

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

209353Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND126753

MEETING PRELIMINARY COMMENTS

Dow Pharmaceuticals Sciences, Inc.
Attention: Sean Humphrey
Senior Manager, Regulatory Affairs
1330 Redwood Way, Suite C
Petaluma, CA 94954

Dear Mr. Humphrey:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tretinoin lotion, 0.05%.

We also refer to your April 27, 2017, correspondence, received April 28, 2017, requesting a meeting to discuss the content and format of a New Drug Application (NDA) for tretinoin lotion, 0.05% for the treatment of acne vulgaris.

Our preliminary responses to your meeting questions are enclosed.

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

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

If you have any questions, call me at (240) 402-0095.

Sincerely,

{See appended electronic signature page}

Angela Brown, MPH
Regulatory Health Project Manager
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

PRELIMINARY MEETING COMMENTS

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 21, 2017 at 9:30-10:30 AM EDT
Meeting Location: Teleconference

Application Number: IND 126753
Product Name: tretinoin lotion, 0.05%
Proposed Indication: Treatment of acne vulgaris
Sponsor Name: Dow Pharmaceuticals, Inc.

Introduction:

This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for June 21, 2017, 9:30-10:30 AM EDT, teleconference between Dow Pharmaceuticals, Inc. and the Division of Dermatology and Dental Products. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

The purpose of this teleconference is to discuss the content and format of a New Drug Application (NDA) for tretinoin lotion, 0.05% for the treatment of acne vulgaris.

Regulatory Correspondence History

We have sent the following correspondence:

- 9/10/2015- Study May Proceed
- 10/21/2015- Initial Pediatric Study Plan- Incomplete
- 11/10/2015- Advice
- 3/31/2016- Initial Pediatric Study Plan- Written Response

- 4/7/2016- Advice
- 6/13/2016- Agreed Initial Pediatric Study Plan- Agreement
- 7/1/2016- Advice

2.0 DISCUSSION

2.1. Regulatory

Question 15:

The Sponsor proposes to submit the IDP-121 Lotion NDA in eCTD format with a complete XML backbone. The proposed content for Modules 1 through 5 is provided in Appendix 1.6.2.13.7.

Does the Agency concur with the content and format of the NDA as outlined in the briefing document?

FDA Response to Question 15:

Yes. The overall content and format of the NDA appears reasonable.

2.2. Chemistry, Manufacturing, Controls (CMC)

Question 1:

DPS is proposing specifications in accordance with current ICH Q6A guidance for the drug substance and drug product. Tretinoin drug substance is described in a USP and PhEur monograph. Details of the proposed specifications are included in Appendix 1.6.2.13.1. We acknowledge that the suitability of the acceptance criteria could be an NDA review issue and are subject to change based on final stability data to be presented in the NDA.

- a. *Based on the specifications provided in the briefing book, does the Agency have any recommendations for the drug substance specifications proposed for tretinoin?*
- b. *Based on the specifications provided in the briefing book, does the Agency have any recommendations for the drug product specifications proposed for use in the commercial drug product?*

FDA Response to Question 1:

- a. Your currently proposed specification of the drug substance appears reasonable; and as you have acknowledged, the final decision on the specification is an NDA review issue. We recommend you provide your justifications of the acceptance criteria in the NDA submission based upon ICH Q6A guidance.
- b. The tests listed in the drug product specification appear reasonable to support your NDA submission. The tests methods and acceptance criteria will be evaluated during NDA review.

Question 2:

Historically, the assay and uniformity in containers testing was performed using the same samples (tested from top, middle and bottom of tubes, as appropriate). The USP<3> uniformity in containers criteria were updated in the December 1, 2016 revision to the USP general chapter. As such, the revised acceptance criteria allow for a single preparation to be outside of the assay range within each tube, as long as the maximum difference is NMT 10.0%. For other topical marketed products, the physician's sample size has not been tested routinely per USP<3> uniformity in containers.

- a. *Does the Agency agree that we can continue to test for assay in this manner and report the average (of top, middle and bottom, as appropriate)?*
- b. *Given that the maximum daily dose is 4 g/day, does the Agency agree that the 3 g physician's sample size is considered a single unit dose and therefore exempt from testing the USP<3> uniformity in containers?*

FDA Response to Question 2:

- a. The assay of the drug product should be reported as the average of test results from 3 tubes, in which each tube can be tested once or 3 times as you proposed.
- b. Your proposal of not conducting the test of uniformity in containers on the 3g physician samples appears reasonable.

Question 3:

With regard to (b) (4), (b) (4)

Does the Agency have a preference for reporting number distribution or volume distribution (b) (4) (b) (4)?

FDA Response to Question 3:

(b) (4) we do not have a preference for the approach you choose to report the test results. However, the approach you choose should be sensitive enough to monitor the (b) (4) change of the drug product.

Question 4:

DPS has conducted ICH registration stability studies in accordance with the ICH Q1A guideline. The design for the ICH stability batches, a sample (3 g fill size) and trade size (45 g fill size), was previously proposed as per the End-of-Phase 2 Meeting held on 06 May 2015 (IND (b) (4), sequence 0002).

The process validation lots and the routine commercial batches will be tested at the long-term condition in the (b) (4)

The details of the stability studies and package types for the tube fill sizes are provided in Appendix 1.6.2.13.1.

- a. Does the Agency agree that the stability program described in the briefing package for the ICH (registration) stability batches adequately meets the filing requirements for the NDA?
- b. Does the Agency agree that the stability programs described in the briefing package for the process validation and routine commercial stability lots are acceptable?

FDA Response to Question 4:

- a. The stability program described in the briefing package for the registration stability batches appears reasonable to support your NDA filing.
- b. Test time points for months 3, 6, and 9 should be included in the stability protocol for annual stability testing.

Question 5:

In accordance with the USP<661> frequently asked questions, the (b) (4) packaging system is to be applied to a different pharmaceutical product (IDP-121 Lotion). As the dosage form and conditions of use are similar for the marketed and proposed product, no USP<661.1> or USP<661.2> testing should be required.

Does the Agency agree with our rationale to not perform full extractables/leachables testing as described in the briefing document?

FDA Response to Question 5:

We agree to your proposal of not conducting all the tests listed in USP<661.1> or USP<661.2>.

Question 6:

(b) (4)

Does the Agency agree that this approach is acceptable for testing this grade of octoxynol-9?

FDA Response to Question 6:

Your quality control approach for the excipient, octoxynol-9, appears reasonable.

Question 16:

Reference is made to the draft guidance titled, “Providing Regulatory Submissions in Electronic Format – Submission of Manufacturing Establishment Information (MEI)” that was issued in December 2016. In this draft guidance, it is proposed that the MEI and contact information be provided within the NDA submission in Section 3.2.R, Regional Information, with the leaf title denoted as “Establishment Information-(date of submission YYYY-MMM-DD)].xml.” Thus, Section 3.2.S.2.1, Manufacturers, and Section 3.2.P.3.1, Manufacturers, and the corresponding Module 2.3 sections would only cross-reference or link to Section 3.2.R. According to the guidance, the Agency may refuse to file or receive an electronic submission unless the MEI conforms to the guidance (with consolidated MEI in proper format).

Does the Agency expect that we will comply with this draft guidance or will there be a grace period for implementation? What is the projected implementation date?

FDA Response to Question 16:

Companies must comply with this guidance within 24 months after a notice of availability of the final guidance is published in the *Federal Register*.

2.3. Nonclinical

Question 7:

Per the Agency advice letter dated 10 November 2015, the following nonclinical studies were conducted by the sponsor:

- a. In vitro phototoxicity (Study V01-121A-601)
- b. In vitro ocular irritancy (Study V01-121A-602)

DPS intends to reference the ATRALIN Gel, 0.05% NDA (022070) for nonclinical safety and does not plan to conduct any additional nonclinical studies to support the IDP-121 Lotion NDA, based on the 2008 FDA draft guidance, “Nonclinical Safety Evaluation of Reformulated Drug Products and Products Intended for Administration by an Alternate Route.”

Does the Agency agree that the existing ATRALIN Gel nonclinical data coupled with the 2 additional studies conducted by the sponsor are sufficient to support a 505(b)(1) NDA for IDP-121 Lotion?

FDA Response to Question 7:

Yes, the Agency agrees that the existing ATRALIN Gel nonclinical data coupled with the 2 additional studies conducted by the sponsor are sufficient to support a 505(b)(1) NDA for IDP-121 Lotion.

2.4. Clinical Pharmacology/Clinical/Biostatistics

Question 8:

The sponsor had proposed a clinical development plan that was agreed upon by the Agency at the EOP2 (meeting minutes dated 08 May 2015). This plan included 2 pivotal, vehicle-controlled

Phase 3 studies and a single Phase 1 PK study. Waivers for phototoxicity/photoallergy, irritation and sensitization potential, and long-term safety studies were agreed to at the meeting.

In addition, a waiver for a thorough QT study will be provided in the NDA based on historic data available on tretinoin and the low systemic exposure of tretinoin observed in the PK study conducted with IDP-121 Lotion under maximal use.

Based on the completion of the clinical program as detailed in the briefing package, does the Agency agree that the clinical program is adequate to support the approval of IDP-121 Lotion with an indication for the topical treatment of acne?

FDA Response to Question 8:

The clinical development program appears adequate to support the submission of a New Drug Application (NDA) for IDP-121 Lotion for the treatment of acne vulgaris. Submit your proposed waiver requests for phototoxicity/ photoallergy, irritation / sensitization potential, long-term safety assessments, and a thorough QT study with your rationale and discussion in your NDA submission.

Question 9:

Approximately 787 human subjects will have been exposed to at least 1 dose of IDP-121 Lotion under IND 126753 and will be included in the NDA submission as part of the safety database.

Does the Agency agree that the total subject exposure is adequate to support approval of the NDA?

FDA Response to Question 9:

The size of your proposed safety database appears reasonable to support the submission of a New Drug Application (NDA) for IDP-121 Lotion for the treatment of acne vulgaris. Ultimately, the adequacy of your safety database will be a review issue.

Question 10:

The Sponsor plans to provide Bioresearch Monitoring (BIMO) Clinical Data in the electronic common technical document (eCTD) format. For each pivotal Phase 3 study, the following will be provided in Module 5, Section 5.3.5.4:

- BIMO STF, containing general study-related information and specific clinical investigator information (if specific items are provided elsewhere in the submission, a location or link will be provided), will include the following:
 - General study-related information and specific clinical investigator information in tabular format (submitted in portable document format [PDF])
 - Data listing by site in tabular format (submitted in PDF)
 - Data listings by study in tabular format (submitted in PDF)
- Site level data sets across studies (clinsite.xpt)

For each pivotal Phase 3 study, the following will be provided in Module 5, Section 5.3.5.1 (data listing datasets):

- Subject level data listings by site (PDF)

- Define file (PDF)

Does the FDA agree to the eCTD location of the BIMO information that will be included in the original NDA?

FDA Response to Question 10:

We agree with the eCTD location of the BIMO information. Please refer to the “Office of Scientific Investigations (OSI) Requests” at the end of this document for more information.

Question 11:

For the 2 pivotal Phase 3 studies (V01-121A-301 and V01-121A-302), the sponsor plans to submit case report forms (CRFs) in Appendix 16.3 by site and subject identifier. The following types of CRFs will be submitted in the NDA:

- Deaths during the study(s)
- Other SAEs during the study(s)
- AEs leading to discontinuation during the study(s)

Does the Agency agree with the CRFs the sponsor proposes to submit in the NDA for the pivotal Phase 3 studies and the long-term safety study?

FDA Response to Question 11:

In addition to the proposed CRFs, provide narratives for all deaths, serious adverse events (SAEs) regardless of causality, subjects who discontinued the study product due to adverse events (AEs), hypersensitivity/drug reactions, and pregnancies. These narratives may also be included in the Clinical Study Reports (CSRs) with links to the narratives provided in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety.

Question 12:

A complete list of clinical studies is presented within this briefing book (Table 8). Datasets for the following clinical studies will be included in the NDA in CDISC format:

- V01-121A-301 (Phase 3 safety and efficacy)
- V01-121A-302 (Phase 3 safety and efficacy)
- V01-121A-501 (Phase 1 PK maximal use)

Does the Agency agree with the provision of the files in this format?

FDA Response to Question 12:

Submit the datasets for Studies 301, 302 and 501 in SAS transport format (.xpt). Submit tabulation datasets in SDTM format and analysis datasets in ADaM format. Ensure that the analysis datasets include all variables needed for conducting all primary, secondary, and sensitivity analyses included in the study reports.

Include dataset documentation (define.xml) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each

variable in the dataset, algorithms for derived variables (including source variables used) and descriptions of the codes used in factor variables.

Because the protocols specified handling missing data using multiple imputation and model-based methods, clarify how you intend to submit the datasets. We recommend submitting the observed-case datasets along with complete statistical programs for conducting the multiple imputation and model based analyses, including all stages of the analyses. Also include any additional statistical programs for non-standard or model-based analyses.

Include the study protocol, all protocol amendments, the statistical analysis plan, and an annotated copy of the case report form as well as the other required elements for the clinical trials.

Question 13:

Statistical analysis of the safety data for the Phase 3 studies (V01-121A-301 and V01-121A-302) conducted with the to-be-marketed formulation of IDP-121 Lotion will be pooled and presented in the integrated summary of safety (ISS). The statistical analysis plan for the ISS is included in Appendix 1.6.2.13.8. The ISS text document will be placed into Module 2, Section 2.7.4, with the appendices and datasets provided in Module 5. As per Option D in “Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document,” each section of the ISS will refer the reader to the appropriate section where the remainder of the ISS is located within the NDA.

Does the Agency agree with the plan to provide the ISS text document in Module 2, Section 2.7.4 and the datasets in Module 5, Section 5.3.5.1?

FDA Response to Question 13:

The integrated summary of safety (ISS) is a detailed integrated analysis of all relevant data from clinical study reports and is required by the regulations to be located in Module 5. If you believe Section 2.7.4 (Summary of Clinical Safety) would be sufficiently detailed to serve as the summary portion of the ISS, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in Section 5.3.5.3. In this case, a description of the contents of each section should be included in both Module 2 and Module 5 {21 CFR 314.50(d)(5)(v) and 21 CFR 377.314.50(d)(5)(vi)(a)}.

For additional information about the location of ISS and ISE in the CTD, refer to guidance for industry Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document at the FDA website.

(<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM136174.pdf>)

Question 14:

Statistical analysis of the efficacy data for the Phase 3 studies (V01-121A-301 and V01-121A-302) conducted with the to-be-marketed formulation of IDP-121 Lotion will be pooled and presented in the integrated summary of efficacy (ISE). The statistical analysis plan for the ISE is included in Appendix 1.6.2.13.9. The ISE text document will be placed into Module 2, Section

2.7.3 with the appendices and datasets provided in Module 5. As per Option D in “Guidance for Industry: Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document,” each section of the ISE will refer the reader to the appropriate section where the remainder of the ISE is located within the NDA.

Does the Agency agree with the plan to provide the ISE text document in Module 2, Section 2.7.3 and the datasets in Module 5, Section 5.3.5.1?

FDA Response to Question 14:

If you believe Section 2.7.3 (Summary of Clinical Efficacy) would be sufficiently detailed to serve as the summary portion of the ISS, then you may place the summary portion of your integrated assessment in Module 2 and place the appendices of tables, figures, and datasets in Section 5.3.5.3. In this case, a description of the contents of each section should be included in both Module 2 and Module 5.

Additional comments:

1. At the time of NDA submission, submit the coding dictionary used for mapping investigator verbatim terms to preferred terms or identify where this will be located in the proposed submission. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).
2. Include the full text version of any referenced articles.
3. The pooled analyses (V01-121A-301 and V01-121A-302) should include the following:
 - Summary Table of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term reported by $\geq 1\%$ of subjects for individual trials and pooled data sets
 - Summary Table of Treatment-Emergent Treatment- Related Adverse Events (Adverse Reactions) by System Organ Class and Preferred Term reported by $\geq 1\%$ of subjects for individual trials and pooled data sets
 - Case report forms (CRFs) and narratives with corresponding electronic links as discussed above.
 - Line listings for all abnormal safety findings (e.g. adverse events, vital signs etc.)
 - Shift tables for all laboratory values. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.
 - Shift tables for all vital signs. Provide the normal values for all parameters used in your analyses.
 - If the product is approved in any other jurisdiction, provide a worldwide safety update in addition to the 120 day safety update.
 - A comparison of safety results from the individual trials and pooled data.

- Safety analyses in subgroups of subjects by sex, race, age group (>65 years versus < 65 years), and baseline severity
- Evaluation of uncommon, rare or unexpected events that may be possibly related to the study drug

4. Provide in the 120-day safety update, a summary of information which was not submitted in the NDA including the following:

- A detailed description of any significant changes or findings in the safety profile.
- A description of any information that suggests a substantial change in the incidence of common, but less serious adverse event.
- A summary of worldwide experience of safety of the proposed drug including an updated estimate of use for the drug marketed in other countries.

5. Clarify if 4-oxo-isotretinoin metabolite has any pharmacological activity.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our May 15, 2017, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to “the Program” under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA’s meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on PDUFA V and the Program is available at
<http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm272170.htm>.

PREA REQUIREMENTS

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

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

- FDA’s established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site

- 552 c. Number of subjects treated who prematurely discontinued for each site by site
553
554 3. Please include the following information in a tabular format in the NDA for each
555 of the completed pivotal clinical trials:
556 a. Location at which sponsor trial documentation is maintained (e.g., , monitoring
557 plans and reports, training records, data management plans, drug accountability
558 records, IND safety reports, or other sponsor records as described ICH E6, Section 8).
559 This is the actual physical site(s) where documents are maintained and would be
560 available for inspection
561 b. Name, address and contact information of all Contract Research Organization
562 (CROs) used in the conduct of the clinical trials and brief statement of trial related
563 functions transferred to them. If this information has been submitted in eCTD format
564 previously (e.g., as an addendum to a Form FDA 1571, you may identify the
565 location(s) and/or provide link(s) to information previously provided.
566 c. The location at which trial documentation and records generated by the CROs
567 with respect to their roles and responsibilities in conduct of respective studies is
568 maintained. As above, this is the actual physical site where documents would be
569 available for inspection.
570
571 4. For each pivotal trial, provide a sample annotated Case Report Form (or identify
572 the location and/or provide a link if provided elsewhere in the submission).
573 5. For each pivotal trial provide original protocol and all amendments ((or identify
574 the location and/or provide a link if provided elsewhere in the submission).
575

576 **II. Request for Subject Level Data Listings by Site**

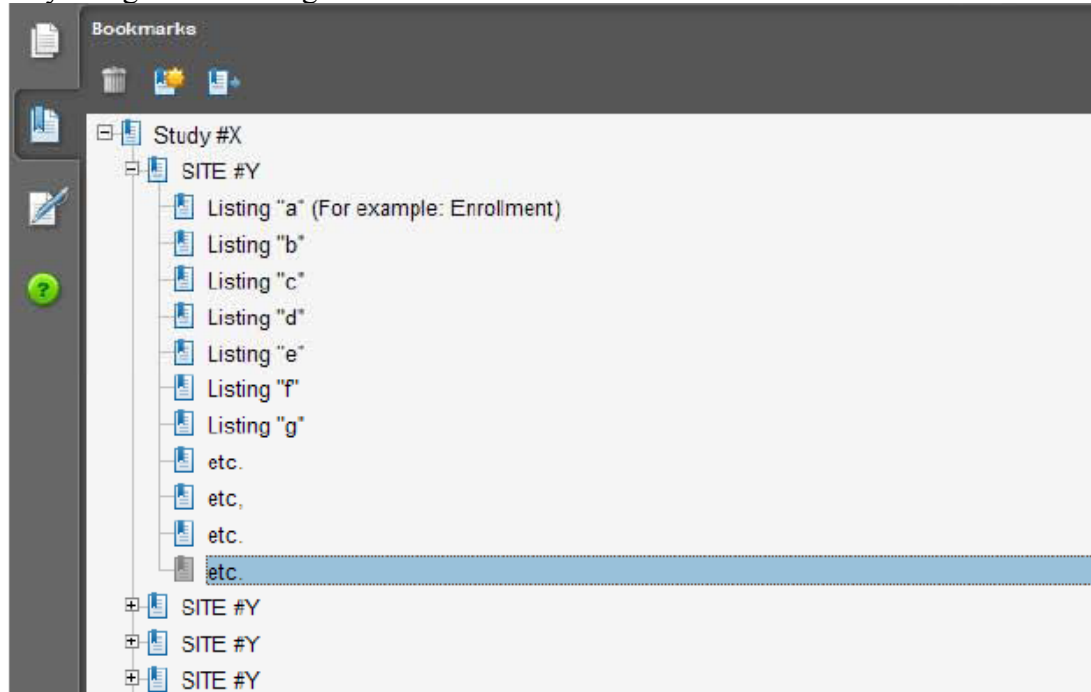
577

- 578 1. For each pivotal trial: Site-specific individual subject data listings (hereafter
579 referred to as “line listings”). For each site, provide line listings for:
580 a. Listing for each subject consented/enrolled; for subjects who were not
581 randomized to treatment and/or treated with study therapy, include reason not
582 randomized and/or treated
583 b. Subject listing for treatment assignment (randomization)
584 c. Listing of subjects that discontinued from study treatment and subjects that
585 discontinued from the study completely (i.e., withdrew consent) with date and reason
586 discontinued
587 d. Listing of per protocol subjects/ non-per protocol subjects and reason not per
588 protocol
589 e. By subject listing of eligibility determination (i.e., inclusion and exclusion
590 criteria)
591 f. By subject listing, of AEs, SAEs, deaths and dates
592 g. By subject listing of protocol violations and/or deviations reported in the NDA,
593 including a description of the deviation/violation
594 h. By subject listing of the primary and secondary endpoint efficacy parameters or
595 events. For derived or calculated endpoints, provide the raw data listings used to
596 generate the derived/calculated endpoint.
597 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.

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

/s/

ANGELA M BROWN
06/20/2017



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 063067

MEETING MINUTES

Dow Pharmaceuticals
c/o Valeant Pharmaceuticals North America, LLC
Attention: (b) (4)
Regulatory Consultant
400 Somerset Corporate Boulevard
Bridgewater, NJ 08807

Dear (b) (4):

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for tretinoin lotion, 0.05%.

We also refer to the teleconference between representatives of your firm and the FDA on May 6, 2015. The purpose of the meeting was to discuss the development plan for tretinoin lotion, 0.05%.

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 Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dental 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: Type B
Meeting Category: End of Phase 2 Meeting

Meeting Date and Time: May 6, 2015; 10:00am
Meeting Format: Teleconference

Application Number: IND 063067
Product Name: tretinoin lotion, 0.05%
Proposed Indication: Topical treatment of acne vulgaris in patients (b) (4) years of age and older
Sponsor Name: Dow Pharmaceutical Sciences, A Division of Valeant Pharmaceuticals North America

Meeting Chair: Kendall Marcus, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Julie Beitz, MD, Director, ODE III
Maria Walsh, RN, MS, ADRA, ODE III
Kendall Marcus, MD, Director, DDDP
David Kettl, MD, Acting Deputy Director, DDDP
Amy Woitach, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Mohamed Alosch, PhD, Biostatistics Team Leader, DB III
Kathleen Fritsch, PhD, Biostatistics Reviewer, DB III
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP III
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP

SPONSOR ATTENDEES

Johnson Varughese, Executive Director, Clinical Development
RK Pillai, Head, Dermatology Development
Sharon Tonetta, Vice President, Regulatory Affairs
William Jo, Associate Director, Nonclinical
Varsha Bhatt, Program Manager
Karen Krstulich, Executive Director, Regulatory Affairs
Anyia Loncaric, Director, Clinical Development
(b) (4) Founder and Chief Scientific Officer
(b) (4) Regulatory Consultant

TELECONFERENCE OBJECTIVES:

To discuss the development plan for tretinoin lotion, 0.05%.

Regulatory Correspondence History

We have had the following meetings:

- June 1, 2006 Pre-NDA
- December 2, 2004 Guidance

We have sent the following correspondences:

- June 10, 2011 Advice
- August 30, 2010 Advice
- May 11, 2010 Advice
- April 27, 2009 Advice
- April 1, 2009 Special Protocol- Agreement (Carcinogenicity)
- May 16, 2008 Advice
- August 14, 2007 Advice
- June 26, 2007 Advice
- April 14, 2007 Advice
- March 7, 2006 Information Request
- October 27, 2005 Advice
- June 9, 2005 Advice
- June 8, 2005 Advice
- March 29, 2005 Special Protocol- No Agreement
- April 24, 2003 Advice
- April 18, 2003 Advice
- January 17, 2003 Advice (2)
- December 12, 2002 Advice
- December 13, 2001 Advice
- November 8, 2001 Advice (2)
- October 24, 2001 Advice
- October 22, 2001 Advice
- October 16, 2001 Advice

General Comments:

You intend to submit a 505(b)(1) NDA and reference NDA 022070 Atralin Gel, 0.05%, to support the nonclinical safety and the clinical safety and effectiveness of tretinoin for the treatment of acne. We note that NDA 022070 Atralin Gel, 0.05%, was itself a 505(b)(2) NDA that relied on NDA 020475 Retin-A Micro Gel, owned by Valeant Pharmaceuticals. You state that DPS now owns Atralin Gel, 0.05%, and therefore, has right of reference (ROR) to the Retin-A Micro Gel, 0.1% toxicity study data. Please note that ROR to data referenced in an NDA from another application does not automatically transfer from the previous owner to the new owner of the NDA.

You also state that your proposed 505(b)(1) NDA will reference NDA 017522 Retin-A Cream, 0.05% to support the safety and effectiveness of tretinoin for the treatment of acne and NDA 019963 Renova Cream, 0.05% and NDA 021108 Renova Cream, 0.02% to support the long-term safety of tretinoin for the mitigation of fine facial wrinkles. We note that these NDAs are also owned by Valeant Pharmaceuticals.

Explain how your proposed marketing application will be a 505(b)(1) NDA if you are referencing NDAs 020475, 017522, 019963, and 021108 owned by Valeant Pharmaceuticals, or provide a ROR to each referenced NDA.

Meeting Discussion:

The sponsor stated that their parent company, Valeant Pharmaceuticals North America, is the owner of the relevant NDA applications. The Agency advised that, for clarity, obtaining a right of reference would be optimal as part of the NDA submission.

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Based on the proposed specifications listed within Appendix 1.6.2.13.1, does the Agency have any concerns or suggestions for the drug substance or drug product specifications proposed for use in Phase 3 and to support the NDA submission?

Response:

A (b) (4) particle size distribution test should be included in the drug substance specification as the drug substance, tretinoin, (b) (4). The rest of the tests proposed in the drug substance specification appear reasonable. The acceptability of the test methods and their acceptance criteria will be evaluated during NDA review.

The tests proposed in the drug product specification appear reasonable. The acceptability of the test methods and their acceptance criteria will be evaluated during NDA review.

Pharmacology/Toxicology

Question 2a:

Does the Agency agree that no additional toxicity studies are required to support the planned clinical studies for IDP-121 Lotion?

Response:

We agree that no additional toxicity studies are required to support the planned clinical studies for IDP-121 Lotion.

Question 2b:

Does the Agency agree that the existing body of nonclinical data for Atralin Gel is sufficient to support a new 505(b)(1) NDA for IDP-121 Lotion?

Response:

If you are able to provide appropriate documentation to support the 505(b)(1) pathway (see General Comments above), then we agree that the existing body of nonclinical data for Atralin Gel is sufficient to support a new 505(b)(1) NDA for IDP-121 Lotion.

Clinical Pharmacology/Clinical/Biostatistics**Question 3a:**

Does the Agency agree that the single adequate and well-controlled study proposed herein is capable of producing substantial evidence to support approval of a 505(b)(1) NDA for the treatment of acne?

Response:

For eventual drug approval one of the following pathways could be followed:

1. Two independent, double-blind, vehicle controlled trials demonstrating superiority to vehicle.
2. One 3-arm (tretinoin lotion, lotion vehicle, and comparator tretinoin active) trial demonstrating superiority of tretinoin lotion to its vehicle and non-inferiority to the comparator. A fourth small comparator vehicle-like arm is recommended for blinding purposes.
3. One persuasive, robust, double-blind, vehicle controlled trial demonstrating superiority to vehicle. The trial should be highly statistically significant with no major flaws and consistent results across centers and subgroups (see response to question 3c).

Question 3b:

Does the Agency agree that the choice of statistical significance ($p \leq 0.05$) is sufficient for the proposed single adequate and well-controlled study?

Response:

If you intend to rely on a single trial, we recommend designing the trial for a smaller significance level than what is needed when two adequate and well-controlled trials are conducted.

Meeting Discussion:

The sponsor conveyed their plan to conduct 1 Phase 3 trial and inquired whether the trial could be powered using alpha 0.025 as information from other formulations can be supportive for the current proposed lotion formulation. The Agency noted that the study needed to be powered to establish the criteria required by a single study submission following the Agency guidance, *“Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products”*. Among these criteria, persuasive statistical findings and consistency of efficacy results across sub-groups, centers, among other classifications. It should be noted that establishing consistency across different subclassification when the treatment effect is small would be less likely compared to the case of when the treatment effect is large. Therefore, the study should be designed with much smaller significance level than the proposed 0.025 so that a judgment about consistency of findings among other criteria can be made based on the study finding.

Question 3c:

Does the Agency agree that the number of proposed subjects in the Phase 3 clinical study will allow for sufficient evidence of 12-week efficacy and safety?

Response:

The number of trial subjects will depend on the development pathway you select. If you intend to rely on a single trial, we recommend powering your trial using a smaller significance level than 0.05, which may impact the number of subjects needed. Also note that changes in formulation may impact efficacy estimates which you may need to take into account when determining the estimates used in your sample size calculations.

Question 3d:

Does the Agency agree with the design, endpoints, subject population, inclusion and exclusion criteria, and planned statistical analyses for the Phase 3 clinical study described within the protocol synopsis?

Response:

You propose to conduct a single, 12-week, vehicle-controlled, randomize Phase 3 trial which will enroll approximately 800 subjects aged 12 and 40 (inclusive), with moderate or severe acne vulgaris (a score of 3 or 4 [moderate or severe] on the EGSS scale), presenting with 20-40 inflammatory facial lesions (papules, pustules, and nodules), 20-100 non-inflammatory facial lesions (open and closed comedones), and < 2 facial nodules.

Your trial design and proposed co-primary endpoints (absolute change in inflammatory lesions, absolute change in non-inflammatory lesions, and clear or almost clear with at least 2 grades reduction on the EGSS) seem reasonable. You should include subjects as young as 9 years of age given that acne vulgaris occurs in a significant population of children 9 to 10 years of age.

You have defined three secondary endpoints (percent change in inflammatory lesions, percent change in non-inflammatory lesions, and at least 2 grades reduction in EGSS) at three timepoints (Weeks 12, 8, and 4). However, you have not specified any method for controlling multiplicity among the secondary endpoints. We recommend defining a limited set of clinically relevant secondary endpoints and adjusting the analyses for multiplicity.

To ensure that your analyses are adequately prespecified, include all necessary details regarding your missing data imputation procedure. For multiple imputation procedures this would include sufficient details regarding the imputation and analysis models, as well as the randomization seed.

We recommend you submit the full protocol for a Special Protocol Assessment for agreement.

Question 4:

Does the Agency agree that the protocol synopsis and design of the planned PK maximal use systemic exposure study is sufficient to support a 505(b)(1) NDA for acne?

Response:

We have the following comments:

- You should enroll subjects 9 years of age and older in the maximal use PK trial. Enrollment should be approximately evenly distributed among the ages to ensure there are adequate numbers of subjects at the lowest ages (i.e., 9 and 10 years).
- We recommend that you include additional pharmacokinetic samplings prior to Day 14 to help assess attainment of steady state.
- You should address the potential for drug interactions. For further information, refer to *Draft Guidance for Industry: Drug Interaction Studies – Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (February 2012)*.

Meeting Discussion:

The sponsor proposed to add additional trough sampling on day 7. The Agency stated that this approach was reasonable.

Question 5:

Does the Agency agree that sufficient data to characterize the safety of tretinoin are available from the 4 marketed topical tretinoin products, with long-term safety adequately established by RENOVA Cream, 0.02% and 0.05%, and that additional long-term safety exposures with IDP-121 Lotion are not needed for a 505(b)(1) NDA approval?

Response:

No additional long-term safety data is anticipated.

Question 6:

Does the Agency agree that a photoallergy/phototoxicity study with IDP-121 Lotion is not needed for NDA approval?

Response:

You propose to label IDP-121 (b) (4) regarding photoallergy/ phototoxicity. If your product is adequately labeled for photoallergy/phototoxicity, then it is reasonable to waive these provocative dermal studies.

Question 7:

Does the Agency agree that an irritation/sensitization study with IDP-121 Lotion is not needed for NDA approval?

Response:

You propose to label IDP-121 (b) (4) regarding irritation/sensitization. If your product is adequately labeled for irritation/sensitization, then it is reasonable to waive these provocative dermal studies. Your phase 3 trial(s) should include an assessment of dermal safety.

Question 8:

Does the Agency agree with the request for a partial waiver for pediatric subjects aged 0 to (b) (4)?

Response:

No, we do not.

(b) (4)

You may request a partial waiver for pediatric subjects aged 0 to 8 years 11 months. See PREA Requirements section below.

Question 9:

Does the Agency agree that the clinical studies conducted in the development of the IDP-121 Lotion may be conducted under IND 063067?

Response:

It would not be acceptable to conduct studies for IDP-121 under IND 63067. A new formulation would require submission of a new IND.

Administrative Comments

1. Comments shared today are based upon the contents of the briefing document, which is considered to be an informational aid to facilitate today's discussion. Review of information submitted to the IND might identify additional comments or information requests.
2. Please refer to the Guidance for Industry: Special Protocol Assessment and submit final protocol(s) to the IND for FDA review as a **REQUEST FOR SPECIAL PROTOCOL ASSESSMENT (SPA)**. Please clearly identify this submission as an SPA in bolded block letters at the top of your cover letter. Also, the cover letter should clearly state the type of protocol being submitted (i.e., clinical or carcinogenicity) and include a reference to this End-of-Phase 2 meeting. Ten desk copies (or alternatively, an electronic copy) of this SPA should be submitted directly to the project manager.
3. For applications submitted after February 2, 1999, the applicant is required either to certify to the absence of certain financial interests of clinical investigators or disclose those financial interests. For additional information, please refer to 21CFR 54 and 21CFR 314.50(k).
4. Pediatric studies conducted under the terms of section 505A of the Federal Food, Drug, and Cosmetic Act may result in additional marketing exclusivity for certain products. You should refer to the Guidance for Industry: Qualifying for Pediatric Exclusivity for details. If you wish to qualify for pediatric exclusivity you should submit a "Proposed Pediatric Study Request". FDA generally does not consider studies submitted to an NDA before issuance of a Written Request as responsive to the Written Request. Applicants should obtain a Written Request before submitting pediatric studies to an NDA.
5. In your clinical development program, you will need to address the clinical evaluation of the potential for QT/QTc interval prolongation (see ICH E14). Please plan to address this issue early in development.
6. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

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>.

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>

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting

mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see [CDER/CBER Position on Use of SI Units for Lab Tests](http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm) (<http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>).

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

/s/

KENDALL A MARCUS
05/08/2015