CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761051Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 101843

MEETING MINUTES

Kyowa Kirin Pharmaceutical Development, Inc.
Attention: Jennifer Jones, MS, RAC
Senior Manager, Regulatory Affairs
212 Carnegie Center, Suite 101
Princeton, NJ 08540

Dear Ms. Jones:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for KW-0761 (mogamulizumab).

We also refer to the meeting between representatives of your firm and the FDA on July 19, 2017. The purpose of the meeting was to discuss the pivotal cutaneous T-cell lymphoma (CTCL) study and safety and efficacy data for mogamulizumab.

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, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

R. Angelo de Claro, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
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-BLA
Meeting Date and Time:	July 19, 2017; 2:00 PM – 3:00 PM (EST)
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1415 Silver Spring, Maryland 20903
Application Number:	IND 101843
Product Name:	KW-0761 (mogamulizumab)
Indication:	Treatment of cutaneous T-cell lymphoma (CTCL) in patients who have received at least one prior systemic therapy
Sponsor/Applicant Name:	Kyowa Kirin Pharmaceutical Development, Inc.
Meeting Chair:	R. Angelo de Claro, MD
Meeting Recorder:	Kris Kolibab, PhD

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP), Division of Hematology Products (DHP):
Albert Deisseroth, MD, PhD, Supervisory Associate Division Director
R. Angelo de Claro, MD, Clinical Team Leader
Yvette Kasamon, MD, Clinical Reviewer
Kris Kolibab, PhD, Senior Regulatory Project Manager

OHOP, Division of Hematology Oncology Toxicology (DHOT):
Christopher Sheth, PhD, Supervisory Pharmacologist/Toxicologist
Michael Manning, PhD, Toxicologist

Office of Biostatistics, Division of Biometrics V (DBV):
Yuan Li Shen, DPH, Statistics Team Leader
Yaping Wang, PhD, Statistics Reviewer

Office of Biotechnology Products (OBP), Division of Biotechnology Research and Review (DBRR III):
Cecilia Tami, PhD, Product Quality Team Leader
Jun Liu, PhD, Product Quality Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V:
Olanrewaju Okusanya, PharmD, MS, Pharmacologist
Vicky Hsu, PhD, Pharmacologist

Office of Pharmaceutical Quality (OPQ), Division of Microbiology Assessment (DMA):
Monica Commerford, PhD, Microbiology Reviewer
Virginia Carroll, PhD, Microbiology Reviewer

Center for Devices and Radiological Health (CDRH), Office of In Vitro Diagnostics and Radiological Health:
Donna Roscoe, PhD, Branch Chief

SPONSOR ATTENDEES
Floyd Fox, PhD, Senior Director, Translational Research
Douglas Greene, PhD, FCP, Senior Director, Clinical Pharmacology
Jeff Humphrey, MD, Chief Medical Officer
Jennifer Jones, MS, RAC, Senior Manager, Regulatory Affairs
Mollie Leoni, MD, Director, Medical Sciences
Stephen Letrent, PharmD, PhD, Senior Vice President, Drug Development
June (Junfang) Li, PhD, Vice President, Biometrics
Mayumi Mukai, MS, Senior Manager, Clinical Pharmacology
Dalal Nesheiwat, PharmD, Director, Drug Development
Naoki Sawada, Project Leader, Oncology R&D
Snehal Shah, PharmD, Vice President, Regulatory Affairs
Phil Weatherill, Vice President, Pharmacovigilance
(b) (4)

1.0 BACKGROUND

Kyowa Kirin Pharmaceutical Development, Inc. (KKD) requested a type B meeting with the FDA on May 26, 2017, to discuss the pivotal cutaneous T-cell lymphoma (CTCL) study and safety and efficacy data for mogamulizumab. KKD is developing mogamulizumab in the United States (US) and Europe for CTCL and various other oncology indications which include ATL and solid tumors. KKD has collaborated with the Agency throughout the CTCL development.

Mogamulizumab is a recombinant, humanized, monoclonal antibody (mAb) composed of complementarity-determining regions (CDRs) derived from mouse anti-human CC chemokine receptor 4 (CCR4) mAb and framework regions, and constant regions derived from human immunoglobulin G subclass 1 (IgG1).

FDA sent Preliminary Comments to Kyowa Kirin Pharmaceutical Development, Inc. on July 12, 2017.

2. DISCUSSION

2.1. Clinical Efficacy

Question 1:
The Sponsor proposes that the single pivotal, adequate and well-controlled Study 0761-010 is sufficient to establish efficacy for mogamulizumab treatment in CTCL. Understanding that the Agency's final opinion regarding the results of this study can only be determined after a full review of the data that accompanies the application, based on the rationale below, does the Agency agree in principle that these data support filing and registration?

FDA Response to Question 1:
The data appear adequate to support a marketing application. Decisions about filing, approvability, and the specific indication will be made after receipt of the BLA.

Meeting Discussion:
No discussion occurred.

Question 2:
Based on the results of Study 0761-010, testing to identify CCR4-positive patients prior to treatment for CTCL does not have clinical utility. The Sponsor proposes that CCR4 expression status does not need to be determined prior to treatment with mogamulizumab for CTCL. Does the Agency agree that a companion diagnostic is not required?

FDA Response to Question 2:
Assuming the >95% prevalence of CCR4 positive cases observed in the Study 0761-010 is representative of the intended population, a companion diagnostic does not appear to be required. However, the need for a companion diagnostic will be a review issue. In the BLA, include published data on the prevalence and range of CCR4 expression specifically in MF/SS.

Meeting Discussion:
No discussion occurred.

Question 3:
The Sponsor proposes that the analyses and presentation of data proposed for the Summary of Clinical Efficacy (M2.7.3) fulfill the requirements of 21 CFR §314.50(d)(5)(v) for an Integrated Summary of Efficacy (ISE). Does the Agency agree with this approach?

FDA Response to Question 3:
Yes.

Meeting Discussion:
No discussion occurred.

2.2. Clinical Safety

Question 4:
The Sponsor proposes that the safety for use of mogamulizumab in the treatment of subjects with CTCL is established by pivotal Study 0761-010. The safety profile is further supported by other clinical trials for the use of mogamulizumab in other indications and post-marketing data. Understanding that the Agency's final opinion regarding the results of these data can only be determined after a full review of the application, based on the rationale below, does the Agency agree in principle that these data support filing and registration?

FDA Response to Question 4:
Refer to response to Question 1.

- In the ISS,
  a. Include a comprehensive characterization of dermatologic toxicity associated with mogamulizumab. Some cases of drug eruption may be challenging to differentiate from CTCL. Include description of how such drug eruptions manifest, the time to first onset, treatment measures and responsiveness to treatment. We recommend flagging of dermatologic toxicities in the AE dataset.
  b. Include a comprehensive characterization of infusion-related reactions associated with mogamulizumab, including time course, responsiveness to treatment and preemptive measures, and risk and timing of recurrence.

- To facilitate review of safety, please follow the recommendations on ADAE and ADLB dataset structure, as communicated in the (b) (4)

Meeting Discussion:
The Sponsor agrees with the Agency's requests for comprehensive characterization of dermatologic toxicities and infusion-related reactions (IRRs). The Sponsor agreed to include a dermatologic toxicity flag and IRR flag in the AE datasets.

Question 5:
Does the Agency agree with the Sponsor's approach for the ISS and SCS?

FDA Response to Question 5:
No.

- You propose a data cut of 12/31/2016 for the safety analysis for study 0761-010. For the primary study, the cut-off date for safety should be no more than 6 months prior to the BLA submission. Although you state that the additional safety data since that time is minimal, 68 subjects had ongoing treatment. Update the safety for study 0761-010 prior to BLA submission, not with the day 120 safety update. We recommend to use the June 2017 cut-off date for safety for the original BLA submission, assuming a September 2017 BLA submission.

- In the draft SAP for the ISS, Section 4.2 proposes to re-count patients as different patients if they were re-administered KW-0761 after relapse. Include safety with the initial treatment course only.

Meeting Discussion:
The Agency accepts the Sponsor's proposal to have a June 2017 safety data cutoff for the BLA submission scheduled for September 2017 for Study 010. The Agency also accepts the Sponsor's proposal for a September 2017 safety data cutoff for the 120 day safety day update.

The Sponsor's proposal to have a CSR addendum is acceptable.

The Sponsor accepts the Agency's request to submit the December 2016 and June 2017 safety data sets as comprehensive stand-alone data sets, and to have the datasets be clearly distinguishable in the BLA submission.

Question 6:
The Sponsor acknowledges the importance to characterize mogamulizumab safety in context of allogeneic HSCT and has incorporated Agency feedback (Type C Safety Proposal from 02 Feb 2017, Sequence 0361) within the approach outlined below for summarizing post-allogeneic-HSCT information and complications for CTCL patient who received mogamulizumab and subsequently had and/or have a transplant. Does the Agency agree with the proposed approach for the application?

FDA Response to Question 6:
Yes.

Meeting Discussion:
No discussion occurred.

Question 7:
Does the Agency agree with the Sponsor's approach for the Day 120 Safety Update?

FDA Response to Question 7:
No. Refer to response to Question 5. Assuming a June 2017 initial cut-off date for safety for a September 2017 BLA submission, we recommend a September 2017 cut-off date for the updated safety analysis.

Meeting Discussion:
Please refer to discussion in question 5.

2.3. Clinical Pharmacology and Immunogenicity

Question 8:
Does the Agency agree the completed overall clinical pharmacology program as presented is adequate for filing and registration?

FDA Response to Question 8:
Yes, your clinical pharmacology program appears acceptable. See additional comments below regarding our general expectations for your BLA submission.

Meeting Discussion:
No discussion occurred.

Question 9:
Does the Agency agree with the Sponsor's proposed approach for the Integrated Summary of Immunogenicity (ISI), as described below?

FDA Response to Question 9:
Although the proposed approach for Integrated Summary of Immunogenicity (ISI) appears reasonable, it is not clear if all the required information related to the immunogenicity is included in your ISI. It is also not clear where your ISI will be reported in the eCTD format. For your BLA provide the ISI report in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This Integrated Summary of Immunogenicity should provide:

a) An immunogenicity risk assessment specific to your product;
b) Details on the tiered immunogenicity strategy that you followed in your clinical program, and validation summaries for the various immunogenicity assay methods you developed in your program;
c) Links to method development and validation reports for the immunogenicity assays used in your clinical studies, particularly those used to test immunogenicity samples from your pivotal clinical study(ies);
d) Immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed;
e) Summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results of your correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data;
f) Traceability of drug product lots used in all your clinical studies.

In addition, we acknowledge that you are developing a new ADA assay with improved drug tolerance due to the high rate of inconclusive samples in your current ADA screening assay. Please provide a timeline for submission of final screening assay validation report, and subsequent ADA testing of clinical study samples. In addition, clarify whether your neutralizing antibody assay also suffers from poor drug tolerance, and if so, describe how this impacts your testing strategy and how you intend to ensure accurate measurements of neutralizing antibodies in you clinical samples.

Meeting Discussion:
The Sponsor outlined their proposal for submission of immunogenicity data which would include submission of immunogenicity results for samples obtain December 2016 to June 2017 with the 120-day safety update. In general, the Sponsor proposal is acceptable to the Agency. The Agency recommends the sponsor submit "120 day safety

update" within 90 days of the original BLA submission in anticipation of a priority review.

2.4. Nonclinical

Question 10:
Does the Agency agree the completed overall nonclinical program as presented in Appendix 7 is adequate for filing and registration?

FDA Response to Question 10:
The nonclinical program appears sufficient to support filing a marketing application. Approvability may only be determined after review of your BLA.

Meeting Discussion:
No discussion occurred.

2.5. Content and Format of the Proposed Filing

Question 11:
Does the Agency agree that the overall contents of the proposed application as outlined below are adequate to support a filing and substantive review?

FDA Response to Question 11:
No. A risk management plan is missing from the outline, but is required in Module 1. Refer to response to Question 1 for additional comments. For additional product quality microbiology and statistics comments, please see the end of the document.

Meeting Discussion:
The Sponsor described core elements of the RMP which would assessed for known and potential risks. The Sponsor proposes an RMP primarily consisting of labeling and pharmacoviligance which would be described in Module 1. The Agency accepts this proposal and recommended the Sponsor to include an assessment of REMS in the RMP.

Question 12:
The Sponsor understands the Agency's final opinion regarding the benefit risk of mogamulizumab for the proposed CTCL indication can only be determined after a full review of the application. To allow this substantive review does the Agency agree in principle that the data proposed to be included in the filing is appropriate to allow an assessment of benefit risk in CTCL patients who have failed one prior systemic therapy?

FDA Response to Question 12:
The ORR with mogamulizumab of 29% is similar to that described with available therapies. Comparison of efficacy and benefit/risk of mogamulizumab versus available therapies is limited by differences in response criteria. To inform the benefit/risk assessment, in the BLA,

- Include an analysis of response rate, BOR, and DOR for mogamulizumab and vorinostat in the skin compartment only (e.g. SWAT), in addition to summarizing efficacy in other individual compartments, per investigator and per IRC.
- Explain the inferior performance of the control arm compared to published experience with vorinostat.

Meeting Discussion:
The Sponsor plans to address the above issues with the BLA submission.

ADDITIONAL CLINICAL COMMENTS:

- Comment on the anticipated submission timelines for the CTCL (b) (4)

Meeting Discussion:
The Sponsor plans to submit the CTCL application at the end of September 2017.

The Sponsor agreed with the Agency recommendation to include a translated version of the Japanese prescribing information for mogamulizumab with the application submission.

ADDITIONAL STATISTICAL COMMENTS:

- The SAS programs that are used to create the derived datasets for the efficacy endpoints and the SAS programs that are used for efficacy data analysis and for the efficacy results to be included in the label should be included in the BLA submission.
- We request that proportional hazard (PH) assumption for PFS analysis should be evaluated. If the PH assumption is not met, please plan to perform additional analyses to address the issues. These additional analyses should take the potential confounding factors into account because the non-PH may be caused by potential intervention treatment. We consider such analyses as post hoc evaluation and will be a review issue.

Meeting Discussion:
The Agency provided advice on assessing the PH assumption and providing justification if non-PH is demonstrated.

ADDITIONAL CLINICAL PHARMACOLOGY COMMENTS:

Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for selecting the doses and dosing regimen used in the registration trial(s) to support your marketing application? Identify individuals who required dose modifications, and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.
2. What are the exposure-response relationships for efficacy, safety and biomarkers?

3. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?
4. What is the impact of immunogenicity on exposure, efficacy and safety?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

5. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.
6. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.
7. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
    - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
    - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
8. Submit the following for the population pharmacokinetic analysis reports:
    - Standard model diagnostic plots
    - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line
    - Model parameter names and units in tables.
    - Summary of the report describing the clinical application of modeling results.

    Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.
9. Submit the following information and data to support the population pharmacokinetic analysis:
    - SAS transport files (*.xpt) for all datasets used for model development and validation
    - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets
    - Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model.

Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt)

10. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

Product Quality Microbiology Additional Comments:

We are providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your BLA submission.

1. All facilities should be registered with FDA at the time of the BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). The facility should be in operation and manufacturing the product during the inspection. A preliminary manufacturing schedule for both the drug substance and drug product should be provided in Module 1 of the BLA submission to facilitate the planning of the pre-license inspections during the review cycle. Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

2. The CMC Drug Substance section of the 351(a) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The provided information should include, but not be limited, to the following:
   - (b) (4)

- (b) (4)

3. The CMC Drug Product section of the 351(a) BLA (Section 3.2.P) should contain validation data summaries (b) (4) For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry *"Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products"* http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

   a. The following information should be provided in sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.
      - (b) (4)

   b. The following study protocols and validation data summaries should be included in Section 3.2.P.3.5:
      - (b) (4)

- (b) (4)
-
-

c. The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:
   - Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry.
   - Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for (b) (4) (if applicable) and the drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers.
   - Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).
   - (b) (4)
   -

3.0 OTHER MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Agency was able to reach agreement with the Sponsor with the content of a complete application for the CTCL indication.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion on the need for a REMS was held and it was concluded that the need for a REMS will be determined during the application review.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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.

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

Office of Scientific Investigations (OSI) Requests

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

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

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

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

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

2. Please include the following information in a tabular format, *by site*, in the original NDA for each of the completed pivotal clinical trials:

a. Number of subjects screened at each site
b. Number of subjects randomized at each site
c. Number of subjects treated who prematurely discontinued for each site by site

3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, IND safety reports, or other sponsor records as described ICH E6, Section 8). This is the actual physical site(s) where documents are maintained and would be available for inspection
   b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, you may identify the location(s) and/or provide link(s) to information previously provided.
   c. The location at which trial documentation and records generated by the CROs with respect to their roles and responsibilities in conduct of respective studies is maintained. As above, this is the actual physical site where documents would be available for inspection.

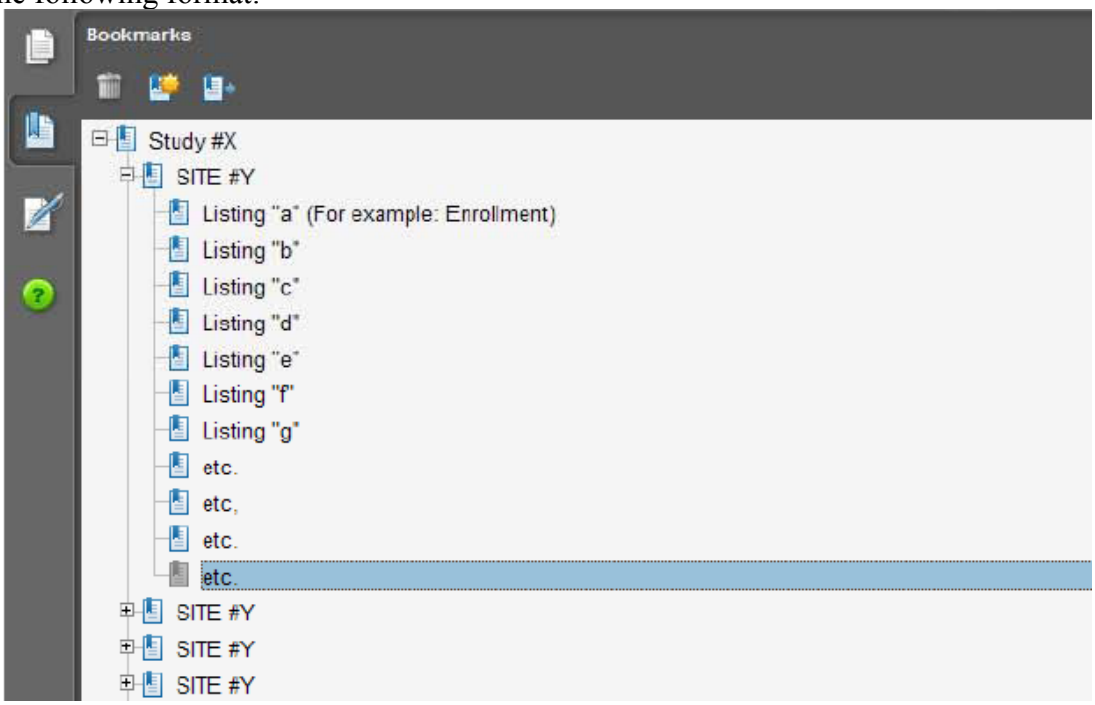
4. For each pivotal trial, provide a sample annotated Case Report Form (or identify the location and/or provide a link if provided elsewhere in the submission).
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

II. Request for Subject Level Data Listings by Site

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

i. By subject listing of concomitant medications (as appropriate to the pivotal clinical trials)
j. By subject listing, of testing (e.g., laboratory, ECG) performed for safety monitoring

2. We request that one PDF file be created for each pivotal Phase 2 and Phase 3 study using the following format:



III. Request for Site Level Dataset:

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

Attachment 1

Technical Instructions:
Submitting Bioresearch Monitoring (BIMO) Clinical Data in eCTD Format

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

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

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

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

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

References:

eCTD Backbone Specification for Study Tagging Files v. 2.6.1
(http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf)

FDA eCTD web page
(http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm153574.htm)

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The sponsor provided no slide deck or handouts for the meeting.

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

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ROMEO A DE CLARO
07/20/2017