted 15 July 2014 in IND serial number 0006. Subsequently, a question from the nonclinical reviewer was received by email on 14 August 2014 to provide the doses of (b) (4) present in the three volume doses as mg/kg instead of volume of fill material (volume dose of 0.3 mL per rabbit ranged from 92.95 to 119.04 mg/kg, volume dose of 0.6 mL per rabbit ranged from 158.53 to 236.28 mg/kg, and the volume dose of 1.2 mL per rabbit ranged from 339.97 to 469.49 mg/kg). Our response was sent via email on 16 September 2014 and formally submitted to the IND in serial number 0023 on 13 May 2015.

Does the Division agree that there are no further questions and that the report and its amending correspondence are the only preclinical assessments necessary to support the planned NDA?

FDA response:
Study report (b) (4) /1013/G/T077 adequately assesses the proposed formulation. However, we refer you to the response to Question 10, as the Division does not agree with a submission that only addresses "de minimis nonclinical requirements" or that the proposed NDA constitutes a 505(b)(1) application. If you have not conducted (and do not plan to conduct) studies of your own to support the complete nonclinical safety of your product, or have a right of reference to the required studies, then you will need to rely on 1) published literature, and/or 2) FDA's previous finding of safety for a listed drug, in order to support the nonclinical safety and labeling for your product.

Discussion:
FDA provided two options for Pharmacology/Toxicology under the 505(b)(2) pathway:

1. Submit published literature for information necessary to inform Section 8 (Use in Specific Populations) and Section 13 (Nonclinical Toxicology) of labeling. If relevant

clinical data in the literature are more informative than animal data, this could be used as an alternative, provided it does not reference a specific product.

2. Refer to a Listed Drug. Under this option, labeling language from the listed drug can be used for your product as long as you establish a bridge demonstrating that your product and the listed drug are sufficiently similar. No literature submissions would be necessary.

2.3 Clinical Pharmacology

Question 5: Pharmacokinetic Data

The TX-004HR Clinical Pharmacology program consisted of three single-dose PK Phase 1 studies: one study evaluating the PK of a 10 µg dose (ESTR-1K-499-12) and two studies evaluating the PK of a 25 µg dose (ESTR-1K-500-12 and ESTR-2036-14), and a multidose PK substudy of subjects within each of the three active treatment arms (4 µg, 10 µg, and 25 µg) of the 12-week, Phase 3, randomized, double-blind, placebo-controlled pivotal safety and efficacy study (TXV14-01). Plasma samples were analyzed for estradiol, estrone, and estrone sulfate from these three PK studies and serum samples will be analyzed for estradiol, estrone, and estrone conjugates in the Phase 3 substudy.

Two of these PK studies (36 postmenopausal subjects each) also included 10 µg (ESTR-1K-499-12) or 25 µg (ESTR-1K-500-12) Vagifem® tablet arms, with the women quiescent for 4 hours after insertion (refer to IND serial number 0005 submitted 09 July 2014). In the third study (ESTR-2036-14), 16 women who had participated in the 25 µg PK study (ESTR-1K-500-12) were again administered TX-004HR 25 µg and were ambulatory.

The PK substudy that is part of the pivotal Phase 3 study (TXV14-01) includes approximately 60 randomly-selected subjects from each of the active dose groups, 4 µg, 10 µg, and 25 µg dose levels and placebo (~15 per group). Timed serum samples for assessment of PK for estradiol, estrone and estrone conjugates are to be obtained on Day 1 and Day 14. A single serum sample for PK parameters is to be obtained during Screening Visit 1A as well as approximately Day 84, 4 days after the last dose.

Information regarding the three Phase 1 PK studies and the Phase 3 PK substudy design (included in the submitted protocol) are further described in the briefing package.

Does the Division agree that these PK studies are sufficient Clinical Pharmacology support for filing of the NDA?

FDA response:
Yes. The identified pharmacokinetic (PK) studies appear to be sufficient for filing the NDA. However, the acceptability of the data generated from these studies will be a review issue.

In addition, we remind you that your bioanalytical method validation and performance should be in compliance with the Agency's Bioanalytical Method Validation Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM368107.pdf).

All bioanalytical method validation and study (performance) reports should be submitted at the

time of the original NDA submission.

Discussion: FDA reminded TherapeuticsMD to submit Sections 2.7.1 Summary of Biopharmaceutics and Analytical Methods and 2.7.2 Summary of Clinical Pharmacology in the NDA. Include all bioanalytical method validation and study (performance) reports in Section 2.7.1.

Therapeutics MD agreed to submit the above information in the appropriate sections of the NDA.

2.4 Integrated Summaries

Question 6: Narratives for Integrated Summaries

The Clinical Program consists of five studies: three single-dose PK studies, one 14-day Phase 2 safety and efficacy study, and one pivotal, 12-week, Phase 3, safety and efficacy study. Per the Guidance for Industry, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* (April 2009), our application meets the exception situation in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the Integrated Summary of Effectiveness (ISE) and Integrated Summary of Safety (ISS), respectively, while still concise enough to meet the suggested size limitations for Module 2. At this time, TherapeuticsMD does not anticipate formal integrated analyses due to the types of studies performed. However, should any tables, figures, and datasets be created for integrated analyses, these would be placed in section 5.3.5.3, as appropriate. The narrative portions will be submitted only once (in 2.7.3 and 2.7.4) and leaf elements will be provided in both locations (Modules 2 and 5, if needed) as instructed in the guidance.

Does the Division agree that sections 2.7.3 and 2.7.4 may serve as the narrative portions of the ISE and ISS as described in the FDA guidance, with any appendices of tables, figures, and datasets located in section 5.3.5.3, as needed?

FDA response:
We agree that your proposed NDA application would meet the exception situation set forth in the Agency's 2009 Guidance for Industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document, in which the narrative portion of section 2.7.3, Summary of Clinical Efficacy, under Module 2 Common Technical Document Summaries, 2.7 Clinical Summary, could be sufficiently detailed to serve as the narrative portion of the Integrated Summary of Efficacy (ISE).

In addition to the Summary of Clinical Safety in section 2.7.4, we recommend that your proposed NDA application include an Integrated Summary of Safety (ISS) in section 5.3.5.3 under Module 5 Clinical Study Reports.

Sponsor accepted FDA response. No discussion.

2.5 Electronic Submission Data Standards

TherapeuticsMD is aware of the May 2015 Guidance for Industry, *Providing Regulatory Submission in Electronic Format – Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, December 2014 Guidance for Industry, *Providing Regulatory Submissions in Electronic Format – Standardized Study Data*, and the March 2015 Technical Specifications Document, *Study Data Technical Conformance Guide*. The proposed Data Standardization Plan is provided in Appendix B.

Question 7: Preclinical Study Datasets

As discussed in Question 4, the rabbit preclinical safety study report (b) (4)/1013/G/T077 was submitted in IND sequence number 0006. The data compilation is in summary tables and appendices; however, Standard for Exchange of Nonclinical Data (SEND) datasets have not been created.

Does the Agency agree that the legacy report and data compilation (scanned, no electronic datasets) is acceptable for NDA submission?

FDA response:
Yes.

Sponsor accepted FDA response. No discussion.

Question 8: Clinical Study Data Standardization Plan

TherapeuticsMD has provided a proposed Clinical Study Data Standardization Plan following the Agency's template in Appendix B. For the Phase 1 studies, we propose to use legacy format tabulation data and data definition files in define.pdf format per Study Data Specifications (SDS) version 2.0 as the exchange standards, with no Clinical Data Interchange Standards Consortium (CDISC) terminology standard. For the Phase 2 study, we propose legacy format tabulation datasets with data definition file in define.pdf format and annotated case report form (CRF) as blankcrf.pdf per SDS version 2.0, and legacy format analysis datasets with define.pdf and SDS version 2.0 for the exchange standards, with no CDISC terminology standard. For the Phase 3 study, we propose Standard Data Tabulation Model Implementation Guide (SDTM IG) version 3.1.3, Analysis Data Module Implementation Guide (ADaM IG) version 1.0, annotated CRF as blankcrf.pdf per SDS version 2.0 and define.xml version 1.0 as the exchange standards, with CDISC controlled terminology.

Does the Division agree with the proposal?

FDA response:
We prefer define.xml version 2. If you submit the define.xml version 1, also submit define.pdf for printing purposes.

SAS programs to generate analysis datasets and efficacy results for the primary and key secondary analyses should also be submitted with data.

Sponsor accepted FDA response. No discussion.

2.6 Patient Instructions

Question 9: Label Comprehension

A copy of the draft instructions for use and illustrations that will be in the patient information leaflet is provided in Appendix C. The capsule will be inserted vaginally by the patient without the aid of a device; therefore a label comprehension study is not needed.

Does the Agency agree no label comprehension study is needed?

FDA response:
We recommend a comprehensive use-related risk analysis of your product to inform whether a labeling comprehension study would be needed. Your proposed product and package design does raise concerns for FDA regarding the potential for wrong route of administration errors (e.g., oral administration of the insert). The absence of an applicator for use with your product may suggest to patients that the 'inserts' can be given by routes other than vaginal. Therefore, we recommend you perform a use-related risk analysis to identify the use-related risks associated with your proposed product. Your risk analysis should include an evaluation of all the steps involved in using your product, the errors that users might commit or the tasks they might fail to perform (consider known problems for similar products), and the potential negative clinical consequences of use errors. Your use-related risk analysis should also discuss the risk-mitigation strategies you employed (e.g., labeling interventions). In your risk analysis, you should evaluate the risk for wrong route of administration errors and consider how this risk can be mitigated. The use-related risk analysis will inform whether a labeling comprehension study is needed to validate your risk mitigation strategies. Your risk analysis, along with any data you may have to support the design of your user interface, should be included in your original NDA submission.

Sponsor accepted FDA response. No discussion.

2.7 Regulatory

TherapeuticsMD would like to gain agreement on the completeness of the proposed structure and format of the NDA.

TherapeuticsMD has reviewed the history of NDA approvals for estradiol containing products for the treatment of Vasomotor Symptoms and Vulvar and Vaginal Atrophy Symptoms (summary provided in Appendix D). The Agency has described the nonclinical pharmacology and toxicology of estradiol as well known, and approved at least nine applications listed on Drugs@FDA as 505(b)(1) applications, with de minimis nonclinical requirements. Based upon our interactions with the Division and our search for regulatory precedents, there appears to be no requirement to compile a literature review or rely upon another application for nonclinical safety.

Question 10: Completeness of the Application

We propose to submit a 505(b)(1) New Drug Application containing the following:

- Module 1: to include all information required by regulation (21 CFR 314)
- Module 2:
  - 2.2 – Introduction
  - 2.3 - Quality Overall Summary
  - 2.4 – Nonclinical Overview - not applicable (only one nonclinical study was conducted)
  - 2.5 - Clinical Overview
  - 2.6 – Nonclinical Written and Tabulated Summaries - not applicable (only one nonclinical study was conducted)
  - 2.7 – Clinical Summaries provided, with 2.7.3 and 2.7.4 serving as the narratives for the integrated summaries as described in Question 6
- Module 3: to include all chemistry, manufacturing and controls information required by regulation (21 CFR 314.50) or by agreement with the Division
- Module 4: to contain the local tolerance study report, (b) (4)/1013/G/T077, as described in Question 4
- Module 5: to contain the five clinical study reports as described in Question 6

Does the Agency agree that our proposal constitutes a complete 505(b)(1) application for review?

FDA response:

No. We do not agree the proposed NDA constitutes a 505(b)(1) application. If you own or have a right of reference to all of the data/information that you are relying upon for approval, then your application would be a 505(b)(1) application. The nonclinical section would need to be supported by the required studies (that you conducted or through right of reference to the application containing the full study reports) to determine the nonclinical safety of your product.

If you intend to rely, in part, on information required for approval that comes from studies not conducted by you or for you or for which you have not obtained a right of reference (e.g., reliance on the FDA's finding of safety and/or effectiveness for a listed drug or published literature), then your marketing application will be a 505(b)(2) application. Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

Additionally, we do not agree that the Summary of Clinical Summary in section 2.7.4 will serve as the narrative portion of the Integrated Summary of Safety (ISS) under Module 5. Include under Module 5 an Integrated Summary of Safety (ISS) including Phase 2 Clinical Trial TXV13-01 and Phase 3 Clinical Trial TXV14-01.

From a technical standpoint (not content related), the placement of files in the eCTD structure, is acceptable. For archival purposes, submit a pdf file of any labeling document submitted in word and make sure the leaf title includes "word", so reviewers can quickly identify the word version of the document.

Discussion:

FDA indicated that the Sponsor's meeting package cites NDA approvals for estradiol products that were considered 505(b)(1) NDAs. However, the Agency's thinking has changed about sex steroids/hormone products since the time of those NDA approvals (1999-2007) and the Agency now considers that NDAs for these products would be 505(b)(2) NDAs. For example, testosterone gel products approved within the last six years were considered 505(b)(2) applications because they relied on published literature or FDA's finding of safety and/or effectiveness for a listed drug to meet the nonclinical requirements.

FDA holds that your application would be a 505(b)(2) application because you do not own or have right of reference to the information needed to meet all the nonclinical and labeling requirements for an NDA. You should refer to the discussion section of Question 4 for details regarding submission of published literature or reliance on a listed drug to support your 505(b)(2) application.

TherapeuticsMD stated that they intend to submit a 505(b)(2) application.

3.0 ADDITIONAL INFORMATION

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.

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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP 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 PSP 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 PSP, including a PSP 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.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential

and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the draft guidance for industry, *Guidance for Industry Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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, in part, 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, in part, 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., trade name(s)).

If you intend to rely, in part, 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 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 relies on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature. 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 in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA's previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing 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 efficacy 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 X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

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). 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. 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. 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. 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

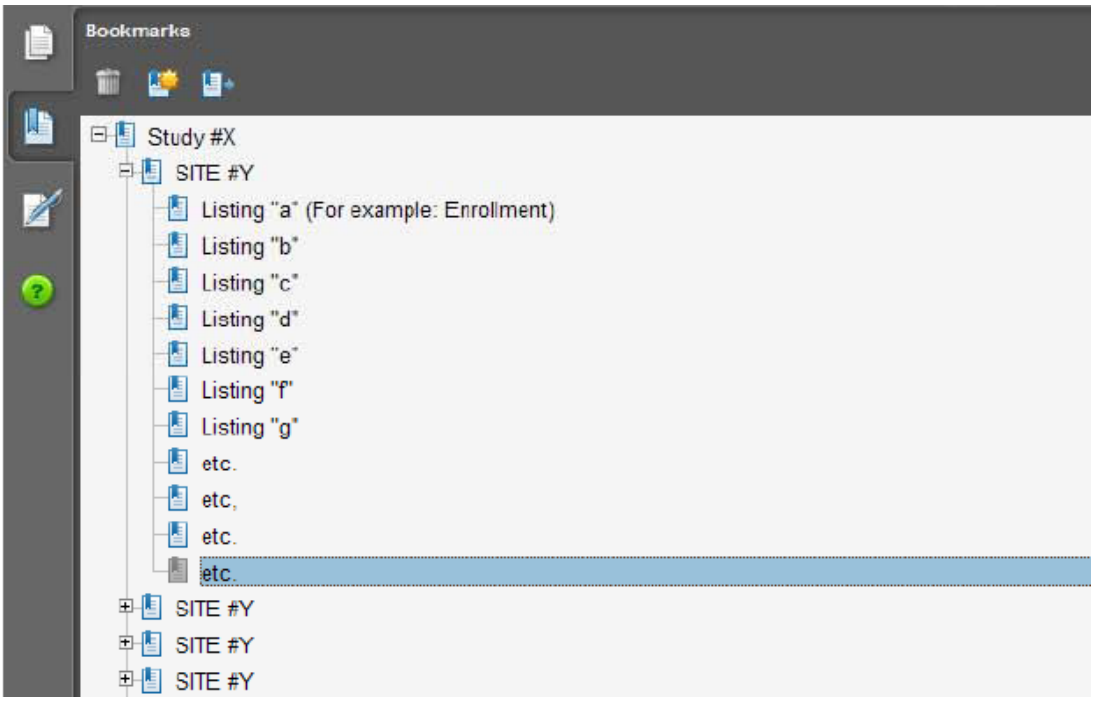
maintained. As above, this is the actual physical site where documents would be available for inspection.

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting Minutes	FDA	January 14, 2016

6.0 ATTACHMENTS AND HANDOUTS

No attachments or handouts for the meeting minutes.

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

/s/

SHELLEY R SLAUGHTER
01/13/2016

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 118439

MEETING MINUTES

TherapeuticsMD Inc.
Attention: Valerie Ahmuty
Sr. Director, Regulator Affairs
6800 Broken Sound Pkwy NW, 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 TX-004HR, Estradiol vaginal (b) (4)

We also refer to the meeting between representatives of your firm and the FDA on July 24, 2015. The purpose of the meeting was to discuss the Agency's responses to your CMC questions.

A copy of the official minutes of the meeting 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) 402-2690.

Sincerely,

Thao M. Vu, R.Ph.
Regulatory Business Process Manager
Office of Program and Regulatory Operations
Office of Pharmaceutical Quality
Center for Drug Evaluation and Research

Enclosure:
Meeting Minute

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	EOP2 CMC
Meeting Date and Time:	July 24, 2015, 11:00-12:00 PM, EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 118439
Product Name:	TX-004HR (estradiol (b) (4) vaginal capsules)
Indication:	Treatment of moderate to severe dyspareunia, a symptom of vulva and vaginal atrophy, due to menopause.
Sponsor/Applicant Name:	TherapeuticsMD Inc.
Meeting Chair:	Mark R. Seggel, Ph.D.
Meeting Recorder:	Thao M. Vu, R.Ph.

FDA ATTENDEES:

Mark Seggel Ph.D.	CMC Lead (Acting)
Celia Cruz, Ph.D.	Branch Chief, Office of Process and Facilities
Vidula Kolhatkar, Ph.D.	Biopharmaceutics Reviewer
Kelly Kitchen, Ph.D.	Biopharmaceutics Quality Assessment Lead
Hong Cai, Ph.D.	CMC Reviewer
Thao M. Vu, R.Ph.	Regulatory Business Process Manager
Rebecca McKnight	Regulatory Business Process Manager

SPONSOR ATTENDEES:

Christine Miller, Pharm.D.	Vice President, Regulatory Affairs, TherapeuticsMD
Valerie Ahmuty	Sr. Director, Regulatory Affairs, TherapeuticsMD
Bharat Warrier	Director, Technical Services, TherapeuticsMD
George Toth	Director, Quality Assurance, TherapeuticsMD
Sebastian Mirkin, MD	Chief Medical Officer, TherapeuticsMD
(b) (4)	
John Milligan	President, TherapeuticsMD

1.0 BACKGROUND

TX-004HR (estradiol (b) (4) vaginal capsule) is being developed for the treatment of moderate to severe dyspareunia, a symptom of vulvar and vaginal atrophy, due to menopause. TherapeuticsMD submitted a Type B meeting request to the Agency on May 14, 2015, to discuss the Agency's response to their CMC questions.

2.0 DISCUSSION

Question 1 - Drug Substance Specifications

TherapeuticsMD has procured and utilized the drug substance, (b) (4) estradiol USP (as estradiol (b) (4) from (b) (4) during development, including the manufacture of 3 registration batches of each product strength, and intends to use this supplier for commercial product. Authorization to reference (b) (4) DMF (b) (4) will be included in the forthcoming NDA. Regulatory specifications proposed are in accordance with the USP and the DMF. The regulatory specifications are presented in Table 17.

Does the Division agree with the approach presented for the proposed specifications for the drug substance or have additional comments and advice?

FDA Response to Question 1:

The approach appears reasonable. However, acceptability of the proposed drug substance specification is a review issue.

Discussion: The Sponsor accepted FDA's response; no further discussion occurred.

Question 2 - Drug Substance – Second Supplier Plan

As noted above, (b) (4) estradiol USP (as estradiol (b) (4) from (b) (4) was used during development and (b) (4) is proposed as the primary supplier of estradiol for commercial product. TherapeuticsMD plans to qualify a secondary estradiol supplier, and include the qualification information in the forthcoming NDA. The proposed plan is based on the CDER/OGD "Questions and Answers Guidance for Stability Testing of Drug Substances and Products" (May 2014). We propose to:

- Provide comparative physicochemical properties and impurities data for 3 unique batches of the alternative active pharmaceutical ingredient (API) to the primary API
- Produce one pilot-scale batch (clinical batch size) of the highest product strength, and provide comparative dissolution data
- Submit 6 months of accelerated and long-term stability data for the product batch manufactured with secondary source API

- Commit to place the first commercial batch of each product strength using the secondary API source on long-term stability in accordance with the stability protocol to be included in the NDA and to provide data in subsequent post-approval NDA annual reports

Does the Division agree with the proposed plan for including a second API supplier in the NDA?

FDA Response to Question 2:

The approach appears reasonable. Although, we don't have any objection to the proposed drug substance comparative information between material from the primary and secondary suppliers; we remind the Sponsor that the required information regarding the quality of the drug substance for a secondary drug substance supplier does not differ from that of the primary supplier. The information on the quality of the drug substance secondary supplier can be either part of the NDA submission or by reference to a pertinent DMF.

Discussion: The Sponsor accepted FDA's response; no further discussion occurred.

Question 3 - Specifications for the Drug Product

The proposed commercial drug product regulatory and stability specifications are presented in Table 20. TherapeuticsMD understands that acceptance of the proposed specifications and impurity limits will be a review issue.

Does the Division agree with the approach presented? Does the Division have additional comments or advice regarding the appropriateness of the proposed specifications?

FDA Response to Question 3:

In general, the approach for presented appears reasonable. However, please add a second identification test (see ICH Q6A).

Regarding your proposed dissolution specification, the following points should be considered:

a. The dissolution profile data from the pivotal clinical batches and primary (registration) stability batches should be used for the setting of the dissolution acceptance criterion of your product (i.e., specification-sampling time point and specification value).

b. The in vitro dissolution profile should encompass the timeframe over which at least

(b) (4) of the drug is dissolved or where the plateau of drug dissolved is reached, if incomplete dissolution is occurring.

c. For immediate release product the selection of the specification time point should be where Q= (b) (4) dissolution occurs.

The acceptability of the proposed dissolution specification for your product will be made during the NDA review process, based on the totality of the provided dissolution data.

Discussion: The Sponsor accepted FDA's response; no further discussion occurred.

***Question 4* - Dissolution Method and Specifications**

A dissolution method development report will be submitted in the NDA supporting the selection of the proposed method. A detailed description of the in vitro dissolution test method being proposed and a summary of the results to date of completed developmental parameters is provided in Section 4.4. TherapeuticsMD understands that acceptance of the dissolution procedure and proposed limits are review issues.

Does the Division agree with the overall approach for selecting the dissolution procedure and setting the regulatory dissolution specification?

FDA Response to Question 4:

Your overall approach appears reasonable. However, we recommend that you 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., (b) (4) change to the specification-ranges of these variables) to demonstrate the discriminating ability of your proposed dissolution method.

The final determination on the acceptability of the dissolution method is a review issue that can be determined during the IND or NDA stage. Also, see our response to Question 3 regarding the proposed dissolution specification.

Discussion: The Sponsor accepted FDA's response; no further discussion occurred.

***Question 5* - Stability Data**

A summary of the ongoing stability program for the primary and supporting stability batches (number of batches, length of study on stability at time of submission, packaging configurations, etc.) is provided in Section 4.5. At the time of NDA submission, TherapeuticsMD intends to provide 9 months of ICH long-term stability data and 6 months of ICH accelerated stability data (or 9 months of ICH intermediate stability data in lieu of accelerated data if necessary) for the 3 primary registration batches of each strength of product that were packaged in the proposed commercial unit-dose blister packaging. TherapeuticsMD proposes to update the NDA with 12 months of long-term stability data on the registration batches within 120 days of submission. (The registration batch sizes are 150,000 capsules and the proposed commercial batch sizes are

500,000 capsules).

In addition to stability data for the registration batches, all available long-term and accelerated stability data will be submitted for the clinical and development batches as supportive stability data; these batches were manufactured at the same site, using the same formulation, and using the same process as the primary stability lots. Note that all clinical and development batches were packaged in HDPE bottles. The phase 3 clinical batches (1 lot of each strength) will have up to 18 months of long-term data and other development batches packaged in bottles will have up to 24 months of long-term data at submission. TherapeuticsMD plans to propose 24-months expiry dating for the commercial unit-dose blister-packaged product.

Does the Division agree that it is acceptable to submit with 9 months of long-term stability data on the registration batches in the for-market blister configuration and update the NDA with12 months of long-term stability data on the registration batches within 120 days of submission, without impact on the PDUFA goal date?

FDA Response to Question 5:

No. The primary stability data for at least 12 months at the proposed storage condition and 6 months at accelerated condition for 3 primary batches should be provided at the time of NDA submission.

Discussion: The Sponsor accepted FDA's response; no further discussion occurred.

Question 6 - Commercial Packaging Site(s) and Stability Commitment

The registration batches were packaged by Catalent in the for-market blister configuration and placed on long-term stability. (b) (4)

Does the Agency agree with this proposal?

FDA Response to Question 6:

(b) (4)

(b) (4)

Discussion: The Sponsor accepted FDA's response; no further discussion occurred.

Question 7 - Container Closure Systems

The proposed commercial package is a blister package utilizing the same materials used to package the registration batches. Letters of authorization to refer to the DMFs will be provided in the NDA as well as specifications, test methods and results for the packaging materials. Based on an assessment of the 1999 FDA Guidance for Industry entitled "Container Closure Systems for Packaging Human Drugs and Biologics" (specifically sections relating to oral solid dosage forms), TherapeuticsMD intends to present data from USP <661> and <671> testing of the packaging materials.

Does the Division agree with this proposal to support use of the packaging materials?

FDA Response to Question 7:

Yes, the proposal to support use of the packaging materials using data from USP <661> and <671> testing appears adequate.

Discussion: The Sponsor accepted FDA's response; no further discussion occurred.

Question 8 - (b) (4)

(b) (4)

FDA Response to Question 8:

(b) (4)

(b) (4)

Discussion:

(b) (4)

***Question 9* -Freeze-Thaw and Photostability Studies**

TherapeuticsMD intends to conduct freeze-thaw and photostability studies based on ICH guidance. We propose that the studies be conducted on one registration batch of the highest strength. The proposed approach is described in Section 4.9.

Does the Division have any comments regarding the approach to the freeze-thaw and photostability studies?

FDA Response to Question 9:

The approach to the freeze-thaw and photostability studies appears adequate.

Discussion: The Sponsor accepted FDA's response; no further discussion occurred.

***Question 10* - Appearance of Capsules and Imprinting**

The clinical batches and the registration batches for all strengths (4, 10 (b) (4) mcg) were light pink, pear-shaped soft gelatin (b) (4) capsules of the same size, with a cloudy fill appearance, and printed with a "#" symbol in white ink. Commercial batches, which include the process validation batches, will be identical in appearance to the development and registration batches, with the exception that a 1- to 2-digit code will be printed on the capsules to differentiate the dosage strengths. The codes will be printed with the same white ink previously utilized (refer to Table 7). Illustrations are provided in Section 4.10. Stability data for the process validation batches will be submitted in NDA annual reports in accordance with the stability protocol to be included in the NDA.

Does the Division have any comments on the proposed commercial product appearance or the stability plan?

FDA Response to Question 10:

The proposal to add a 1- to 2-digit code to the commercial capsules is acceptable. See, however, the response to Question 6 regarding the [redacted (b) (4)].

Discussion:

The sponsor questioned the reference to Question 6. [redacted (b) (4)] s. The commercial products would be imprinted with the actual capsule strength. See Attachment 2, Tables 1 and 2. FDA acknowledged the acceptability of this approach.

Additional Comments:

1. Please note that, in accordance with the USP, the established name for the drug product is "estradiol vaginal insert."

Discussion: FDA referred to the Estradiol Vaginal Insert, USP monograph and to USP General Chapter <1121>, Nomenclature. The Sponsor expressed concern with the potential for medication error. The FDA agreed to discuss the issue internally and respond to the Sponsor in a post-meeting comment.

Post-Meeting Comment: Additional internal discussion is needed. The FDA will notify the Sponsor as soon as a decision is made.

2. All applications must be accompanied by either an Environmental Assessment (EA) or a claim of categorical exclusion. For more information, please access the link below: http://www.fda.gov/aboutfda/centersoffices/officeofmedicalproductsandtobacco/cder/ucm088969.htm

CDER's Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications (Issued 7/1998) provides detailed information on a variety of topics related to preparing and filing EAs. Please see the link below: http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070561.pdf

If this application substitutes directly for an approved product (see Attachments A and B of the GFI, above), the application may qualify for a claim of categorical exclusion under 25.31(a). If you plan to submit a claim for categorical exclusion under 25.31(b) or an EA, refer to Draft Guidance for Industry: Environmental Assessment, Environmental Assessment: Questions and Answers Regarding Drugs With Estrogenic, Androgenic, or Thyroid Activity.

Attachments: Attachments 1, 2, and Table 1 are from TherapeuticsMD.

ATTACHMENT 1

TherapeuticsMD® requested clarification regarding the FDA 17 July 2015 Preliminary Comments for the End-of-Phase 2 Chemistry, Manufacturing and Controls Meeting via email to FDA on 22 July 2015:

Clarification Question A

With respect to the Agency's response to Question 6, TherapeuticsMD understands that (b) (4)

Does the Division agree that data from batches manufactured at the (b) (4) *?*

Clarification Question B

The Agency's response to Question 10 regarding the capsule printing indicated that the codes proposed were acceptable, and then directed us to the Agency's response to Question 6 regarding stability data to support the commercial packaging site. We are unsure of the meaning of this reference to the response to Question 6. TherapeuticsMD believes that the printing on registration batches represents the ink and codes that will be commercially utilized.

Does the Division agree that stability data from the registration batches support printing of codes for commercial batches?

Clarification Question C

Under *Additional Comments*, the Agency noted that, in accordance with the USP, the established name for the drug product is considered "estradiol vaginal insert."

Our product is a (b) (4) with (b) (4) estradiol, and does not fit the FDA's insert dosage form description/definition (i.e., a specially formulated and shaped ***non-encapsulated solid preparation*** intended to be placed into a non-rectal orifice of the body, where drug is released, generally for localized effects[1]).

There are many vaginally inserted estradiol products, but to the best of our knowledge, no vaginally inserted estradiol product is labeled with an established name of "estradiol vaginal insert." Refer to Table 1 below. Please note that use of the term "insert" is commonly applied to those products with a device component, such as the vaginal rings and sachets which is readily illustrated by the descriptions given on Drugs@FDA and the DailyMed. The only example of a hormone product with "insert" in the established name we found is Cervadil® (not a product containing estradiol). Labeling our (b) (4) capsule product "estradiol vaginal

insert" may be confusing to physicians, pharmacists, and consumers, respectively, who prescribe, dispense, or use other vaginally inserted estradiol products.

[1] FDA Standards Manual (monographs) > Dosage Form (Version Number 008) http://www fda.gov/drugs/developmentapprovalprocess/formssubmissionrequirements/electronicsubmissions/datastandardsmanualmonographs/ucm071666 htm (accessed 21 July 2015)

Table 1: Select Examples of Vaginally Inserted Hormone Products

Brand Name	Established Name in Label	DailyMed Title	Drugs@FDA
Vagifem®	(estradiol vaginal tablets)	Vagifem (estradiol) tablet, film coated	Tablet, vaginal
Estring®	(estradiol vaginal ring)	Estring (estradiol) ring	Insert, extended release, vaginal
Femring®	(estradiol acetate vaginal ring)	Femring (estradiol acetate) ring	Insert, extended release, vaginal
Nuvaring®	(etonogestrel/ethinyl estradiol vaginal ring)	Nuvaring (etonorgestrel and ethinyl estradiol) insert, extended release	Ring, vaginal
Cervadil®	(dinoprostone vaginal insert)[a]	Cervidil – dinoprostone insert, extended release	Insert, extended release, vaginal

[a] Cervadil is described as a thin, flat polymeric slab, rectangular in shape, with rounded corners contained within the pouch of an off-white knitted polyester retrieval system

In summation, our [redacted] (b) (4) product does not meet the FDA definition of an insert, is a different dosage form than other currently marketed vaginally inserted products, has no pharmaceutical equivalent, and a New Drug Application is to be submitted for approval of this new dosage form. TherapeuticsMD suggests that a separate USP monograph for estradiol vaginal [redacted] (b) (4) may be appropriate upon product approval.

Does the Agency agree that the established name for labeling purposes is estradiol vaginal [redacted] (b) (4) *?*

ATTACHMENT 2

FDA Query (July 23, 2015)

Please provide a tabular summary of the stability protocol(s) for the commercial/validation batches that will be submitted to support [redacted], the commercial product manufacturing site, and [redacted]. The table should include the number of batches of each strength to be placed on stability, batch sizes, the storage conditions, the proposed duration, and the time-points to be reported in the NDA.

TherapeuticsMD Response

Table 1 and Table 2 describing the registration batches and validation batches, respectively, and the associated stability data that will be generated to support [redacted], the commercial product manufacturing site, and [redacted], are provided below.

There are [redacted]

[redacted]

1 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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

/s/

THAO M VU
08/18/2015