CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209529Orig1s000

ADMINISTRATIVE AND CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 058135

MEETING MINUTES

Astellas Pharma Global Development, Inc.
Attention: Jennifer M. LaMora, M.S., R.A.C.
Sr. Manager, Global Regulatory Affairs
1 Astellas Way
Northbrook, IL 60062

Dear Ms. LaMora:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for YM905 (solifenacin succinate) tablets.

We also refer to the meeting between representatives of your firm and the FDA on October 14, 2016. The purpose of the meeting was to discuss the submission plans for: 1) a new drug application for solifenacin oral suspension for the treatment of neurogenic detrusor overactivity (NDO) in pediatric patients, 2) a supplemental new drug application for VESIcare, and 3) a request for pediatric exclusivity determination.

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, please call Nenita Crisostomo, Regulatory Health Project Manager at (301) 796-0875.

Sincerely,

{See appended electronic signature page}

Mark S. Hirsch, M.D.
Medical Team Leader
Division of Bone, Reproductive and Urologic Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	October 14, 2016
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1421 Silver Spring, MD 20903
Application Number:	IND 058135
Product Name:	YM905 (solifenacin succinate) tablets
Indication:	treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older
Sponsor/Applicant Name:	Astellas Pharma Global Development, Inc.
Meeting Chair:	Mark S. Hirsch, M.D.
Meeting Recorder:	Nenita Crisostomo

FDA ATTENDEES

Christine Nguyen, M.D. – Deputy Director for Safety, Division of Bone, Reproductive and Urologic Products (DBRUP)
Mark Hirsch, M.D. – Medical Team Leader, DBRUP
Guodong Fang, M.D. – Medical Officer, DBRUP
Jordan Dimitrakoff, M.D. – Medical Officer, DBRUP
Mark Seggel, Ph.D. – CMC Lead, Division of New Drug Products II (DNDPII), ONDP
James Laurenson, M.S. – Toxicologist/Environmental Assessment Reviewer, ONDP
Doanh Tran, Ph.D. – Clinical Pharmacology Team Leader, Division of Clinical Pharmacology III (DCPIII), Office of Clinical Pharmacology (OCP)
Mukesh Summan, Ph.D., DABT – Pharmacology/Toxicology Supervisor, DBRUP
Laurie McLeod-Flynn, Ph.D. – Pharmacology/Toxicology Reviewer, DBRUP
Jia Guo, Ph.D. – Statistician, Division of Biometrics III (DBIII)
Nenita Crisostomo – Regulatory Health Project Manager, DBRUP
John Alexander, M.D. – Acting Deputy Director, Division of Pediatric and Maternal Health (DPMH)
Mona Khurana, M.D. – Medical Team Leader, DPMH
Carolyn L. Yancey, M.D. – Medical Officer, DPMH
Meshaun Payne, M.H.C.A., B.S.M.T. – Regulatory Health Project Manager, DPMH
Roy Blay, Ph.D. – Reviewer, DGCP, Office of Scientific Investigation (OSI)

FDA ATTENDEES (continued)

Somya Dunn, M.D. – Risk Management Analyst, Division of Risk Management (DRISK), Office of Surveillance and Epidemiology (OSE)

ASTELLAS PHARMA GLOBAL DEVELOPMENT, INC.

Jeremy PW Heaton, MD, BA, MASc, MBA, FRCS(C) – Vice President, Development Medical Science, Urology/Nephrology Development
Martina Agema, MSc, MPharmDev – Senior Global Development Project Director, Therapeutic Area – Urology
Donald Newgreen, PhD, UP PharmMed – Medical Director, Medical Science, Urology
Annelieke K. Peters, PhD, ERT – Associate Scientific Director, Toxicologist, Drug Discovery Science and Management
Martin den Adel, MSc, MPharMed – Science Associate Director, Clinical Pharmacology and Exploratory Development
Stacey Tannenbaum, PhD, FISoP – Director Pharmacokinetics, Modeling, and Simulation, Clinical Pharmacology and Exploratory Development
Robert Snijder, MSc-Associate Director Biostatistics, Data Science
Billy Franks, PhD – Director Biostatistics, Data Science
Klaudia Traudtner – Medical Safety Director, Urology, Nephrology and Metabolic Global Therapeutic Area
Karin Vlugt-Wensink – Associate Director CMC, Project Product Management
Frank Verheggen – Director, Development Operations Clinical Science
Jim Keirns, PhD – Vice President, Senior Clinical Pharmacology Fellow, Clinical Pharmacology and Exploratory Development
Pamela Bradt, MD, MPH – Executive Medical Director, Urology, Medical Affairs
Judy Kannenberg, MBA, RAC – Executive Director, Therapeutic Area Head – Frontier Medicine, Regulatory Affairs
Jena Giese-Pagac – Associate Director, Americas Regional Therapeutic Area Head (Acting) – Urology,Regulatory Affairs
Jennifer LaMora, MS, RAC – Senior Manager, Regulatory Affairs

(b) (4)

1 BACKGROUND

VESIcare® (solifenacin succinate), 5 and 10 mg tablets, were approved on November 19, 2004, under NDA 021518 for the treatment of overactive bladder in adult patients. The approval for NDA 021518 included a postmarketing commitment for pediatric studies under PREA for "the treatment of overactive bladder in pediatric patients aged 5 years to 11 years and adolescents aged 12 years to 17 years." On January 20, 2006, an agreement was reached to enroll only pediatric patients with overactive bladder due to known neurological disease (referred to as neurogenic detrusor overactivity, or NDO).

A Written Request (WR) for the evaluation of solifenacin in pediatric NDO patients was issued on July 27, 2012, with subsequent amendments dated September 14, 2012, April 17, 2014, and December 12, 2014. Under the terms of the WR, clinical studies 905-CL-079 and 905-CL-047 have been conducted: a pediatric pharmacokinetic study (Study 1) and a pediatric safety and

efficacy study (Study 2), respectively. An oral suspension was developed to facilitate swallowing and accuracy of dosing. Astellas requested this meeting to discuss the adequacy of their clinical and nonclinical programs to support a new NDA for the oral suspension, a supplemental NDA for VESIcare tablets, and a path towards pediatric exclusivity.

Preliminary comments and responses to the specific questions were sent via email to the Sponsor on October 11, 2016. On October 13, 2016, the Sponsor responded in an email that they wanted to discuss the FDA responses to Questions 3, 4, 5, 6, 8, and 10.

2 DISCUSSION

Sponsor's Opening Remarks: The Sponsor stated that there is an unmet medical need in the treatment of pediatric neurogenic detrusor overactivity (NDO). The Sponsor also stated that solifenacin oral suspension is expected to be of benefit in the treatment of this condition. The Division acknowledged the Sponsor's effort in completing their pediatric solifenacin drug development program, and agreed with Sponsor that the availability of additional safe and effective treatment options for pediatric NDO would aid management of the condition.

2.1 Chemistry, Manufacturing and Controls

Question 1: Does the Agency agree with the proposal to cross-reference to NDA 021518 for drug substance information for solifenacin in the planned NDA for solifenacin oral suspension?

FDA Response: Yes, it is acceptable to cross-reference NDA 021518 for information on the drug substance. If changes have been made to the drug substance information since the time of original approval, provide specific references to the most current information (e.g., provide the supplement number[s] with submission and approval dates).

Discussion at the meeting: No further discussion.

2.2 Nonclinical

Question 2a: Does the Agency agree that the appropriate nonclinical studies were conducted to support administration of solifenacin in the pediatric population aged 2 years and older?

FDA Response: Yes.

Discussion at the meeting: No further discussion.

Question 2b: Does the Agency agree with the proposed (b) (4) (b) (4)

FDA Response: No, we do not agree. (b) (4) (b) (4)

Reference ID: 4616891

(b) (4)

Discussion at the meeting: No further discussion.

2.3 Clinical

Question 3: Proposed Indication - The proposed indication for solifenacin oral suspension is "treatment of neurogenic detrusor overactivity in pediatric patients aged 2 years and older." The indication is supported by data from pivotal clinical studies 905-CL-047 and 905-CL-074. Does the Agency agree with the proposed indication?

FDA Response: While we agree with your proposed indication in principle, we remind you that the final indication will be based on the adequacy of the efficacy and safety data to support approval in pediatric patients as young as 2 years of age.

Discussion at the meeting: The Sponsor stated that the availability of solifenacin oral suspension to pediatric patients, including pediatric patients as young as 2 years of age, would improve the overall care of children with NDO. The Division acknowledged the Sponsor's position, and pointed out that the number of pediatric patients aged 2-5 years is small (n=21). For this reason, the Division recommends that the Sponsor provide detailed justification in the NDA for an acceptable risk/benefit profile in the younger (2 – 5 years) subgroup, including data comparisons between the younger and older pediatric age subgroups for systemic exposure, efficacy and safety.

Question 4: Integrated Summary of Efficacy - Does the Agency agree with the proposed approach for the integrated analysis of efficacy described in Module 2.7.3 and that an ISE in Module 5.3.5.3 is not required for the planned NDA?

FDA Response: No, we do not agree to the proposed approach. Instead, we request that you provide a Summary of Clinical Efficacy (SCE), including within-text tables, in module 2.7.4, and an abridged Integrated Summary of Efficacy (ISE) in module 5.3.5.3. The abridged ISE may refer the reader to the SCE for text, but should provide tables, appendices and the pooled datasets for clinical studies 905-CL-047 and 905-CL-074.

Discussion at the meeting: The Sponsor agreed with the above recommendations, and clarified that efficacy data from pediatric patients aged 2-18 years would be included in the SCE. While efficacy data from the four (4) pediatric patients aged less than 2 years of age from Study 905-CL-074 would not be included in the SCE, these data would be included in the Efficacy section of the individual study report. The Division stated that this plan was acceptable.

Question 5: Integrated Summary of Safety - Does the Agency agree with the proposed safety analyses to be presented in the ISS in Module 5.3.5.3 for use of solifenacin oral suspension in the treatment of NDO in pediatric patients aged 2 years and older?

FDA Response: No. While you may provide integrated safety data for studies 905-CL-076, 905-CL-077, 905-CL-074 and 905-CL-047 (the "*Phase 3"* population), we remind you that the target population for the indication and the primary safety population in the ISS should be the "*Phase 3 NDO"* population (studies 905-CL-047 and 905-CL-074 only). We remind you that (b) (4)

In addition, the ISS should include a detailed subsection concerning the observed increases in the corrected QT interval in clinical trials.

Discussion at the meeting: Astellas expressed their understanding that labeling will focus only on the NDO population. In the planned application, the Sponsor proposed to provide the ISS in a manner similar to their plan for providing the ISE, and the Division agreed. The Division reiterated that the key safety data for risk/benefit analysis comes from the phase 3 NDO Studies 074 and 047, and the Sponsor agreed. The Division stated that all available safety data, including safety data from the larger safety database that includes pediatric idiopathic OAB patients, would be reviewed and considered for potential safety signals. The Sponsor understood the Division's plan for review of the safety data.

The Sponsor informed the Division that a stand-alone research report on QT would be provided in Module 5 and the Division agreed.

Question 5: Dosing and Administration – Does the Agency agree with the plan for presentation of the dosing and administration information for use of solifenacin oral suspension in the pediatric population in Section 2.1 of the prescribing information?

FDA Response: We acknowledge that the proposed dosing in Section 2.1 (of labeling) is based on physiologically-based pharmacokinetic (PBPK) modeling analyses, which is different from the dosing used in the clinical studies. During our review of the NDA, we will evaluate whether the proposed dosing based on PBPK modeling is supported by the available data. For that reason, the presentation of pediatric dosing information in Section 2 of labeling will be a review issue.

Additional comment: (b) (4) (b) (4) it does not appear that the effect of food on the bioavailability of the to-be-marketed formulation (formulation B) was evaluated in a food effect study. Provide information (b) (4).

Discussion at the meeting: In regard to the effect of food on bioavailability of the formulation B, the Division asked how the Sponsor planned to use data from studies using formulation A to address the food effect of formulation B. The Sponsor stated there was no food effect data for formulation A, nor for the tablet formulation. In addition, the Sponsor stated that formulation B, formulation A, and the tablet had been demonstrated to be bioequivalent under fasting condition. The Sponsor added that population pharmacokinetic (PK) data, which have not yet been submitted, showed that clearance is similar in following two studies: 1) Phase 3 Study 905-CL-047, where subjects were dosed

without regards to meals, and 2) Phase 1 Study 95-CL-079, where subjects were dosed under fasting condition. The Sponsor further clarified that both Phase 3 trials (Studies 95-CL-047 and 95-CL-074) were dosed without regards to meals and that the drug substance was not changed between formulation A and B. The change in drug product from formulation A to formulation B was (b) (4) not in the key component of the formulation.

The Sponsor was advised to submit their rationale in full detail, including information regarding the formulation and the population PK data in the NDA, to support their proposed dosing condition.

In addition, the Division informed the Sponsor that they would need to submit the codes and dataset for population PK and PBPK. The details regarding data format would be provided in a Post-Meeting Note.

Post-Meeting Note: We request that you submit codes, datasets, reports, and define files for both the population PK and PBPK analyses as part of your submission. Details on the submission of materials for the population PK analysis can be accessed at the following link: http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

For the PBPK files, we recognize that the file types (.cmpx, .lbrx, .wksx and .xlxs) are not supported by FDA at this time (2003, File Format Types Using eCTD Specifications). However, an exception has been made for these file types as it is recognized that such files are needed by reviewers for review of these types of submissions. We request that you provide the PBPK files (.cmpx, .lbrx and .wksx) in their native format and as .txt files (archival format). We understand that a PBPK XLSX file cannot be converted to .txt or another format without impacting the usefulness of the file. In the interim, we request that PBPK XLXS files be submitted in their native format and as PDF (archival format).

Question 7a: Labeling – Does the Agency agree with the proposed labeling approach for the development of separate US prescribing information for solifenacin oral suspension?

FDA Response: Yes, we agree that solifenacin oral suspension is a different dosage form developed for a new indication, and therefore, it should be submitted under a new original application that includes separate prescribing information.

Discussion at the meeting: No further discussion.

Question 7b: Labeling – Does the Agency agree with the proposed labeling approach for revisions to the US prescribing information for VESIcare (solifenacin succinate) tablets?

FDA Response: Yes, we agree with the proposed labeling approach for VESIcare tablets, including the proposed update to be consistent with the Pregnancy and Lactation Labeling Final Rule (PLLR).

Discussion at the meeting: No further discussion.

2.4 Regulatory

Question 6: Categorical Exclusion for Environmental Assessment – Does the Agency agree that the planned NDA for use of solifenacin in the pediatric population with NDO may be granted a categorical exclusion from preparing an environmental assessment under 21 CFR 25.31(b)?

FDA Response: In light of both a published aquatic plasma-based critical effect concentration (CEC) for solifenacin of 0.014 ppb (Fick et al., 2010), which is lower than the current expected introduction concentration (EIC) of (b) (4) ppb, and recent FDA Guidance (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM444658.pdf), the following additional data are needed to support the categorical exclusion: (1) calculations showing both the current EIC and the planned increase; (2) available data on measured concentrations of the substance in the aquatic environment; (3) a discussion of solifenacin's potential for aquatic effects, including those relevant to the above FDA Guidance, taking into account the substance's mechanism of action, nonclinical and other toxicity data, the plasma-based analysis noted above (including any updates), and any other relevant information such as available environmental risk assessments (e.g., from literature, for EMA). Submission of this information prior to the planned application will assist in the timely initiation of any needed assays should an environmental assessment be needed. Reference: Fick, J., Lindberg, R.H., Tysklind, M. and Larsson, D.J., 2010. Predicted critical environmental concentrations for 500 pharmaceuticals. *Regulatory toxicology and pharmacology*, 58(3), pp.516-523.

Discussion at the meeting: The Sponsor asked whether this information could be submitted as an amendment to the IND 058135. The Division agreed.

Post-Meeting Note: Submission of the requested Environmental Assessment data to the IND will expedite the review. We remind you, however, to submit the same data in the NDA.

Question 7: Proposed NDA Content – Datasets – Does the Agency agree with the proposed plan for submission of electronic datasets in the planned NDA for solifenacin oral suspension?

FDA Response: No. See our responses to Questions 4 and 5 concerning the integrated analyses of efficacy and safety, respectively.

Discussion at the meeting: No further discussion.

Question 8: Submission Plan for Request for Pediatric Exclusivity – Does the Agency agree with the proposed submission plan and timing for the Request for Pediatric Exclusivity for VESIcare (solifenacin succinate)?

FDA Response: Yes, we agree with the submission plans for the Request for Pediatric Exclusivity. We remind you that pediatric exclusivity attaches only to existing patent protection or exclusivity that would otherwise expire nine or more months after pediatric exclusivity is granted, and FDA has 180 days from the date that the study reports are submitted to make a pediatric exclusivity determination. Therefore, it is advisable to submit the study reports at least 15 months before such patent or exclusivity is otherwise due to expire.

Discussion at the meeting: The Sponsor asked whether the planned NDA and sNDA qualify for priority reviews. The Division will provide a response to this question in a Post-Meeting Note.

The Sponsor also asked whether there is a potential for an Advisory Committee meeting during the NDA review. The Division responded that it is premature to determine whether an Advisory Committee meeting will be required because this determination is made after the NDA is submitted.

The Division inquired about the timing of the Sponsor's NDA and sNDA submission. The sponsor responded that they are planning to submit the applications in the first quarter of 2017.

Post-Meeting Note: Any application or supplement to an application under the FDA Safety and Innovation Act, Section 505A, Pediatric Studies of Drugs, proposing a labeling change as a result of any pediatric study conducted, is considered to be a priority application or supplemental application.

3 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 27, 2016, communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA V. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Finally, in accordance with the PDUFA V agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

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

4 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.

5 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.

6 SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA to applicants when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), applicants must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

7 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.				

8 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).

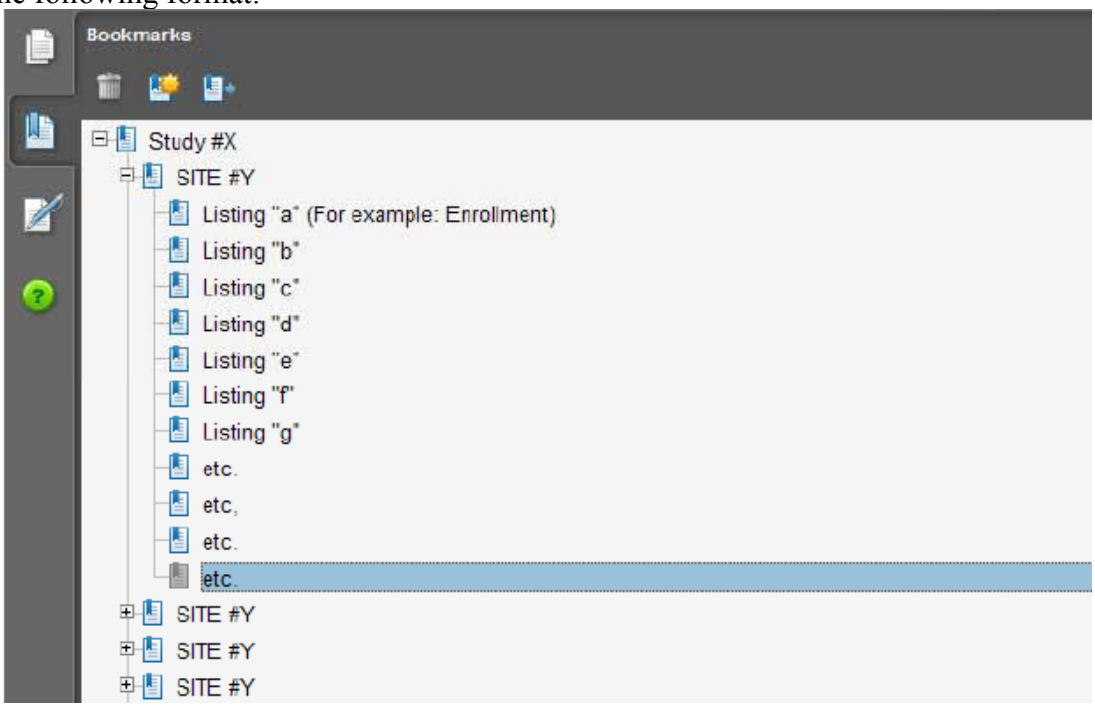
5. For each pivotal trial provide original protocol and all amendments ((or identify the location and/or provide a link if provided elsewhere in the submission).

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.

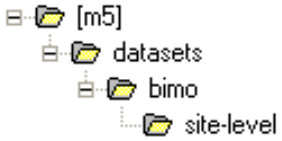
Attachment 1

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

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/s/

MARK S HIRSCH
11/07/2016

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