CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208352Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 109300

MEETING MINUTES

Evofem, Inc.
Attention: Wendell Guthrie
Chief Operating Officer
8910 University Center Lane, #120
San Diego, CA 92122

Dear Mr. Guthrie:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for lactic acid, citric acid and potassium bitartrate gel.

We also refer to the meeting between representatives of your firm and the FDA on December 9, 2014. The purpose of the meeting was to discuss results of your phase 3 study and your planned NDA submission.

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

If you have any questions, call Charlene Williamson, Regulatory Project Manager at (301) 796-1025.

Sincerely,

{See appended electronic signature page}

Lisa Soule, M.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 09, 2014, 10:00 AM – 11:00 AM
Meeting Location:	10903 New Hampshire Avenue, Bldg. 22, Room 1421 Silver Spring, MD 20993
Application Number:	109300
Product Name:	Lactic acid, citric acid and potassium bitartrate gel
Indication:	A non-hormonal vaginal contraceptive gel indicated for use in preventing pregnancy
Sponsor Name:	Evofem, Inc.
Meeting Chair:	Lisa Soule, M.D.
Meeting Recorder:	Charlene Williamson

FDA ATTENDEES

Audrey Gassman, M.D., Deputy Director, Division of Bone, Reproductive and Urologic Products (DBRUP)
Lisa Soule, M.D., Clinical Team Leader, DBRUP
Daniel Davis, M.D., Medical Officer, DBRUP
Kimberly Hatfield, Ph.D., Toxicologist/Pharmacology Reviewer, DBRUP
Myong-Jin Kim, Pharm.D. Clinical Pharmacology Team Leader, Office of Clinical Pharmacology III (OCP III)
Li, Li, Ph.D., Clinical Pharmacology Reviewer, OCP III
Mahboob Sobhan, Ph.D., Statistical Team Leader, Office of Biometrics III (OB III)
Kate Dwyer, Statistician, OB III
Donna Christner, Ph.D., CMC Lead, Office of New Drug Quality Assessment (ONDQA)
Mark Seggel, Ph.D., Chemist, ONDQA
Roy Blay, Ph.D., OSI Reviewer, Office of Scientific Investigations (OSI)
Irene Z. Chan, Pharm.D., Associate Director, Division of Medication Error Prevention and Analysis (DMEPA)
Denise Baugh, Pharm.D., Safety Evaluator, DMEPA
Cathy A. Miller, M.P.H., B.S.N., Risk Management Analyst, Office of Surveillance and Epidemiology (OSE), Division of Risk Management (DRISK)
Maria Walsh, M.S.N., R.N., Associate Director, Regulatory Affairs, Office of Drug Evaluation III (ODE III)
Jennifer Mercier, Chief, Project Management Staff, DBRUP
Shawnetta Jackson, OSE Regulatory Project Manager
Charlene Williamson, Regulatory Project Manager, DBRUP

SPONSOR ATTENDEES

Evofem, Inc.

Wendell Guthrie, Chief Operating Officer
Mary Jarosz , R.Ph., RAC, FTOPRA, Senior Vice President, Regulatory and Quality
Kelly Culwell, M.D., M.P.H., Chief Medical Officer
(b) (4) CMC Consultant
John Fair, Chief Commercial Officer

(b) (4)

BACKGROUND

Lactic acid, citric acid and potassium bitartrate gel is a non-hormonal vaginal spermicide. The gel was approved under the name Acidform Gel under the 510(k) process by the Center for Devices and Radiological Health (CDRH) for use as a lubricant (#K033776) in June 2004 and has been licensed to Evofem, Inc. (formerly Instead Healthcare) for commercialization as a spermicidal gel. It has never been marketed in any country.

The Sponsor had a pre-IND meeting with the Division, and has conducted a comparative phase 3 trial to support an indication for contraception. The Division reviewed the protocol and amendments and provided guidance on the conduct of the trial. The purpose of this meeting is to discuss and confirm the adequacy of the CMC, non-clinical and clinical development programs to support an NDA submission.

SPONSOR'S QUESTIONS AND DIVISION'S RESPONSES

CHEMISTRY, MANUFACTURING, AND CONTROLS

Question 1

Does the FDA concur with these formulation component designations?

FDA Response to Question 1:

The designation of lactic acid, citric acid, and potassium bitartrate as active pharmaceutical ingredients (APIs) appears reasonable. However, the Division noticed that benzoic acid level (b) (4) is close to the level of active components. In order to support that benzoic acid is not an active ingredient, the Sponsor will need to demonstrate that benzoic acid does not significantly contribute to the acidity of drug product, e.g., by showing that the acid neutralization value remains unchanged when benzoic acid is removed from the formulation.

Additional Discussion at the Meeting:

The Sponsor will provide data on benzoic acid but believes it is unlikely that it would change the acid neutralization value because the benzoic acid is absorbed into the plastic applicator. FDA agreed that a bench test for the benzoic acid should be sufficient to address the concern.

Question 2:
Is this approach [submitting Drug Master File (DMF) references] to providing manufacturing information for the active ingredients acceptable to the Agency?

FDA Response to Question 2:
It is acceptable to provide CMC information on the drug substances by cross-reference to a DMF with an appropriate Letter of Authorization provided in the NDA submission. The following information should be provided in the NDA for ease of review: General information, physico-chemical properties, and Specifications. Also submit a Certificate of Analysis of the drug substances.

Note that the DMFs will be reviewed as Type II (drug substance) DMFs, where the standard can be more rigorous compared to Type IV (excipient) DMFs in areas such as characterization of the substance and impurities or stability.

Question 3:
Does the Agency agree that this approach to setting the acceptance criteria for acid neutralization is acceptable?

FDA Response to Question 3:
No; the Division recommends that the specification for the acid neutralization value have both an upper and lower limit.

Question 4:
Does the Agency find this approach to setting and justifying the benzoic acid level acceptable?

FDA Response to Question 4:
The Division recommends that the specification be set with a range that is supported by both the stability data and the results of the antimicrobial effectiveness testing. Information to justify the range should be submitted in the "Justification of Specification" section of the NDA and data provided for review. A final determination will be made at that time. Note that as outlined in response to Question 1, the Sponsor will need to provide data to demonstrate that benzoic acid does not contribute to the therapeutic activity of the drug product.

Question 5:
Considering the nature of these active ingredients, (widely used, safe, small molecules) and their potential degradates, does the Agency agree with the analytical approach?

FDA Response to Question 5:
The approach appears reasonable. A decision on the final specifications will be made at the time of NDA review. Properly designed supporting stability studies (photostability, forced degradation) are recommended for characterization of potential impurities and are helpful in establishing that analytical procedures are stability-indicating. Information will need to be provided that the potential degradation products have been appropriately qualified from a Pharmacology/Toxicology perspective.
Clarify whether the placebo control proposed for use as comparator for analysis of impurities is an aged placebo and specify the storage conditions.

Question 6:
Does the Agency find the proposed tests and acceptance criteria acceptable for the commercial product?

FDA Response to Question 6:
Overall, the proposed tests appear reasonable for this stage of development. In addition to the proposed tests, include a test for delivered dose for the prefilled applicator. Final agreement on the proposed acceptance criteria will be made at the time of NDA review.

The Division notes the proposal to include a test on stability (b) (4) and that the Sponsor plans to perform extractable and leachable testing on the container closure systems. Provide data on these tests in the NDA.

Question 7:
Will this plan for stability data submission be acceptable to the Agency?

FDA Response to Question 7:
No, the proposed strategy for stability studies is not acceptable. The NDA application should be complete upon submission and at least 12 months of stability data should be submitted on the primary stability batches to support the requested expiry. If additional stability data are required, it will be requested during the review.

While accelerated stability studies are used in lieu of real-time data for device products, for drug products, accelerated stability data are used to support excursion labeling and, depending on the quality of the data, may allow support for expiration dating extension. Note that stability timing starts when drug product is placed under controlled conditions, so six months at long-term cannot be considered equivalent to 14 months based on the fact that the lots were packaged several months after manufacture.

Additional Discussion at the Meeting:
The Sponsor clarified that after the product was manufactured; it was immediately packaged and held at room temperature while the stability testing method was finalized. Therefore, the six-month stability data actually represents product that is 12-14 months old. FDA will take this into consideration and will provide a post-meeting comment as to whether this could be accepted as 12-month stability data.

The Sponsor has also tested three new registration batches, for which it has three-month and accelerated stability data.

Post-meeting Comment:
FDA acknowledges the clarification that the primary stability batches were packaged into both the applicator (b) (4) within a month of manufacturing, and that these samples were held at controlled room temperature for 6-7 months prior to initiation of formal stability studies. Therefore, the Agency agrees that the six month timepoint for the formal stability studies corresponds to drug product that is 12 months old, and these data would be acceptable for filing. Include the explanation in the NDA, at a minimum in the narrative in the stability section and as footnotes in the stability tables.

Question 8:
Will this type of simulated use study sufficiently confirm the acceptability of stability of Amphora® gel (b) (4)

FDA Response to Question 8:
The simulated use data could help to support the in-use period for the gel. The design of the in-use studies should mimic the actual use pattern (b) (4)

Data should be provided in the NDA to support any proposed labeling. Standard ICH stability studies should be conducted to support expiry (b) (4)

Question 9:
Is the design of the registration stability study and the proposed tests and acceptance criteria sufficient for the Agency to determine the product shelf-life?

FDA Response to Question 9:
Stability studies should be performed under ICH conditions in the proposed container closure systems. With the addition of the recommended tests and the extra stability data, the NDA submission is expected to provide enough data to determine an expiration dating period.

NON-CLINICAL

Question 10:
Given the nonclinical data presented and the long history of use with Amphora® gel's key components in food compounds and FDA-approved products, and their natural occurrence in the human body, does the Agency agree that the nonclinical data package is sufficient for an NDA?

FDA Response to Question 10:
Yes. If the Sponsor is still planning to cross-reference nonclinical data in IND 64,623, it should provide an official letter in the NDA submission with permission to cross-reference data in IND 64,623. Also, if there are any literature references on which the Sponsor plans to rely, or additional nonclinical information not included in IND 64,623, that information should also be included with the NDA submission.

HUMAN SYSTEMIC ABSORPTION

Question 11:
Given the known systemic exposure information (presented in Appendix C), and the fact that all key components of Amphora® gel have received a type 1 conclusion from the Select Committee on GRAS Substances (SCOGS), Evofem did not measure the systemic exposure of Amphora® gel's key components in humans. Is this approach acceptable and adequate for an NDA?

FDA Response to Question 11:
Yes.

RESULTS FROM CLINICAL STUDIES

Question 12:

Does the Agency agree that the safety and efficacy information presented from clinical studies, including the Phase 3 clinical study, are sufficient to support an NDA?

FDA Response to Question 12:

It appears that the phase 3 trial will provide the number of evaluable cycles and the number of women completing one year of treatment requested by the Division. However, the Sponsor is asked to address the following in the NDA regarding the phase 3 study:

- Clarify how many women in each of the analysis populations were from the US.
- It appears that only about 74% of the enrolled population (1,259 out of 1,695 in the active gel arm) qualified for the primary efficacy analysis. Address why a relatively large segment of the population was not included in the analysis.
- Similarly, it appears that only about 47% of the enrolled population (793 out of 1,695 in the active gel arm) completed seven cycles of treatment. This high premature discontinuation rate is a potential review issue. Specify reasons for this high dropout rate, and provide a rationale as to why this does not adversely impact the generalizability of the data.
- Provide a clear flow-chart of subject disposition from screening, through enrollment, through study completion and inclusion in efficacy populations.
- As noted in the advice letter of August 2, 2011, the Division defines on-treatment pregnancy as any conceptions that occur within 7 days after the last use of the gel.
- Clarify why the efficacy analysis will consider day of ovulation (page 51). Estimated day of ovulation is not considered sufficiently accurate to use for dating of conception; rather, the date of conception (based on first trimester ultrasound, last menstrual period, physical examination, etc.) is used as the basis for determining whether or not a pregnancy occurred during use of the gel or within 7 days after the last use of gel.
- Provide data on ALL pregnancies occurring in the trial, regardless of whether they are determined to have been conceived on treatment or not. The Division will conduct its own evaluation of which pregnancies it considers to be on-treatment. Also describe how often pregnancy testing (urine or serum) was done, and under what conditions home pregnancy tests were recommended and how the results were recorded.
- Provide justification for the non-inferiority margin selected.
- It does not appear that a Statistical Analysis Plan for the phase 3 protocol was ever submitted. The Division typically relies upon the Pearl Index to evaluate effectiveness of contraceptive products. Address the large discrepancy between the Kaplan-Meier (KM) pregnancy rate and the Pearl Index, as this is a potentially serious review issue.
- Justify the Kaplan-Meier (KM) methodology that "compressed" cycles following a cycle in which back-up or emergency contraception was used, in order to provide contiguous cycles.
- Provide data on the timing of gel application relative to intercourse, and perform a sensitivity analysis stratified by time of application. Also provide data on use of gel application with repeated acts of intercourse.

In addition, clarify the following regarding other aspects of the development program:

- Whether the FDA-requested studies of safety in male partners and of concomitant use with condoms and diaphragms have been completed
- Address the effect of concomitant use of other vaginal products, such as antimicrobials, on the performance of the vaginal gel
- Whether line-listings and data sets for studies cited as literature references in the meeting package will be provided, or whether the NDA will include only published literature
- The proposed drug product is a fixed combination, as defined in 21 CFR 300.50. Discuss the contribution of each API to the safety and/or effectiveness of the drug product

Additional Discussion at the Meeting:

The Sponsor commented on bullet 9, regarding use of the Pearl Index as the primary efficacy parameter. The Sponsor believes that use of time-to-event statistics has merit and is consistent with advice from the 2007 Advisory Committee on oral contraceptive trials. The Sponsor will provide both Pearl Index and KM statistics.

The Sponsor asked for further clarification on the comment about the large discrepancy between the Pearl Index and KM statistics in the trial. The Division acknowledged that these two parameters do not measure the pregnancy rate in the same way, and typically vary slightly, with the KM usually providing a lower estimate of the pregnancy rate. However, in this trial, the difference was very large – at 6 months, the Pearl Index was 24.3 while the KM pregnancy rate was 10.5; at 12 months, the Pearl Index was 20.7 while the KM was 14.8. While this is not necessarily an approvability issue, the Division requests that the Sponsor explore the reasons for this large difference, and address this in the NDA submission.

The Sponsor discussed bullet 10 regarding "compressed" cycles and proposed that it would address use of back-up contraception in two ways:

- Use "compressed" cycles – i.e., include all cycles in which back-up was NOT used (e.g., Months 1-5 and 7-13)
- Include all cycles, regardless of whether or not back-up contraception was used

This plan was acceptable to the Division.

The Sponsor has done a small comparative study (n=24) of male partners (using its gel vs. KY lubricant). Women in the phase 3 trial were asked at each visit about partner discomfort and data will be provided in the NDA. The Sponsor reported that no male subjects discontinued the study because of local symptoms.

The Sponsor will provide data from a completed study on concomitant use with condoms and diaphragms.

Regarding concomitantly used vaginal products, the Division is interested in information on any impact on safety, efficacy, vaginal pH and vaginal flora. The Sponsor noted that it has data from the phase 3 trial on any incidental concomitant use, but has not done a formal study. In the NDA submission, the Sponsor should address the effect of these products on the gel and provide scientific justification for its conclusions with respect to whether there is an impact. The Sponsor will consider evaluating efficacy and adverse event reports specifically in those cycles in phase 3 in which other vaginal products were used concomitantly. The Sponsor could also consider addressing this issue based on studies cited in the medical literature or with *in vitro* testing of a few representative products.

The Sponsor will address the fixed combination issue in the pharmaceutical development section of the NDA.

PROPOSED LABELING PLAN

Question 13:
Does the Agency agree with the Rx designation for Amphora gel?

FDA Response to Question 13:
Other spermicides are marketed over-the-counter (OTC). The Sponsor should provide its rationale for seeking to market this product as prescription-only.

Additional Discussion at the Meeting:
The Sponsor stated that spermicides have low rates of utilization and it believes that women are not particularly knowledgeable about them. For this reason, it felt it would be best to introduce this "novel" product via interaction with a healthcare provider (learned intermediary), who could answer questions when prescribing, rather than through OTC access. The Division acknowledged this, and asked that this rationale be provided in the NDA submission. There is no regulatory basis to insist that the product be marketed OTC.

Based on this anticipated marketing plan, the Division agreed that the proposed labeling submitted in the NDA should be prescription labeling.

Question 14:
Is the proposed Rx label (see Appendix E) acceptable to the Agency?

FDA Response to Question 14:
It is premature to discuss labeling at this time.

GENERAL

Question 15:
Does the Agency agree with the proposed overall content and layout of the NDA, including the proposed 505(b)(2) submission route and the plan to reference the 510(k) for Acidform Gel (#K033776) and CONRAD IND (#64623)?

FDA Response to Question 15:
The Sponsor should specify exactly what portions of the NDA will be addressed using the 505(b)(2) approach. The plan to reference the 510(k) for Acidform Gel and IND 64,623 is appropriate provided that appropriate letters of authorization are submitted.

The NDA should be submitted in Electronic Common Technical Document (eCTD) format and the submission needs to comply with ICH and FDA specifications. Please refer to the *Guidance for Industry: Providing Regulatory Submissions in Electronic Format – Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications*, located at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072349.pdf

For eCTD Specifications and Guidance, please refer to the eCTD website, located at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm

The Sponsor should also refer to the Center-specific document for study datasets submission available at:
http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM312964.pdf

In addition to the datasets, include the programs used for efficacy analyses. These programs need to allow the Division to reproduce the results in the submission.

Question 16:
Should Evofem include a copy of the 510(k) for Acidform gel (#K033776) and CONRAD's IND (#64623) in the NDA submission?

FDA Response to Question 16:
Yes. Clarify whether the applicator(s) are identical to those approved by CDRH for Acidform gel. If the proposed applicator has changed, the Division will request comments from CDRH and provide them as a separate communication.

Additional Discussion at the Meeting:
The Sponsor stated that CDRH had considered the same packaging of the gel at the time it reviewed Acidform gel for use as a lubricant, but that it had not reviewed the current applicator. The Division will request comments from CDRH about the applicator and provide the Sponsor with these comments in a-subsequent advice letter.

Additional Human Factors Comments:

1. The Sponsor has not provided details regarding the proposed co-packaged applicators, and it will need to ensure that users can administer doses safely and correctly with the applicator(s) that it intends to provide. The Sponsor must perform a comprehensive use-related risk analysis to identify the use-related risks associated with its proposed product.
   The comprehensive risk analysis must include a comprehensive evaluation of all the steps involved in using the product (e.g., based on a task analysis or known problems), the errors that users might commit or the tasks they might fail to perform, the potential negative clinical consequences of use errors and task failures, the risk-mitigation strategies employed to reduce any use errors or task failures, and the method of validating the risk mitigation strategies. This information is needed to ensure that all potential risks involved in using the product have been considered and adequately mitigated and that the residual risks are acceptable (i.e., not easily reduced further and outweighed by the benefits of the product). Based on this comprehensive use-related risk analysis, the Sponsor will have a better idea of the extent to which simulated use testing is required. The risk analysis will also guide the Division in the design of a human factors validation study protocol for this product if it is warranted based on the risk analysis.

   If a validation study is needed, to ensure that the Sponsor's approach and methodology are acceptable, submit the use-related risk analysis and study protocol prior to study implementation for Agency review and comment. Note that FDA requests 90 days to review and provide comments for the human factors validation protocol under the IND.
   Guidance on human factors procedures for devices can be found in *Medical Device Use-Safety: Incorporating Human Factors Engineering into Risk Management*, available online at:
   http://www.fda.gov/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm094460.htm.

Note that FDA has also published three draft guidance documents that, while not yet finalized, might also be useful in understanding its current thinking and approach to human factors and product design:

a. *Applying Human Factors and Usability Engineering to Optimize Medical Device Design*, available at http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/UCM259760.pdf.

b. *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM349009.pdf

c. *Safety Considerations for Product Design to Minimize Medication Errors*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

2. Provide five samples of the applicator device for each configuration at the meeting on December 9, 2014.

3. FDA notes the use of the name "Amphora Gel," which appears to be a proprietary name. If the Sponsor wishes to have a proprietary name for its product, see information on developing proprietary names for drugs and proposing alternative proprietary names for consideration in the draft *Guidance for Industry, Best Practices in Developing Proprietary Names for Drugs*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM398997.pdf.

   Additionally, see the *Guidance for Industry, Contents of a Complete Submission for the Evaluation of Proprietary Names*, available at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf

Additional Discussion at the Meeting:

The Sponsor will conduct a risk analysis and does not expect that a simulated use study will be needed. The proposed applicator is very similar to that provided with other vaginal products. The results of the risk analysis and the Sponsor's conclusion about the need for a simulated use study will be submitted prior to the NDA submission. The Sponsor was also asked to identify the other products using this applicator.

The Sponsor clarified that it plans to (b) (4) FDA also requested that if any signals of difficulty in using the

product were observed in the trial, this information should be considered in the risk analysis and provided to the Agency.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (PSP) 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.

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

Additional Discussion at the Meeting:
The Sponsor plans to propose extrapolation of adult data to postmenarcheal women < 18 years. The Division agreed that this was reasonable, and added that the Sponsor should also address males and premenarcheal females, for whom it could request that PREA studies be waived because they are not at risk of pregnancy. The Sponsor was advised to submit its PSP as soon as possible.

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. As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- 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 42 important format items from labeling regulations and guidances.

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

DATA STANDARDS FOR STUDIES

CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for investigational new drugs and product registration. Such implementation should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers. The web page may be found at: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

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*

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 the 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.

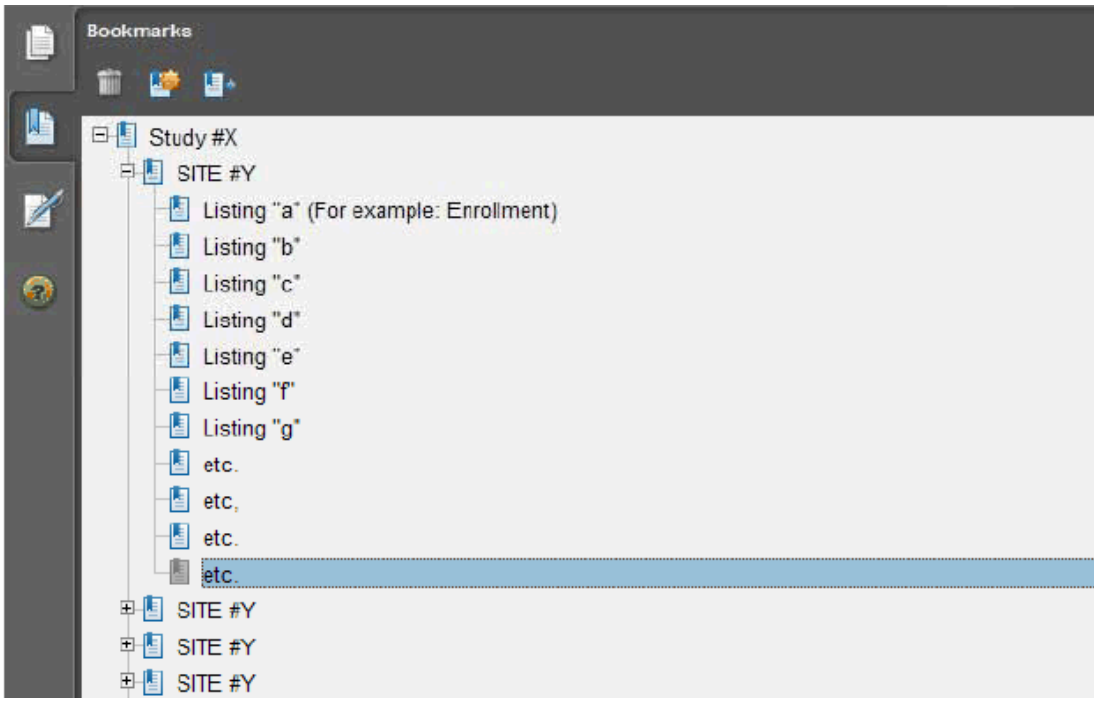
c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

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

ACTION ITEMS

Action Item/Description	Owner	Due Date
Meeting minutes due to the Sponsor	FDA	January 8, 2015

Reference ID: 4614956

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

/s/

LISA M SOULE
01/07/2015