

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208552Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107983

MEETING MINUTES

Allergan, Inc.
Attention: Bonnie Safyurtlu
Director, Global Regulatory Affairs
2525 Dupont Drive; PO Box 19534
T1-2A
Irvine, CA 92623-9534

Dear Ms. Safyurtlu:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Rhofade™ (oxymetazoline HCl) Cream, 1%.

We also refer to the teleconference between representatives of your firm and the FDA on October 14, 2015. The purpose of the meeting was to discuss the content and format of your proposed NDA submission for Rhofade™ (oxymetazoline HCl) Cream, 1%.

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}

Jill A. Lindstrom, MD, FAAD
Deputy 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: Pre-NDA

Meeting Date and Time: October 14, 2015; 10:30am
Meeting Format: Teleconference

Application Number: IND 107983
Product Name: Rhofade™ (oxymetazoline HCl) Cream, 1%
Indication: For the reduction of erythema in patients with erythematous rosacea
Sponsor Name: Allergan, Inc.

Meeting Chair: Jill Lindstrom, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Jill Lindstrom, MD, Deputy Director, DDDP
Jane Liedtka, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP
Yichun Sun, PhD, Quality Assessment Lead, Branch V, DNDQA II
Kathy Fritsch, PhD, Biostatistics Reviewer, DB III
Chinmay Shukla, PhD, Clinical Pharmacology Reviewer, DCP III

SPONSOR ATTENDEES

Bhushan Hardas, MD, Vice President, Chief Medical Officer (Devices), Therapeutic Area Head, Dermatology and Medical Aesthetics
Sam Kerr, PhD, Vice President, Drug Development Operations, EU & Asia Pacific
Gurpreet Ahluwalia, PhD, Senior Director, Clinical Development, Dermatology
David Berk, MD, Director, Clinical Development, Dermatology
Pramod Sarpotdar, PhD, Senior Director, Pharmaceutical Sciences
Emily Weng, ScD, MBA, Senior Manager, Biostatistics
Pan-yu Lai, PhD, Senior Director, Biostatistics
Edward Chow, PhD, DABT, Research Investigator, Nonclinical and Translational Sciences
David Hovland, PhD, Vice President, Global Regulatory Affairs
Bonnie Safyurtlu, MS, RAC, Director, Global Regulatory Affairs
Vincent Nanevie, MS, MBA, RAC, Senior Manager, Global Regulatory Affairs CMC
Erin Collins, MS, RAC, Senior Specialist, Global Regulatory Affairs

Regulatory Correspondence History

We have had the following meetings:

- December 18, 2013 End of Phase 2
- July 27, 2011 End of Phase 2

We have sent the following correspondences:

- July 9, 2015 Proprietary Name Granted
- October 7, 2014 Advice
- July 18, 2014 Agreed iPSP
- May 27, 2014 Advice
- May 7, 2014 iPSP Written Response
- March 7, 2014 Advice
- March 5, 2014 Advice
- December 13, 2012 Advice
- December 3, 2012 Advice
- August 13, 2012 Advice
- May 31, 2012 Special Protocol Agreement (carcinogenicity)
- April 23, 2012 Advice
- August 18, 2011 Advice
- May 10, 2011 Advice
- April 28, 2011 Special Protocol- No Agreement (carcinogenicity)
- September 16, 2010 Advice
- July 22, 2010 Advice
- May 3, 2010 Advice

Regulatory

Question 1:

A draft electronic Common Technical Document (eCTD) Table of Contents (TOC) for the proposed NDA, including details on the planned submission of specific study reports for Module 4 and Module 5, are provided in Appendix 1 of the Meeting package.

Does the Agency agree that the proposed organization of the submission is acceptable?

If the Agency does not agree, please provide recommendations.

Response:

From a technical standpoint (not content related) yes, the proposed organization of the submission is acceptable. Please see cross referencing information, below.

Cross referencing information – eCTD section m1.4.4

Sponsors options of cross referencing information submitted to another application, would be, to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.

1. To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (non- eCTD or paper) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.,) of the referenced document.
2. To use the second option (cross application links), both applications would need to be in eCTD format. The applications need to include the appropriate prefix in the href links (e.g. (e.g. xlink:href=" ../../ind000000/0009/m2/24-nonclin-over/nonclinical-overview.pdf"). In the leaf titles of the documents, it is recommended that the leaf title indicate the word "cross reference to" and the application number (e.g. Cross Ref to dmf000000). The cross reference information in the leaf title allows the reviewer to know that the document resides in another application.

Prior to using cross application linking in an application, it is recommended that sponsor submits an "eCTD cross application links" sample, to ensure successful use of cross application links.

To submit an eCTD cross application links sample, sponsor would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>.

Question 2a:

Allergan plans to generate a pooled analysis for safety (an ISS). Summary tables and data listings of the pooled data, along with statistical analysis plan, will be provided in Module 5 Section 5.3.5.3. The primary text description of safety data will be included in the Summary of Clinical Safety in Module 2, Section 2.7.4.

Does the Agency agree?

Response:

This is acceptable.

Question 2b:

Allergan does not plan to generate a pooled analysis for efficacy. Data will be presented within the Summary of Clinical Efficacy in Module 2, Section 2.7.3. An ISE statistical analysis plan will be provided in Module 5, Section 5.3.5.3, to describe the plan for the description of data. Does the Agency agree?

Response:

This is acceptable.

Question 3:

For all studies in which at least one group was treated with Oxymetazoline HCl cream at a concentration of 1.0% or higher (Studies 199201-001, 199201-002, 199201-004, 199201-005, and 199201-006), Allergan plans to provide Case Report Forms (CRFs) for the following categories of patients: deaths, serious adverse events, severe adverse events, and discontinuations for any reason. Based on ICH *E3, Structure and Content of Clinical Study Reports (CSRs)*, Allergan proposes that the CRFs be organized and submitted by study in Module 5 Section 5.3.5.1. All CRFs will have their respective study's accompanying study tagging file.

Does the Agency agree?

Response:

This is acceptable.

Question 4:

For all studies in which at least one group was treated with Oxymetazoline HCl cream at a concentration of 1.0% or higher (Studies 199201-001, 199201-002, 199201-004, 199201-005, and 199201-006), Allergan intends to include patient narratives for deaths, serious adverse events, and discontinuation due to adverse events within the respective CSR submitted as part of Module 5 of the NDA and also in Module 5 Section 5.3.5.3, as a separate file separated by event type (death, serious adverse event, discontinuation due to adverse event) and study number.

Does the Agency agree?

Response:

Include narratives for subjects experiencing a severe adverse event as well as those proposed above.

Question 5:

At the time of the NDA submission, the pivotal phase 3 studies (199201-004 and 199201-005) and the long-term safety study (199201-006) will have been completed. No additional studies will be ongoing during the NDA review period. (b) (4)

Does the Agency agree?

Response:

No, please submit a 4-month safety update. If no new safety information is available at the time of this submission then that should be stated.

Chemistry, Manufacturing and Controls (CMC)

Question 10:

During the EOP2 meeting in December 2013, the Agency advised Allergan to include evaluation of pump functionality (number of actuations for priming, actuation force, amount dispensed per actuation, total deliverable amount and hold-up weight) in the drug product registration stability studies. Subsequent to the EOP2 meeting, during a Pre-NDA meeting for a [REDACTED] (b) (4)

[REDACTED], Allergan obtained agreement from the Agency to include three key parameters for pump functionality testing (i.e., number of actuations for priming, amount dispensed per actuation, and total deliverable amount). Allergan believes that these three parameters are sufficient for Oxymetazoline HCl Cream, 1.0% as well.

Does the Agency agree?

Response:

The parameters (i.e., number of actuations for priming, amount dispensed per actuation, and total deliverable amount) you propose for pump functionality testing appear reasonable.

Question 11:

Allergan has been diligently working to develop a commercial container closure system(s), which meets the Agency's advice (see Section 10.4.4 for summary). At this time, we have 2 container closure systems (both with child-resistant closures) under development; a laminate tube and an airless pump system. Registration stability studies with both container closure systems are currently ongoing. [REDACTED] (b) (4)

We propose the following options:

Option 1 (Allergan's preferred option): Provide directions for patient use to prime the pump and discard the first 2-3 discharges prior to use.

Justification:

1. Similar instructions are provided for use of the Zyclara pump, a currently marketed product.
2. All content uniformity data generated from the bottle portion of the pump is consistent and meets USP <3> requirements.
3. Phase 2 dose-ranging clinical studies have demonstrated that there were no significant differences between the 1% and 1.5% Oxymetazoline HCl Cream for safety or dermal tolerability.

Option 2: If Option 1 is unacceptable, then Allergan proposes to file the NDA with only product filled in CRC laminate tubes and submit the pumps as a postapproval change.

Justification: The CRC tube meets the current child-resistant requirements set forth by the Agency and have been part of Allergan's phase 2 clinical trials. Prescription dermatological products with similar CRC requirements have been approved and currently marketed (Mirvaso, Lidoderm, etc.)

Please comment on the Agency's preferred option.

Response:

Your proposal described in option 1 appears reasonable.

Meeting Discussion:

The Agency noted that the sponsor's proposal of submitting the child resistant closure (CRC) laminate tube as a back-up is reasonable; however, the to-be-marketed packaging configuration should be identified in the NDA submission.

Question 12:

[Redacted] (b) (4)

Response:

No. You can only submit additional stability data within 30 days after the NDA submission without Agency's request.

Question 13:

Registration stability and pivotal phase 3 clinical study supplies were manufactured at pilot scale (b) (4) at DPT, San Antonio, TX. In addition to DPT as a manufacturing site for the commercial product, Allergan plans to manufacture commercial supplies (b) (4) (b) (4). The equipment to be used at (b) (4) is comparable to that of DPT.

[Redacted] (b) (4)

(b) (4)

Additional CMC Request:

Provide drug product samples for dosage form evaluation with your NDA submission.

Meeting Discussion:

The sponsor confirmed that they plan to submit 3-month stability data from 3 batches tested at 30°C/65% humidity. The Agency reminded the sponsor that 12-month long-term stability data of the 3 batches should also be submitted in the annual report after NDA approval. Additionally, the Agency reminded the sponsor that [REDACTED] ^{(b) (4)}

Pharmacology/Toxicology

Question 9:

The proposed organization of Module 4 of the NDA for Oxymetazoline HCl Cream, 1.0% is presented in the TOC provided in Appendix 1 of the Meeting Package. Allergan has submitted all nonclinical reports that the Agency has previously indicated at the End-of-Phase 2 meeting to be required for registration. Dermal carcinogenicity studies were not conducted since the Agency has granted a waiver for these after reviewing the waiver request and the report for a 6-month transgenic mouse (Tb.rasH2) study.

Does the Agency agree with the proposed organization of Module 4?

Does the Agency consider the submitted reports as adequate to support the registration of Oxymetazoline HCl Cream, 1.0%.

Response:

Yes, we agree with the proposed organization of Module 4 and that the submitted reports will support the NDA submission. The adequacy of the submitted reports will be determined during the NDA review.

Clinical/Biostatistics

Question 6a:

No pooling is planned for efficacy data.

Data from the following studies will be presented for efficacy and analysis:

- Phase 2b: 199201-002 (dose response) – data for the 1.0% QD and vehicle QD groups only
- Phase 3: 199201-004 (pivotal study 1)
- Phase 3: 199201-005 (pivotal study 2)
- Long-Term Safety: 199201-006 (open label)

Side-by-side tabular displays of efficacy data are planned to be presented in the Summary of Clinical Efficacy (Module 2 Section 2.7.3) based on the pivotal phase 3 studies 199201-004 and 199201-005. Supportive efficacy data from the Oxymetazoline HCl Cream, 1.0% QD and vehicle QD groups of phase 2 Study 199201-002 will be presented and discussed where relevant. Efficacy data from the open-label study (199201-006), in which all patients were treated with Oxymetazoline HCl Cream, 1.0% QD, will be included in the Summary of Clinical Efficacy for the discussion of persistence of efficacy and tolerance effects with long-term (52 weeks) treatment. A draft ISE statistical analysis plan, to describe the proposed presentation of efficacy data within the Summary of Clinical Efficacy, is provided in Appendix 2 of the Meeting Package.

Does the Agency agree with the strategy for the presentation of efficacy data?

Does the Agency have any additional recommendations for the presentation of efficacy data?

Response:

This is acceptable. For additional information regarding the recommended content of the ISE, refer to the guidance for industry *Integrated Summary of Effectiveness*.

Question 6b:

The ISS is planned to include 2 integrated populations: one based on the safety populations from all vehicle-controlled studies of Oxymetazoline HCl Cream, 1.0% that included at least a 28-day treatment period (Studies 199201-002, 199201-004, and 199201-005, hereafter referred to as the “core studies”), including the data from only the Oxymetazoline HCl Cream, 1.0% QD and vehicle QD arms, and one based on the safety populations of the 2 pivotal studies (Studies 199201-004 and 199201-005, hereafter referred to as the “pivotal studies”).

Other listed studies will not be part of the integrated analysis because design, treatment exposure, dose, and objectives of those studies were different than phase 2 199201-002 and the phase 3 pivotal, 199201-004 and 199201-005.

Allergan proposes to present integrated analyses of vital signs and adverse events, including subgroup analyses of adverse events, using the core studies population. Allergan proposes to present integrated analyses of dermal tolerability, IGA, CTA, inflammatory lesion count, skin blanching, and worsening of erythema from baseline using the pivotal studies population.

For the discussion of adverse events within the Summary of Clinical Safety in Module 2 Section 2.7.4, data from the first 29 days of the long-term safety study (199201-006) is planned to be presented in a side-by-side tabular format next to integrated data for the core studies, using the following 3 columns:

- 1.0% Oxy QD – (integrated core studies population)
- 1.0% Oxy QD – first 29 days of 199201-006 (open label long-term safety)
- Vehicle QD – (integrated core studies population)

Long-term safety data from Study 199201-006 are also planned to be presented separately within the Summary of Clinical Safety, as well as details from the legacy studies conducted by Vicept Therapeutics for the evaluation of dermal safety.

A draft statistical analysis plan for the ISS is provided in Appendix 3 of the Meeting Package.

Does the Agency agree with the data integration strategy for the ISS?

Does the Agency have additional recommendations on the proposed SAP for the ISS?

Response:

Your pooling strategy seems acceptable.

Question 7:

Allergan plans to submit the following for phase 3 study 199201-002, each of the 2 pivotal phase 3 studies (199201-004 and 199201-005), and the open-label study (199201-006) in Module 5:

1. Raw dataset (RDS) definition file
2. Analysis dataset (ADS) definition file
3. Raw data Statistical Analysis Software (SAS) transport file
4. ADS SAS transport files
5. Annotated CRFs

The draft RDS definition file (Appendix 4), draft ADS definition file (Appendix 5), and draft annotated CRFs for protocol 199201-004 (Appendix 6), which had a similar study design and/or data collection method as compared to protocols 199201-005 and 199201-006, are provided in the Meeting Package. In addition, the draft raw data SAS transport file will be included in Appendix 7 of the Meeting Package, but will be provided in PDF format instead of the native .xpt format.

Allergan plans to submit the ISS ADS and ADS definition file, e.g., pooled pivotal studies (199201-004 and 199201-005) or pooled core studies (199201-002, 199201-004, and 199201-005) in the NDA, as specified in the draft analysis plan provided in Appendix 3 of the Meeting Package.

The dataset files will be provided according to Study Data Technical Conformance v2.2 wherever possible. Any deviation from the Study Data Technical Conformance will be documented in the Analysis Data Reviewer's Guide. The datasets from Studies 199201-002, 199201-004, and 199201-005 are legacy compliant but not SDTM or ADaM compliant. Allergan does not plan to convert the datasets to SDTM or ADaM formats.

The ADS and tables, listings, and graphs were developed using SAS programs. The SAS programs will be available upon request by the Agency.

Does the Agency agree with the proposed package of datasets and the corresponding documentation to be provided in the proposed NDA?

Response:

The approach is acceptable based on the standard data guides. The programs for creating ADS are required also.

Submit the SAS programs needed to conduct all primary and secondary analysis (GEE modeling, multiple imputation programs, etc.) with the application. Also include supportive information such as the randomization seeds for multiple imputation calculations.

Question 8:

Allergan plans to submit 2 Dossiers in Module 5 of the NDA, summarizing the content validity, measurement properties, scoring, and other pertinent evidence supporting Patient-Reported Outcomes (PRO) endpoints used in the 2 pivotal phase 2 studies (199201-004 and 199201-005). The proposed TOC for the 2 PRO Dossiers is provided in Appendix 8 of the Meeting Package, detailing (1) Subject Self-Assessment for Rosacea Redness (SSA) with Photoguide and (2) the Symptom and Satisfaction Assessments for Rosacea Facial Redness (SA-RFR and SAT-RFR).

Does the FDA agree with the content being submitted as part of the PRO Dossiers and with it going in Module 5.3.5.4 of the eCTD?

Response:

The PRO should be placed in eCTD section 5.3.5.3 with a file tag of "study-report-body" and a leaf title of "PRO dossier" or something similar; so it will be easy for reviewers to easily identify the document.

Clinical Pharmacology:

There were no questions for Clinical Pharmacology, however we have the following comments.

1. We remind you of our comments related to in-vitro drug interaction potential assessment conveyed at the End of Phase 2 meeting and recommend you to submit this information in your NDA.

2. Clarify if the formulation used in your Phase 2b trial 199201-002 was the to-be-marketed formulation. Also submit information about formulations used for all trials in your clinical development program in a tabular format in the NDA.
3. Submit the raw pharmacokinetic (PK) data and calculated PK parameters results in SAS transport format (XPT format) in your NDA.
4. Submit bioanalytical method validation reports and bioanalysis reports in your NDA, including information to support the long term storage stability of your PK samples.

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 or NDA might identify additional comments or information requests.
2. 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 21 CFR 54 and 21CFR 314.50(k).
3. 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.

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 (EOP2) meeting. In the absence of an End-of-Phase 2 meeting, refer to the draft guidance below. The PSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The PSP should be submitted in PDF and Word format. Failure to include an agreed iPSP with a marketing application could result in a refuse to file action.

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

PRESCRIBING INFORMATION

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

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

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) SITE INSPECTIONS

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.

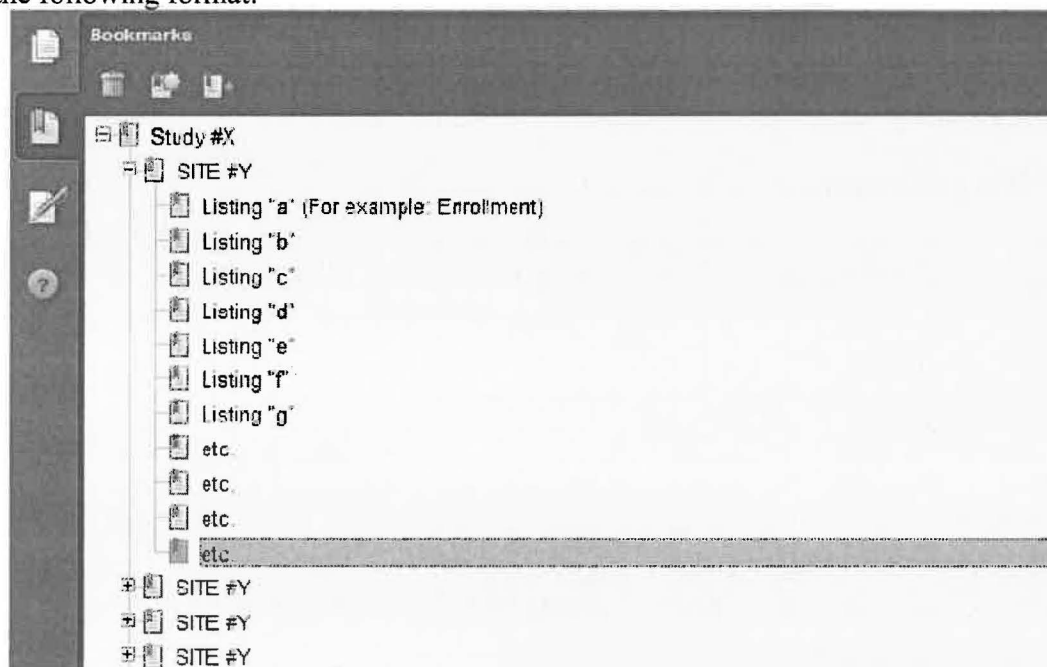
This request also provides instructions for where OSI requested items should be placed within an eCTD submission (Attachment 1, Technical Instructions: Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format).

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. Include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. Location of Principal Investigator: Address (e.g. Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
2. Include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:
 - a. Number of subjects screened at each site
 - b. Number of subjects randomized at each site
 - c. Number of subjects treated who prematurely discontinued for each site by site
3. Include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
 - a. Location at which sponsor trial documentation is maintained (e.g., monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
 - b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g. as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
 - c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

1. For each pivotal trial: Site-specific individual subject data listings (hereafter referred to as “line listings”). For each site, provide line listings for:
 - a. Listing for each subject consented/enrolled; for subjects who were not randomized to treatment and/or treated with study therapy, include reason not randomized and/or treated
 - b. Subject listing for treatment assignment (randomization)
 - c. Listing of subjects that discontinued from study treatment and subjects that discontinued from the study completely (i.e., withdrew consent) with date and reason discontinued
 - d. Listing of per protocol subjects/ non-per protocol subjects and reason not per protocol
 - e. By subject listing of eligibility determination (i.e., inclusion and exclusion criteria)
 - f. By subject listing, of AEs, SAEs, deaths and dates
 - g. By subject listing of protocol violations and/or deviations reported in the NDA, including a description of the deviation/violation
 - h. By subject listing of the primary and secondary endpoint efficacy parameters or events. For derived or calculated endpoints, provide the raw data listings used to generate the derived/calculated endpoint.
 - i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
 - j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring
2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

I. Attachment 1

Technical Instructions:

Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

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

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



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

References:

- 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>)

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

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

Summary Level Clinical Site Data for Data Integrity Review and Inspection Planning in NDA and BLA Submissions

I. INTRODUCTION

The purpose of this electronic submission of a single new clinical site dataset is to facilitate the timely evaluation of data integrity and selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process.

II. DESCRIPTION OF THE SUMMARY LEVEL CLINICAL SITE DATASET

The summary level clinical site data are intended (1) to clearly identify individual clinical investigator sites within an application or supplement, (2) to specifically reference the studies to which those clinical sites are associated, and (3) to present the characteristics and outcomes of the study at the site level.

For each study used to support efficacy, data should be submitted by clinical site and treatment arm for the population used in the primary analysis to support efficacy. As a result, a single clinical site may contain multiple records depending on the number of studies and treatment arms supported by that clinical site.

The site-level efficacy results will be used to support site selection and are not intended to support evaluation of efficacy. To this end, for each study used to support efficacy, the summary level clinical site dataset submission should include site-specific efficacy results by treatment arm and the submission of site-specific effect sizes.

The following paragraphs provide additional details on the format and structure of the efficacy related data elements.

Site-Specific Efficacy Results

For each study and investigator site, the variables associated with efficacy and their variable names are:

- Treatment Efficacy Result (TRTEFFR) – the efficacy result for each primary endpoint, by treatment arm (see below for a description of endpoint types and a discussion on how to report this result)
- Treatment Efficacy Result Standard Deviation (TRTEFFS) – the standard deviation of the efficacy result (treatEffR) for each primary endpoint, by treatment arm
- Site-specific Efficacy Effect Size (SITEEFFE) – the effect size should be the same representation as reported for the primary efficacy analysis
- Site-specific Efficacy Effect Size Standard Deviation (SITEEFFS) – the standard deviation of the site-specific efficacy effect size (SITEEFFE)
- Endpoint (endpoint) – a plain text label that describes the primary endpoint as described in the Define file data dictionary included with each application.
- Treatment Arm (ARM) – a plain text label for the treatment arm that is used in the Clinical Study Report

In addition, for studies whose primary endpoint is a time-to-event endpoint, include the following data element:

- Censored Observations (CENSOR) – the number of censored observations for the given site and treatment.

If a study does not contain a time-to-event endpoint, record this data element as a missing value.

To accommodate the variety of endpoint types that can be used in analyses please reference the below endpoint type definitions when tabulating the site-specific efficacy result variable by treatment arm, “TRTEFFR”.

- Discrete Endpoints – endpoints consisting of efficacy observations that can take on a discrete number of values (e.g., binary, categorical). Summarize discrete endpoints by an event frequency (i.e., number of events), proportion of events, or similar method at the site for the given treatment.
- Continuous Endpoints – endpoints consisting of efficacy observations that can take on an infinite number of values. Summarize continuous endpoints by the mean of the observations at the site for the given treatment.
- Time-to-Event Endpoints – endpoints where the time to occurrence of an event is the primary efficacy measurement. Summarize time-to-event endpoints by two data elements: the number of events that occurred (TRTEFFR) and the number of censored observations (CENSOR).
- Other – if the primary efficacy endpoint cannot be summarized in terms of the previous guidelines, a single or multiple values with precisely defined variable interpretations should be submitted as part of the dataset.

In all cases, the endpoint description provided in the “endpoint” plain text label should be expressed clearly to interpret the value provided in the (TRTEFFR) variable.

The site efficacy effect size (SITEEFFE) should be summarized in terms of the primary efficacy analysis (e.g., difference of means, odds ratio) and should be defined identically for all records in the dataset regardless of treatment.

The Define file for the dataset is presented in Exhibit 1.

III. CREATING AND SUBMITTING THE DATA FILE (SUBMISSION TEMPLATE AND STRUCTURE)

A sample data submission for the variables identified in Exhibit 1 is provided in Exhibit 2. The summary level clinical site data can be submitted in SAS transport file format (*.xpt). The file may be submitted electronically through the FDA Electronic Submission Gateway (ESG) referencing the active IND number or via secure CD addressed to the Division of Scientific Investigations point of contact.

II. Exhibit 1: Table 1 Clinical Site Data Elements Summary Listing (DE)

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
1	STUDY	Study Number	Char	String	Study or trial identification number.	ABC-123
2	STUDYTL	Study Title	Char	String	Title of the study as listed in the clinical study report (limit 200 characters)	Double blind, randomized placebo controlled clinical study on the influence of drug X on indication Y
3	DOMAIN	Domain Abbreviation	Char	String	Two-character identification for the domain most relevant to the observation. The Domain abbreviation is also used as a prefix for the variables to ensure uniqueness when datasets are merged.	DE
4	SPONNO	Sponsor Number	Num	Integer	Total number of sponsors throughout the study. If there was a change in the sponsor while the study was ongoing, enter an integer indicating the total number of sponsors. If there was no change in the sponsor while the study was ongoing, enter "1".	1
5	SPONNAME	Sponsor Name	Char	String	Full name of the sponsor organization conducting the study at the time of study completion, as defined in 21 CFR 312.3(a).	DrugCo, Inc.
6	IND	IND Number	Num	6 digit identifier	Investigational New Drug (IND) application number. If study not performed under IND, enter -1.	010010
7	UNDERIND	Under IND	Char	String	Value should equal "Y" if study at the site was conducted under an IND and "N" if study was not conducted under an IND (i.e., 21 CFR 312.120 studies).	Y
8	NDA	NDA Number	Num	6 digit identifier	FDA new drug application (NDA) number, if available/applicable. If not applicable, enter -1.	021212
9	BLA	BLA Number	Num	6 digit identifier	FDA identification number for biologics license application, if available/applicable. If not applicable, enter -1.	123456
10	SUPPNUM	Supplement Number	Num	Integer	Serial number for supplemental application, if applicable. If not applicable, enter -1.	4
11	SITEID	Site ID	Char	String	Investigator site identification number assigned by the sponsor.	50
12	ARM	Treatment Arm	Char	String	Plain text label for the treatment arm as referenced in the clinical study report (limit 200 characters).	Active (e.g., 25mg), Comparator drug product name (e.g., Drug x), or Placebo
13	ENROLL	Number of Subjects Enrolled	Num	Integer	Total number of subjects enrolled at a given site by treatment arm.	20
14	SCREEN	Number of Subjects Screened	Num	Integer	Total number of subjects screened at a given site.	100
15	DISCONT	Number of Subject Discontinuations	Num	Integer	Number of subjects discontinuing from the study after being enrolled at a site by treatment arm as defined in the clinical study report.	5
16	ENDPOINT	Endpoint	Char	String	Plain text label used to describe the primary endpoint as described in the Define file included with each application (limit 200 characters).	Average increase in blood pressure

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
17	ENDPTYPE	Endpoint Type	Char	String	Variable type of the primary endpoint (i.e., continuous, discrete, time to event, or other).	Continuous
18	TRTEFFR	Treatment Efficacy Result	Num	Floating Point	Efficacy result for each primary endpoint by treatment arm at a given site.	0, 0.25, 1, 100
19	TRTEFFS	Treatment Efficacy Result Standard Deviation	Num	Floating Point	Standard deviation of the efficacy result (TRTEFFR) for each primary endpoint by treatment arm at a given site.	0.065
20	SITEEFFE	Site-Specific Efficacy Effect Size	Num	Floating Point	Site effect size with the same representation as reported for the primary efficacy analysis.	0, 0.25, 1, 100
21	SITEEFFS	Site-Specific Efficacy Effect Size Standard Deviation	Num	Floating Point	Standard deviation of the site-specific efficacy effect size (SITEEFFE).	0.065
22	CENSOR	Censored Observations	Num	Integer	Number of censored observations at a given site by treatment arm. If not applicable, enter -1.	5
23	NSAE	Number of Non-Serious Adverse Events	Num	Integer	Total number of non-serious adverse events at a given site by treatment arm. This value should include multiple events per subject and all event types (i.e., <u>not limited to</u> only those that are deemed related to study drug or treatment emergent events).	10
24	SAE	Number of Serious Adverse Events	Num	Integer	Total number of serious adverse events excluding deaths at a given site by treatment arm. This value should include multiple events per subject.	5
25	DEATH	Number of Deaths	Num	Integer	Total number of deaths at a given site by treatment arm.	1
26	PROTVIOL	Number of Protocol Violations	Num	Integer	Number of protocol violations at a given site by treatment arm as defined in the clinical study report. This value should include multiple violations per subject and all violation type (i.e., <u>not limited to</u> only significant deviations).	20
27	FINLMAX	Maximum Financial Disclosure Amount	Num	Floating Point	Maximum financial disclosure amount (\$USD) by any single investigator by site. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	20000.00
28	FINLDISC	Financial Disclosure Amount	Num	Floating Point	Total financial disclosure amount (\$USD) by site calculated as the sum of disclosures for the principal investigator and all sub-investigators to include all required parties. Under the applicable regulations (21 CFR Parts 54, 312, 314, 320, 330, 601, 807, 812, 814, and 860). If unable to obtain the information required to the corresponding statements, enter -1.	25000.00
29	LASTNAME	Investigator Last Name	Char	String	Last name of the investigator as it appears on the FDA 1572.	Doe
30	FRSTNAME	Investigator First Name	Char	String	First name of the investigator as it appears on the FDA 1572.	John
31	MINITIAL	Investigator Middle Initial	Char	String	Middle initial of the investigator, if any, as it appears on the FDA 1572.	M

Variable Index	Variable Name	Variable Label	Type	Controlled Terms or Format	Notes or Description	Sample Value
32	PHONE	Investigator Phone Number	Char	String	Phone number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
33	FAX	Investigator Fax Number	Char	String	Fax number of the primary investigator. Include country code for non-US numbers.	44-555-555-5555
34	EMAIL	Investigator Email Address	Char	String	Email address of the primary investigator.	john.doe@mail.com
35	COUNTRY	Country	Char	ISO 3166-1-alpha-2	2 letter ISO 3166 country code in which the site is located.	US
36	STATE	State	Char	String	Unabbreviated state or province in which the site is located. If not applicable, enter NA.	Maryland
37	CITY	City	Char	String	Unabbreviated city, county, or village in which the site is located.	Silver Spring
38	POSTAL	Postal Code	Char	String	Postal code in which site is located. If not applicable, enter NA.	20850
39	STREET	Street Address	Char	String	Street address and office number at which the site is located.	1 Main St, Suite 100

The following is a fictional example of a data set for a placebo-controlled trial. Four international sites enrolled a total of 205 subjects who were randomized in a 1:1 ratio to active or placebo. The primary endpoint was the percent of responders. The site-specific efficacy effect size (SITEEFFE) is the difference between the active and the placebo treatment efficacy result. Note that since there were two treatment arms, each site contains 2 rows in the following example data set and a total of 8 rows for the entire data set.

III. Exhibit 2: Example for Clinical Site Data Elements Summary Listing (Table 1)

STUDY	STUDYT L	DOM AIN	SPON NO	SPONN AME	IND	UNDER IND	NDA	BL A	SUPPN UM	SIT EID	ARM	ENR OLL	SCREE N	DISCO NT
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Active	26	61	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	001	Placebo	25	61	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Active	23	54	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	002	Placebo	25	54	4
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Active	27	62	3
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	003	Placebo	26	62	5
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Active	26	60	2
ABC-123	Double blind...	DE	1	DrugCo, Inc.	000001	Y	200001	-1	0	004	Placebo	27	60	1

ENDPO INT	ENDT YPE	TRTE FFR	TRTE FFS	SITEE FFE	SITEE FFS	CENS OR	NS AE	SA E	DEA TH	PROTV IOL	FINL MAX	FINLD ISC	LASTN AME	FRSTN AME
Percent Responders	Binary	0.48	0.0096	0.34	0.0198	-1	0	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.14	0.0049	0.34	0.0198	-1	2	2	0	1	-1	-1	Doe	John
Percent Responders	Binary	0.48	0.0108	0.33	0.0204	-1	3	2	1	0	45000.00	45000.00	Washin gton	George

Percent Responders	Binary	0.14	0.0049	0.33	0.0204	-1	0	2	0	3	20000.00	45000.00	Washington	George
Percent Responders	Binary	0.54	0.0092	0.35	0.0210	-1	2	2	0	1	15000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.19	0.0059	0.35	0.0210	-1	3	6	0	0	22000.00	25000.00	Jefferson	Thomas
Percent Responders	Binary	0.46	0.0095	0.34	0.0161	-1	4	1	0	0	0.00	0.00	Lincoln	Abraham
Percent Responders	Binary	0.12	0.0038	0.34	0.0161	-1	1	2	0	1	0.00	0.00	Lincoln	Abraham

MINITAL	PHONE	FAX	EMAIL	COUNTRY	STATE	CITY	POSTAL	STREET
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
M	555-123-4567	555-123-4560	John@mail.com	RU	Moscow	Moscow	103009	Kremlin Road 1
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	020-3456-7891	020-3456-7890	george@mail.com	GB	Westminster	London	SW1A 2	10 Downing St
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	01-89-12-34-56	01-89-12-34-51	tom@mail.com	FR	N/A	Paris	75002	1, Rue Road
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk
	555-987-6543	555-987-6540	abe@mail.com	US	Maryland	Rockville	20852	1 Rockville Pk

Pre-NDA

General Advice for Planned Marketing Applications

NDA and BLA applications must comply with all applicable statutes and regulations (e.g. 21 CFR 314, 21 CFR Part 201, and 21 CFR Parts 600 and 601). In addition, FDA has published many guidance documents (available at www.fda.gov/RegulatoryInformation/Guidances/default.htm) that contain important information necessary for preparing a complete, quality application.

Based on our experience with marketing applications, the following tables focus on specific areas of an application and are intended to help you plan and prepare for submitting a quality application. These comments do not include all issues you need to consider in preparing an application, but highlight areas where we have seen problems and/or issues that can delay our timely review of applications. These are general comments; if you believe some are inapplicable to your planned application we encourage you to provide justification and discuss it with us.

The **Study Data Standards Common Issues Document** can be found at: <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm> The purpose of the document is to highlight important aspects of CDISC and STDM datasets that should be addressed by the Sponsor/Applicant regarding submission of CDISC data in support of an application for registration.

NDA/BLA content and format
CLINICAL
1) Original versions of all protocols, statistical analysis plans, Data Safety Monitoring Board (DSMB) and adjudication committee charters, and all amendments.
2) Minutes of all DSMB and efficacy endpoint review/adjudication committee meetings.
3) Investigator instructions that may have been produced in addition to the protocol and investigator brochure
4) All randomization lists and, if used, IVRS datasets (in SAS transport format)
5) All datasets used to track adjudications (in SAS transport format), if any
6) A Reviewers Guide to the data submission that includes, but is not limited to the following: a) description of files and documentation b) description of selected analysis datasets c) key variables of interest, including efficacy and safety variables d) SAS codes for sub-setting and combining datasets e) coding dictionary used f) methods of handling missing data g) list of variable contained in every dataset h) listing of raw data definitions i) analysis data definitions j) annotated CRF (the annotated CRF should contain links connecting to the document that defines the variable name and lists the data sets that contain the specific item) k) documentation of programs
7) Clinical study report(s) for all trials (should follow the ICH E3 Structure and Content of Clinical Study Reports guidance)

http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm073113.pdf).
8) Pediatric Studies: All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is exempt (i.e. orphan designation), waived or deferred. We request that you submit a pediatric plan that describes development of your product to provide important information on the safe and effective use of in the pediatric population where it may be used. If the product will not be used in pediatric populations your application must include a specific waiver request with the NDA submission, including supporting data. A request for deferral, must include a pediatric plan, certification of the grounds for deferring the assessments, and evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time.
9) A statement that the manufacturing facilities are ready for inspection upon FDA receipt of the application
10) A chronology of prior substantive communications with FDA and copies of official meeting/telecom minutes.
11) References: There should be active links from lists of references to the referenced article.
Studies, Data And Analyses
12) Provide a table listing all of the manufacturing facilities (e.g. drug product, drug substance, packaging, control/testing), including name of facility, full address including street, city, state, country, FEI number for facility (if previously registered with FDA), full name and title, telephone, fax number and email for on-site contact person, the manufacturing responsibility and function for each facility, and DMF number (if applicable).
13) Provide a table with the following columns for each of the completed Phase 3 clinical trials: - Site number - Principle investigator - Location: City State, Country - Number of subjects screened - Number of subjects randomized - Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection) - Number of protocol violations (Major, minor, including definition)
14) Provide an assessment of safety as per the Guidance for Industry: Premarketing Risk Assessment (www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072002.pdf).
15) Provide detailed information, including a narrative (data listings are not an acceptable substitute for a narrative), for all patients who died while on study or who terminated study drug or participation in the study prematurely including those categorized as other, lost to follow up, physician decision, or subject decision. Narrative summaries should contain the following components: - subject age and gender - signs and symptoms related to the adverse event being discussed - an assessment of the relationship of exposure duration to the development of the adverse event - pertinent medical history - concomitant medications with start dates relative to the adverse event - pertinent physical exam findings - pertinent test results (for example: lab data, ECG data, biopsy data)

h) discussion of the diagnosis as supported by available clinical data i) a list of the differential diagnoses, for events without a definitive diagnosis j) treatment provided k) re-challenge and de-challenge results (if performed) l) outcomes and follow-up information m) an informed discussion of the case, allowing a better understanding of what the subject experienced.
16) Provide complete case report forms (CRFs) for all patients with serious adverse events, in addition to deaths and discontinuations due to adverse events. You should be prepared to supply any additional CRFs with a rapid turnaround upon request. 17) Provide reports for any autopsies conducted on study.
18) For patients listed as discontinued to due “investigator decision,” “sponsor request,” “withdrew consent,” or “other,” the verbatim reason for discontinuation (as written in the CRF) should be reviewed to ensure that patients did not dropout because of drug-related reasons (lack of efficacy or adverse effects). If discrepancies are found between listed and verbatim reasons for dropout, the appropriate reason for discontinuation should be listed and patient disposition should be re-tabulated. In addition, the verbatim description from the CRF should be included as a variable in the adverse event data set.
19) Regulations require that the safety and effectiveness data be presented for subgroups including “by gender, age, and racial subgroups”. Therefore, as you are gathering your data and compiling your application, we request that you include this data and pertinent analysis
20) The clinical information contained in the NDA/BLA will be reviewed utilizing the CDER Clinical Review Template. Details of the template may be found in the Manual of Policies and Procedures (MAPP) 6010.3 (www.fda.gov/downloads/AboutFDA/ReportsManualsForms/StaffPoliciesandProcedures/ucm080121.pdf). To facilitate the review, we request you provide analyses and discussion, where applicable, that will address the items in the template, including: a) Other Relevant Background Information – important regulatory actions in other countries or important information contained in foreign labeling. b) Exposure-Response Relationships – important exposure-response assessments. c) Less common adverse events (between 0.1% and 1%). d) Laboratory Analyses focused on measures of central tendency. Also provide the normal ranges for the laboratory values. e) Laboratory Analyses focused on outliers or shifts from normal to abnormal. Also provide the criteria used to identify outliers. f) Marked outliers and dropouts for laboratory abnormalities. g) Analysis of vital signs focused on measures of central tendencies. h) Analysis of vital signs focused on outliers or shifts from normal to abnormal. i) Marked outliers for vital signs and dropouts for vital sign abnormalities. j) A comprehensive listing of patients with potentially clinically significant laboratory or vital sign abnormalities should be provided. Also, a listing should be provided of patients reporting adverse events involving abnormalities of laboratory values or vital signs, either in the “investigations” SOC or in a SOC pertaining to the specific abnormality. For example, all AEs coded as “hyperglycemia” (SOC metabolic) and “low blood glucose” (SOC investigations) should be tabulated. Analyses of laboratory values should include assessments of changes from baseline to worst value, not simply the last value. k) Overview of ECG testing in the development program, including a brief review of the nonclinical results. l) Standard analyses and explorations of ECG data. m) Overdose experience. n) Analysis and summary of the reasons and patterns of discontinuation of the study drug. Identify for each patient the toxicities that result in study discontinuation or dose reduction.

- o) Explorations for:
- i) Possible factors associated with a higher likelihood of early study termination; include demographic variables, study site, region, and treatment assignment.
 - ii) Dose dependency for adverse findings, which should be supported by summary tables of the incidence of adverse events based on the cumulative dose and the average dose administered.
 - iii) Time dependency for adverse finding, which should be supported by analyses summarizing the length of time subjects experience adverse events and whether recovery occurs during treatment.
 - iv) Drug-demographic interactions
 - v) Drug-disease interactions
- p) Drug-drug interactions
- i) Dosing considerations for important drug-drug interactions.
 - ii) Special dosing considerations for patients with renal insufficiency, patients with hepatic insufficiency, pregnant patients, and patients who are nursing.

Financial Disclosure Information

- 21) Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. This requires that investigators provide information to the sponsor during the course of the study and after completion. See Guidance for Industry - Financial Disclosure by Clinical Investigators (<http://www.fda.gov/downloads/regulatoryinformation/guidances/ucm341008.pdf>).

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/s/

JILL A LINDSTROM
10/29/2015



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107983

MEETING MINUTES

Allergan, Inc.
Attention: Thu Doan, PharmD
Senior Manager, Global Regulatory Affairs
2525 Dupont Drive
PO Box 19534
Irvine, CA 92623-9534

Dear Dr. Doan:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for (oxymetazoline) cream, 1%.

We also refer to the teleconference between representatives of your firm and the FDA on December 18, 2013. The purpose of the meeting was to discuss proposed development program.

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

If you have any questions, call Dawn Williams, Regulatory Project Manager at (301) 796-5376.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, MD, FAAD
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: December 18, 2013; 9:00 am
Meeting Location: White Oak Building 22, Room 1419

Application Number: IND 107983
Product Name: (oxymetazoline) cream, 1%
Indication: For the reduction of erythema in patients with erythematous rosacea
Applicant Name: Allergan, Inc.

Meeting Chair: Susan J. Walker, MD
Meeting Recorder: Dawn Williams, BSN

FDA ATTENDEES

Susan J. Walker, MD, Director, DDDP
Jill Lindstrom, MD, Clinical Team Leader, DDDP
Jane Liedtka, MD, Clinical Reviewer, DDDP
Barbara Hill, PhD, Pharmacology Supervisor, DDDP
Daivender Mainigi, PhD, Pharmacology Reviewer, DDDP
Jennifer Dao, Regulatory Health Project Manager, DDDP
Dawn Williams, BSN, Regulatory Health Project Manager, DDDP
Doanh Tran, PhD, Clinical Pharmacology Team Leader, DCP III
An-Chi Lu, PhD, Clinical Pharmacology Reviewer, DCP III
Mohamed Alesh, PhD, Biostatistics Team Leader, DB III
Yuqing Tang, PhD, Biostatistics Reviewer, DB III
Shulin Ding, PhD, Pharmaceutical Assessment Lead, DNDQA II
Hitesh Shroff, PhD, Product Quality Reviewer, DNDQA II, Branch IV

SPONSOR ATTENDEES

Scott Whitcup, MD, Executive Vice President, Research and Development and Chief Scientific Officer
Eric Carter, MD, PhD, Senior Vice President, Chief Medical Officer, Head Global Drug Development
Karen Smith, MD, PhD, MBA, LLM, Senior Vice President, Global Medical Affairs and Interim Therapeutic Area Head, Dermatology
Gurpreet Ahluwalia, PhD, Senior Director, Clinical Development, Dermatology Clinical Research and Development

Chin-Ming Chang, PhD, Senior Director, Pharmaceutical Sciences
Gary Charbonneau, MS, Vice President, Global Regulatory Affairs
Thu Doan, PharmD, Senior Manager, Global Regulatory Affairs
Andrea Kim, PhD, MBA, DABT, Principal Scientist, Toxicology
Vince (Cheyi) Lin, PhD, Manager, Biostatistics
Selena Daniels, PharmD, Manager, Global Health Outcomes

Regulatory Correspondence History

We have had the following meeting with you:

- July 27, 2011 End of Phase 2

We have sent the following correspondences:

- December 13, 2012 Advice
- December 3, 2012 Advice/Information Request
- August 13, 2012 Advice
- April 23, 2012 Advice
- August 18, 2011 Advice/Information Request
- May 10, 2011 Advice/Information Request
- September 16, 2010 Advice
- July 22, 2010 Advice
- May 3, 2010 Advice

Chemistry, Manufacturing and Controls (CMC)

Question 1:

Does the Agency agree with this approach?

Response:

Yes, provided that there are no toxic components in the formulation-contacting plastics. You should provide (or reference to a DMF) the chemical composition information for each formulation-contacting packaging component.

Question 2:

Does the Agency agree with this approach?

Response:

Yes, provided that there are no toxic components in the formulation-contacting plastics. You should provide (or reference to a DMF) the chemical composition information for each formulation-contacting packaging component.

Additional Comments

1. Include evaluation of pump functionality (number of actuations for priming, actuation force, amount dispensed per actuation for the first 20 and last 10 actuations before exhaustion, total deliverable amount and hold-up weight), weight loss, and package integrity (interior and exterior) in registration stability studies. The registration stability studies should also investigate different orientations of the pump.

Meeting Discussion:

The sponsor requested clarification regarding evaluation of packaging integrity. The Agency clarified that the test of packaging integrity for the interior surface (i.e., all of the surfaces that contact the formulation) can be a visual examination for signs (discoloration, expansion, or shrinkage) of deterioration of formulation-contacted packaging components.

2. Provide in-use study results to demonstrate that the proposed pump configuration can maintain its physical, chemical and functional integrity throughout the in-use period. The in-use study protocol should include (but not limited to) pump functionality and viscosity tests.
3. The analytical samples for registration stability and in-use studies should be taken from the pumped-out formulation whenever feasible. Revise relevant drug product analytical procedures for the pump configuration to reflect this sampling requirement.
4. Add pump functionality tests with appropriate acceptance criteria to drug product specification for the proposed pump configuration.

Meeting Discussion:

[REDACTED] (b) (4)
[REDACTED] (b) (4)
The Agency will review the data generated from the registration stability and in-use studies before considering which functionality tests should be included in the drug product specification.

Pharmacology/Toxicology

Question 3a:

Does the Agency agree that the completed nonclinical studies are adequate to support the Phase 3 studies?

Response:

In principle, we agree that the completed and ongoing non-clinical studies are in appropriate order to support the drug development. However, the final decision will be taken after review of the 9-month dermal minipig study report.

Question 3b:

Does the Agency agree that the proposed nonclinical plan is adequate to support registration?

Response:

We shall respond after review of your waiver request for conduct of a dermal carcinogenicity study.

Clinical Pharmacology/Biopharmaceutics

Question 4:

Does the Agency agree that the [REDACTED] (b) (4)

Response:

No. We have the following comments.

1. In your phase 2 dose-ranging trial 199201-002, subjects with moderate to severe facial erythema associated with rosacea were enrolled to receive a pea-sized volume of treatments to the entire face for 28 days. In addition, your protocol submitted in November 2012 stated that 0.5 gram of oxymetazoline cream will be applied. It is not clear if the "pea-sized" volume or 0.5 gram of treatments will be comparable to the dose subjects may apply in Phase 3 (thin layer) or when used clinically. We recommend that you provide information on the actual amount applied in Trial 199201-002, as well as measure and record the actual amount that will be applied in the Phase 3 trials to help assess whether the dosing conditions in trial 199201-002 was under maximal use conditions.

Meeting Discussion:

The sponsor stated that they would include instructions regarding "pea-sized" in Phase 3 trials to [REDACTED] (b) (4)

2. We cannot comment on whether steady state was reached in your trial because detailed PK data were not provided.

Question 5:

Does the Agency agree that the clinical PK data collected in the patient population to date is adequate to support registration?

Response:

We recommend that you conduct in vitro inhibition and induction studies to assess the potential of oxymetazoline to inhibit or induce any CYP450 isoforms. For further information, refer to Draft Guidance for Industry: Drug interaction Studies - Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations - February 2012. Moreover, for the

potential effect of CYP2C19 inhibitors on the PK of oxymetazoline, submit in the NDA detailed analysis methods, results and rationale for review.

You proposed a 505(b)(1) pathway for development of your product. [REDACTED] (b) (4)

Meeting Discussion:

The sponsor clarified that they will be submitting a 505(b)(1) [REDACTED] (b) (4) for any bridging purpose.

Clinical/Biostatistics

Question 6:

Does the Agency agree with the proposed dose of oxymetazoline HCl cream 1.0% applied QD for Phase 3 development?

Response:

You propose a dose/regimen of oxymetazoline HCL cream 1.0% QD for Phase 3 studies. This seems reasonable at this time.

Question 7:

Does the Agency agree that Allergan does not need to repeat the above listed panel of dermal safety studies with oxymetazoline cream, 1% QD?

Response:

Vicept (former sponsor) conducted a 21 day cumulative irritancy trial, a RIPT trial, a phototoxicity trial and a photocontact allergy trial with the 0.5% oxymetazoline HCL cream. Evaluation for irritancy and allergy (Dermal Tolerability Assessment) has been incorporated into your phase 3 trials.

At this time it seems reasonable not to conduct further dermal safety trials.

Question 8a:

Does the Agency agree with the overall study design of the Phase 3 studies to support registration?

Response:

You propose two identical multicenter, randomized, double-blind, parallel-group, vehicle-controlled trials comparing oxymetazoline HCL cream 1% to vehicle applied once daily to the

entire face for 29 days in subjects with moderate to severe persistent facial erythema associated with rosacea.

This seems reasonable at this time.

Question 8b:

Does the Agency agree with the durations of the planned treatment and follow-up periods, visit schedule, inclusion/exclusion criteria, and efficacy and safety measures?

Response:

You propose a 29 day treatment period followed by a 28 day observation period off treatment. You propose visits on days 1, 15, 29, 43 and 57. This seems reasonable at this time.

You propose the following key inclusion criteria:

- Male or female patients 18 years of age or older with a moderate to severe persistent facial erythema associated with rosacea as determined by a grade of ≥ 3 on both the CEA scale with a photo-numeric guide and the SSA scale with a photo-guide;
- Women of childbearing potential must have a negative urine pregnancy test and not be lactating.

You propose the following key exclusion criteria: any of the following conditions:

- greater than 3 inflammatory lesions on the face
- any uncontrolled systemic disease; Raynaud's syndrome, narrow angle glaucoma, orthostatic hypotension, cerebral or coronary insufficiency, thromboangiitis obliterans, scleroderma, Sjogren's syndrome, severe or unstable or uncontrolled cardiovascular disease
- current treatment with monoamine oxidase (MAO) inhibitors
- previous participation in clinical trials associated with oxymetazoline cream for facial rosacea

These criteria seem reasonable at this time.

You propose the following CEA and SSA for primary efficacy measures

Grade	CEA Scale Descriptor	SSA Scale Descriptor
0	Clear skin with no signs of erythema ^a	No signs of unwanted redness
1	Almost clear; slight redness	Almost clear of unwanted redness
2	Mild erythema; definite redness	Mild redness
3	Moderate erythema; marked redness	Moderate redness
4	Severe erythema; fiery redness	Severe redness

CEA = Clinician Erythema Assessment; SSA = Subject Self-Assessment for Rosacea Facial Redness

^a Normal healthy skin color as seen in individuals without rosacea

This seems reasonable at this time.

Question 9a:

Does the Agency agree with the proposed primary efficacy endpoint and measures?

Response:

You propose the following for the primary efficacy endpoint

The primary efficacy variable is defined as the proportion of patients with at least a 2-grade decrease (improvement) on both CEA and SSA from baseline at each hour 3, 6, 9, and 12 on day 29. Baseline is defined as the measurement at predose on day 1.

This seems reasonable at this time.

Question 9b:

Does the Agency agree with the proposed primary variable and statistical methodology to analyze the variable?

Response:

Your plan to use the Generalized Estimating Equation (GEE) with the logit link and to have the dependent variables as a composite success at Hours 3, 6, 9, 12 and to include treatment arms, investigational sites, time points and treatment by site interaction as the independent variables is acceptable.

Question 10a:

Does the Agency agree with the proposed secondary efficacy endpoints and measures?

Response:

You propose the following secondary efficacy measures

- Digital Image Analysis (DIA) of facial photographs for redness
- Satisfaction Assessment for Rosacea Facial Redness (Follow-up version) - Item #9
- Symptom Assessment for Rosacea Facial Redness (Skin Sensations Domain: Item #3 and #4)

See response to Question 10c.

Question 10b:

Does the Agency agree with the proposed secondary variables and statistical methodologies for the secondary efficacy variables?

Response:

You propose the following secondary efficacy variables

- the proportion of patients with at least a 2-grade decrease (improvement) from baseline on SSA at each hour 3, 6, 9, and 12 on day 29
- the percent change from baseline in Rosacea Facial Redness as measured by DIA at each hour 3, 6, 9, and 12 on day 29
- the proportion of patients who report “satisfied” or “very satisfied” in Item #9 (“*Right now, how satisfied are you with the effect your study medication had on your facial redness?*”) of Satisfaction Assessment for Rosacea Facial Redness (follow-up version) at each hour 3, 6, 9, and 12 on day 29
- the proportion of patients who achieve at least a minimally important difference (MID) from baseline in the Skin Sensations Domain score from the Symptom Assessment for Rosacea Facial Redness measure at each hour 3, 6, 9, and 12 on day 29. The Skin Sensations Domain includes 2 items (Item #3, “*Right now, how warm does your face feel because of your facial redness?*” and Item #4, “*Right now, how much does your face burn because of your facial redness?*”). Each item is on a 5-point scale from 0 to 4. The total score on the Skin Sensations Domain will be converted to a 0 to 100 scale. To determine if a patient achieves at least a MID for each timepoint, a change from baseline on day 29 in the converted score will be compared to the MID. More details will be provided in the analysis plan.
- the proportion of patients with at least a 1-grade decrease (improvement) from baseline on SSA at hour 1 postdose on day 1 to establish time-to-onset

The protocol listed a large number of secondary endpoints. Some of your proposed secondary endpoints are patient reported outcomes (b) (4). The Agency recommends limiting the secondary endpoints to a few clinically meaningful endpoints.

See response to Question 10c.

Question 10c:

Does the Agency agree that these proposed secondary endpoints (b) (4)

Response:

(b) (4) secondary endpoints need to be clinically relevant, limited in number, and analyzed with appropriate multiplicity control.

Providing the results of a component of the primary endpoint (b) (4)

The Symptom and Satisfaction Assessment for Rosacea Facial Redness Dossier provided in the meeting background package is undergoing review. Additional comments will be forthcoming.

Question 10d:

Does the Agency have any other comments on the attached Statistical Analysis Plan (Attachment 3)?

Response:

The Agency does not have additional comments for the Statistical Analysis Plan at this time.

Question 11:

Does the Agency agree these PRO measures are well-defined, reliable, and valid instruments?

Response:

See response to Question #10c.

Question 12:

Does the Agency agree that a thorough QT/QTc study for oxymetazoline HCl cream 1.0% is not needed?

Response:

We need additional information. Provide the results, if available, of hERG assay assessment. Provide information about repolarization effect of related members of the chemical and/or pharmacologic class. Provide information about sudden cardiac death associated w/use of the active moiety.

Question 13a:

Does the Agency agree with the proposed study design for a 1-year, open-label study and its adequacy to support registration?

Response:

You propose an open label study of safety and efficacy of oxymetazoline HCL cream 1% in subjects with erythematous rosacea. You plan to enroll 400 subjects on therapy for 52 weeks.

It is difficult to interpret data from an open-label, uncontrolled trial. Therefore we recommend that you include a vehicle control to allow discrimination of subject outcomes caused by the drug from those resulting from other factors. We will need information about rebound, tachyphylaxis, and duration of effect upon withdrawal; consider incorporation of randomized withdrawal in your study design. Include vital signs (HR, BP), and investigator assessment of global disease severity in your safety assessments.

Meeting Discussion:

There was general discussion regarding this response. The Agency clarified that information should be provided in the NDA regarding rebound. The data should be collected at an appropriate time (temporally related to discontinuation of therapy) and obtained through active assessment, not spontaneous reporting.

Question 13b:

Does the Agency agree that the total exposure data available from the completed and proposed oxymetazoline studies at the time of filing will be sufficient to support registration?

Response:

The size of the safety database required for approval of your product will be determined by the adverse event profile and any signals detected in your phase 3 trials.

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. 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. 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 Pediatric and Maternal Health Staff 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>

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/s/

SUSAN J WALKER
12/26/2013



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 107983

MEETING MINUTES

Allergan, Inc.
Attention: Michele LaRussa-Goepel
Director, Global Regulatory Affairs
2525 Dupont Drive
Irvine, CA 92612-1599

Dear Ms. LaRussa-Goepel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for V-101 (oxymetazoline HCl) Cream.

We also refer to the meeting between representatives of your firm and the FDA on July 27, 2011. The purpose of the meeting was to discuss the development program for V-101 (oxymetazoline HCl) Cream.

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

If you have any questions, call Margo Owens, Project Management Team Leader at (301) 796-0966.

Sincerely,

{See appended electronic signature page}

Susan J. Walker, M.D., F.A.A.D.
Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

ENCLOSURE:
Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: End of Phase 2

Meeting Date and Time: July 27, 2011, 10:30 am
Meeting Location: WO22

Application Number: 107983
Product Name: V-101 (oxymetazoline HCl) Cream
Indication: Reduction of erythema in patients with erythematous rosacea
Sponsor/Applicant Name: Allergan, Inc.

Meeting Chair: Susan Walker, M.D.
Meeting Recorder: Margo Owens

FDA ATTENDEES

Susan Walker, M.D., F.A.A.D., Director, DDDP
Tatiana Oussova, M.D., M.P.H., Deputy Director for Safety, DDDP
Jill Lindstrom, M.D., Clinical Team Leader, DDDP
Milena Lolic, M.D., Clinical Reviewer, DDDP
Jane Liedtka, M.D., Clinical Reviewer, DDDP
Shulin Ding, Ph.D., Pharmaceutical Assessment Lead, DNDQA II
Hitesh Shroff, Ph.D., Product Quality Reviewer, ONDQA II, Branch VI
Barbara Hill, Ph.D., Pharmacology Supervisor, DDDP
Kumar Mainigi, Ph.D., Pharmacology Reviewer, DDDP
Mohamed Alosch, Ph.D., Biostatistics Team Leader, DBIII
Yuqing Tang, Ph.D., Biostatistics Reviewer, DBIII
Doanh Tran, Ph.D., Clinical Pharmacology Team Leader, DCP3
Abimbola Adebawale, Ph.D., Clinical Pharmacology Reviewer, DCP 3
Margo Owens, Team Leader, Project Management Staff, DDDP

SPONSOR ATTENDEES

(b) (6)
(b) (6)

Eric Carter, Sr. VP & CMO, Allergan (via telephone)
Scott Whipcup, EVP & CSO, Allergan (via telephone)
Frederick Beddingfield, VP Clinical Development, Allergan
Thomas Lin, VP Biostatistics, Allergan
Gurpreet Ahluwali, Sr. Director, Clinical Development, Allergan
Brian Short, Sr. Director, Pathology, Allergan
Abe Espiritu, Sr. Scientist, Process Development
Michele Larussa, Director, Regulatory Affairs, Allergan

Purpose of the Meeting:

To discuss the development plan for V-101 (oxymetazoline HCl) Cream.

Regulatory Correspondence History (include Regulatory History of past correspondences/interactions)

We have sent the following correspondences:

- May 03, 2010 – Advice/Information Request
- July 22, 2010 – Advice/Information Request
- September 16, 2010 – Advice/Information Request
- April 28, 2011 – Special Protocol – No Agreement
- May 10, 2011 – Advice/Information Request

Regulatory

Question 1:

Does the Division agree that the NDA should be filed pursuant to Section 505(b)(2) of the FD&C Act?

Response:

Based on the information provided, it is not clear why you intend to file a 505(b)(2) application. A 505(b)(2) pathway is appropriate for applications which rely (for approval) on data which the applicant neither owns nor has a right to refer, e.g., applications relying on published literature or our findings of safety and effectiveness for a listed drug. (b) (4)

is not listed in the Orange Book and therefore, you may not rely upon it. Alternatively, you may rely upon the OTC monograph for oxymetazoline hydrochloride and/or published literature but it is not clear what portions of your application you intend to support through that reliance. Identify those components of your application which you intend to address through reliance on the OTC monograph and/or published literature and clarify how you will construct a clinical bridge to support such reliance.

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 October 1999 Draft Guidance for Industry "Applications Covered by Section 505(b)(2)" available at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm079345.pdf>. 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 challenging the Agency's interpretation of this statutory provision (see Dockets 2001P-0323, 2002P-0447, and 2003P-0408 (available at <http://inside.fda.gov:9003/downloads/CDER/OfficeofNewDrugs/ImmediateOffice/ucm027521.pdf>)).

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified. If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature is scientifically appropriate.

Note that 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.

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 that drug and eligible for approval under section 505(j) of the act, we may 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 ANDA that cites the duplicate product as the reference listed drug.

Meeting Discussion:

The sponsor stated that they plan to pursue the 505(b)(1) pathway.

Question 2:

Can the Division comment and provide general direction with regards to the draft product label.

Response:

Proposed prescribing information (PI) submitted with your application must conform to the content and format regulations found at 21 CFR 201.56 and 201.57.

Summary of the Final Rule on the Requirements for Prescribing Information for Drug and Biological Products, labeling guidances, sample tool illustrating Highlights and Table of Contents, an educational module concerning prescription drug labeling, and fictitious prototypes of prescribing information are available at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>. We encourage you to review the information at this website and use it as you draft prescribing information for your application.

Question 3:

Can the Division comment on the Sponsor's plan to identify and submit for review the potential trade names?

Response:

Tradename proposals can be submitted during the IND phase. See Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names.

Chemistry, Manufacturing and Controls (CMC)

Question 4:

Does the Division have any comment regarding the above plan?

Response:

Yes. We have the following CMC comments related to the drug product for the proposed Phase 3 study.

- [REDACTED] (b) (4)
(b) (4) Please see USP <905> for further information.
- Include the inverted (or side-way) orientation in the registration stability protocol.
- If you plan to market multiple packaging sizes of the drug product then you may apply bracketing and matrixing to stability studies conducted in accordance with ICH Q1A(R) and ICH Q1D.
- Revise the acceptance criterion of the drug product appearance test to read: [REDACTED] (b) (4)
[REDACTED] (b) (4)
- Include a visual evaluation of package integrity in the registration stability protocol. The evaluation should include an examination of the interior surface of the immediate container.
- Include viscosity test in the specification with a numeric range as the acceptance criterion.
- Monitor degradants in the clinical/toxicology lots and registration stability batches. Please comply with ICH guidelines Q3B in reporting/identification/qualification of degradants.

Additional comments:

- Be advised that if the designated commercial manufacturing site for drug product is different from the Phase 3 site, appropriate bridging studies may be required for NDA. Examples of the bridging studies can be found in SUPAC-SS.
- You designated [REDACTED] (b) (4)
[REDACTED]. We recommend that you designate the function of each inactive ingredient based on its physicochemical characteristics.

Pharmacology/Toxicology

Question 5:

Does the Division have any comments on the toxicology program?

Response:

The sponsor has planned to conduct all the recommended non-clinical studies as were relayed in an Advice Letter sent on September 20, 2010. Therefore, the proposed toxicology program looks acceptable. It is emphasized that these studies must be conducted using the to be marketed formulation. Further suggestions/comments or need for additional studies may be made after review of newly conducted studies and studies in progress.

Clinical Pharmacology/Biopharmaceutics

Question 12:

Does the Division agree that the Sponsor has established a clinical safety bridge?

Response: It is not clear why you need to establish a clinical safety bridge. However, we do not agree that an adequate clinical systemic safety bridge has been established. The reasons are as follows.

[REDACTED] (b) (4)

[REDACTED] (b) (4)

In addition, it is not clear whether you evaluated the bioavailability of your drug product under maximal use conditions. We recommend that a maximal use PK study be undertaken in a suitable number of subjects with the dermatological disease of interest at the upper range of severity as anticipated in both your clinical trials and proposed labeling. Such a trial would attempt to maximize the potential for drug absorption to occur by incorporation of the following design elements:

- a) Frequency of dosing
- b) Duration of dosing
- c) Use of highest proposed strength
- d) Total involved surface area to be treated at one time
- e) Amount applied per square centimeter
- f) Method of application/site preparation

The study itself could be a stand alone study in phase II or could be a sub-group of subjects in a larger phase III trial. Either approach is acceptable and has been used successfully by other sponsors. The sponsor is encouraged to submit a protocol to the FDA for review prior to initiating the study with sufficient lead time to allow the Agency to provide comments.

(b) (4)

Clinical/Biostatistics

You provided the following list of the clinical trials conducted with your product

Study No.	Protocol Title	No. Subjects	No. Subjects per Arm
V-101-ROSE-201	A Single-center, Two-way Crossover Relative Bioavailability Study of V-101 (oxymetazoline) Cream 0.15% Administered Topically and Oxymetazoline HCl Solution (Afrin®) 0.05% Administered Intranasally to Subjects with Moderate to Severe Erythematous Rosacea	22	22
V-101-ROSE-202	A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Group Study of the Dose-Response Profile of V-101 Cream in Subjects with erythematous Rosacea	183	Vehicle – N=37 0.01% - N=37 0.06% - N=37 0.1% - N=37 0.15% - N=35
V-101-ROSE-205	A Single-center, Two-way Crossover Relative Bioavailability Study of V-101 (oxymetazoline) Cream 0.5% Administered Topically and Oxymetazoline HCl Solution (Afrin®) 0.05% Administered Intranasally to Subjects with Moderate to Severe Erythematous Rosacea	28	28
V-101-ROSE-206	A Randomized, Double-Blind, Vehicle-Controlled, Parallel-Group Study of the Pharmacodynamic Profile of V-101 Cream in Subjects with Erythematous Rosacea	85	Vehicle – N=27 0.15% - N=29 0.5% - N=29
V-101-HDSS-101	21-Day Cumulative Irritation Test	35	A - Petrolatum B - Vehicle C - 0.5% SLS D - 0.5%
V-101-HDSS-102	Repeat Insult Patch Test	225	Vehicle 0.5%
V-101-HDSS-103	Phototoxicity Test	32	32
V-101-HDSS-104	Photocontact Allergy Test	49	Vehicle 0.5%

Your product, which is not curative, will be used chronically. However, you conducted only one repeat-dose study (ROSE 202), which did not include the proposed concentration (0.5%).

You propose once daily dosing with 0.5% cream but you did not explore other dosing frequencies. Data from study ROSE-206 show that the effect of your product lasts less than 10 hours. Additionally, your timepoints for assessment (3, 6 and 8 hrs) do not cover the dosing interval you propose.

Question 6:

The Sponsor requests the Division's comments on the adequacy of the study design to make a determination of safety and efficacy of V-101 cream for the treatment of erythema in patients with erythematous rosacea.

Response:

You propose randomized, double blind, vehicle controlled, parallel group design for Phase 3 trial using protocol ROSE 301. We have the following comments regarding adequacy of your protocol:

- We do not agree with [REDACTED] (b) (4) (see response on Q8)
- Clarify which secondary end points you plan to analyze and which ones you intend for labeling. Secondary endpoints intended for labeling should be clinically meaningful and few in number and their analysis should include adjustment for multiplicity to control Type I error.
- Your indication and primary endpoint focus on one manifestation of rosacea (erythema), but exacerbation or progression of the disease itself is not assessed. Add assessment of global disease severity.
- Safety assessment should include possible manifestations of vasoconstriction such as unwanted streaking or blanching of skin or excessive/unwanted whitening.
- The no treatment follow-up period should be longer than one week to document potential recurrence of erythema to baseline levels. It appears that you estimated that time to be 3 weeks according to the washout period in Study ROSE-201.

Meeting Discussion:

The Agency clarified that the assessment of Global Disease Severity is a safety assessment.

Question 7:

The Sponsor intends to use a composite endpoint. Does the Division have any comment on the Clinician's Erythema Assessment scale and Subject's Self Assessment scale identified on Page 9 of this document?

Clinician's Erythema Assessment		Subject's Self Assessment	
Grade	Description	Grade	Description
0	Clear skin with no signs of erythema	0	Clear of unwanted redness
1	Almost clear, slight erythema	1	Nearly clear of unwanted redness
2	Mild erythema, definite redness	2	Somewhat more redness than I prefer
3	Moderate erythema, marked redness	3	More redness than I prefer
4	Severe erythema, fiery redness	4	Completely unacceptable redness

Response:

For scales used to measure the primary efficacy endpoint, content validity, construct validity, reliability and ability to detect change need to be established. Your proposed scales (CEA and

SSA) may provide good basis for erythema evaluation, however the comprehensive internal consultative review of your scales is pending.

The following is our comment on submitted statistical validation of the scales from the meeting package.

You submitted the validation study report (Study V-101-ROSE-201) and requested for the Agency comments on the validity of the proposed CEA and SSA scales. Please note that you enrolled subjects with a rating of at least 3 on both CEA and SSA however intended to validate the full 5-point scales. Furthermore, you validated the scale by conducting the statistical testing with the null hypothesis that the correlation coefficient between the scales equal to zero. It should be noted that the two subjective measurements (CEA and SSA) are expected to be highly correlated with the objective measurements (chromameter measurement). However, rejection of the null hypothesis of no correlation (correlation coefficient equals zero) does not imply the high correlation between the scales. From the study results you reported, only moderate correlations are observed.

Question 8:

The Sponsor requests the Division's comments on the statistical methods designed to determine efficacy.

Response:

You submitted a Phase 3 protocol to the Agency for comments. Your protocol is not sufficiently clear on the primary endpoints used for establishing efficacy claim. It appears that you propose a composite primary end point assessed on day 28 and defined as averaged reduction from pre-application baseline of more than 1.5 points across the hour 3, 6, and 8 for both scales to qualify as responder.

For the components of the composite endpoint, namely, (i) CEA and (ii) SSA, a minimum of 2-grade reduction from the corresponding measurements baseline is needed when using 5-point scale in order to declare a success. A smaller grade reduction is difficult to appreciate as clinically significant. Using 2-grade reduction ensures that subjects with moderate to severe disease will achieve clear or almost clear status at the end of the treatment if they are true responders. We recommend that composite success be defined as 2-grade improvement on both CEA and SSA at each time point.

You propose once-daily dosing, but propose time points for success assessment only at hour 3, 6 and 8. Provide additional assessment timepoints (e.g. hours 12, 15 and 24) to characterize the performance of your product over the dosing interval.

The success rate may change over 28 days and we recommend that you consider composite success not only at day 28 but also on day 14 for which you have planned to collect data.

Furthermore, as the efficacy measurements are collected at multiple time points you might also propose a statistical analysis approach that takes into account the repeated measurements.

The ITT population including all randomized subjects should be used for the primary analysis. In addition, you stated the sample size calculation is based on the observed treatment differences of a similar study however such information was not provided. You are at risk of under powering your Phase 3 study if inaccurate estimates are used to calculate the sample size.

Meeting Discussion:

The Agency requested that the sponsor conduct the efficacy evaluation over a minimum of 12 hours at equally spaced intervals (e.g., 3, 6, 9, 12 hours). The sponsor will consider using equally spaced intervals along with repeated measurements to assess efficacy.

The Agency reiterated that a 2 grade reduction is needed at each timepoint for a subject to be classified as a responder.

The sponsor proposed to assess the performance of their product at additional timepoints up to 24 hours in the PK study.

Question 9:

The Sponsor requests the Division's comments on the adequacy of the design and analysis of the long-term safety study.

Response:

You propose open label study of safety and efficacy of the to-be marketed formulation of V-101 cream 0.5% in subjects with erythematous rosacea. You plan to enroll 300-600 subjects on therapy for 6 months and 100 subjects on therapy for 12 weeks.

It is difficult to interpret data from an open-label, uncontrolled trial. Therefore we recommend that you include a vehicle control to allow discrimination of subject outcomes caused by the drug from those resulting from other factors. We will need information about rebound, tachyphylaxis, and duration of effect upon withdrawal; consider incorporation of randomized withdrawal in your study design. Include vital signs (HR, BP), and investigator and subject assessments of global disease severity in your safety assessments.

Meeting Discussion:

The sponsor stated that retention would be challenging with a one year vehicle controlled study; they proposed a design in which subjects in the vehicle arm would roll over to active treatment after an interval of time. The Agency requested that they submit their proposal to the IND for review.

Question 10:

The Sponsor intends to submit [REDACTED] (b) (4)
[REDACTED] Will the Division accept these data in accord with this plan?

Response:

No, safety data base including long term safety data should be complete at the NDA filing.

Question 11:

The following human dermal sensitization safety studies have been completed

1. Protocol No. V-101-HDSS-101: 21-Day Cumulative Irritation Test
2. Protocol No. V-101-HDSS-102: Repeat Insult Patch Test.
3. Protocol No. V-101-HDSS-103: Phototoxicity Test.
4. Protocol No. V-101-HDSS-104: Photocontact Allergy Test.

The Sponsor does not intend to conduct additional work with regard to Human Dermal Safety studies. Does the Division have any comments?

Response:

Generally, the appropriate topical safety studies are cumulative irritancy (not less than 30 evaluable subjects), contact sensitization (not less than 200 evaluable subjects), photoallergenicity (not less than 50 evaluable subjects, and phototoxicity (not less than 30 evaluable subjects). Dermal safety studies are conducted with the final to-be-marketed drug products.

It appears that you conducted appropriate studies. The adequacy of your dermal safety studies will be review issue.

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. We remind you of the Pediatric Research Equity Act of 2007 which requires all applications for a new active ingredient, new dosage form, new indication, new route of administration, or new dosing regimen to contain an assessment of the safety and effectiveness of the drug for the claimed indications in all relevant pediatric subpopulations unless this requirement is

waived or deferred.

5. 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.
6. 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.
7. You are encouraged to request a Pre-NDA Meeting at the appropriate time.

DATA STANDARDS FOR STUDIES

Applicants will be expected to include electronic study data (data tabulation and analysis datasets) as part of the submission for an NDA or BLA. The Study Data Specifications document, located at the following link, describes the submission of these data:

<http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM199759.pdf>. CDER strongly encourages IND sponsors to consider the implementation and use of data standards for the submission of applications for 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 studies. CDER has produced a web page that provides specifications for sponsors regarding implementation and submission of 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 the following link:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm>

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

/s/

JILL A LINDSTROM on behalf of SUSAN J WALKER
08/09/2011