CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

210166Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 055078

MEETING MINUTES

Shire Development LLC
Attention: Marie Minassian
Associate Director, Global Regulatory Affairs
300 Shire Way,
Lexington MA 02421

Dear Ms. Minassian:

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

We also refer to the meeting between representatives of your firm and the FDA on August 8, 2017. The purpose of the meeting was to discuss the completion of the product development program that includes the quality, nonclinical and the clinical section of the planned NDA submission.

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 me at (240) 402 – 2786.

Sincerely,

{See appended electronic signature page}

Lawrence Allan
Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	preNDA
Meeting Date and Time:	August 8, 2017 @ 1:00 EST
Meeting Location:	WO #22, Room: 1201
Application Number:	055078
Product Name:	Prucalopride
Indication:	Chronic idiopathic constipation
Sponsor/Applicant Name:	Shire Development
Meeting Chair:	Victor Baum
Meeting Recorder:	Lawrence Allan

FDA ATTENDEES

Division of Gastroenterology and Inborn Errors Products
Donna Griebel, MD. Division Director
Victor Baum, MD. Clinical Team Leader
Irena Lavine, MD. Clinical Reviewer
Lawrence Allan. Regulatory Project Manager
Sushanta Chakder, PhD. Supervisory Nonclinical Pharmacologist
Emmanuel Akinshola, PhD. Nonclinical Pharmacology Reviewer

Division of Clinical Pharmacology III
Insook Kim, PhD. Clinical Pharmacology Team Leader
Dilara Jappar, PhD. Clinical Pharmacology Reviewer

Division of Biometrics III
Yeh-Fong Chen, PhD. Statistical Team Leader
Sara Jimenez, PhD. Statistical Reviewer

Division of New Drug Products, Office of Pharmaceutical Quality
Hitesh Shroff, PhD. Product Quality Team Leader

Office of Scientific Investigations, Office of Compliance
Susan Thompson, MD. GCP Team Leader

Susan Leibenhaut, MD. GCP Reviewer

SPONSOR ATTENDEES

Shire Development
Stewart Cole, PhD. Director, Global Regulatory Affairs Lead
Olivia Maurel, PharmD. Vice President, Global Regulatory Affairs Therapeutic Area Head
Marie Minassian, PharmA. Associate Director, Global Regulatory Affairs, US Strategy Lead
David Rush, MSc. Associate Director, Global Regulatory Affairs, CMC Lead
Michael Coffey, PhD. Associate Director, API Technical Lead
Neil Kanabar. Principal Scientist, Analytical Technology
Kathy Derakhchan, PhD. Director, Pharmacology, Nonclinical Development
Heinrich Achenbach, MD. Senior Director, Global Development Lead
Jaromir Mikl PhD, MSPH Director, Global Health Economics & Outcomes Research-Epidemiology Lead
Debra Silberg, MD, PhD. Vice President, Acting GI Therapeutic Clinical Lead
John Caminis, MD. Therapeutic Area Head, Global Drug Safety, GI & Metabolism
Manoj Thakur, MS. Associate Director, R&D Global Clinical Operations, Biostatistics

(b) (4)

BACKGROUND

On June 21, 2000, this IND was placed on partial clinical hold by the Agency due to carcinogenicity and isolated genotoxicity concerns. The sponsor decided to discontinue development of the compound and consequently submitted an inactivation request on April 14, 2004 and the request was acknowledged on July 30, 2004.

On August 1, 2012, the sponsor submitted a partial hold response to address the previous genotoxic and carcinogenicity concerns and subsequently submitted a complete response to the clinical hold issues on August 7, 2012. The clinical hold was lifted on August 31, 2012 and the IND reactivated on September 7, 2012. Since the reactivation, the sponsor and Agency have met six times to discuss the safety and efficacy plans for the NDA submission. On April 6, 2017, the sponsor submitted a preNDA meeting request, which was granted on April 12, 2017 as a type B face-to-face meeting. FDA sent Preliminary Comments to Shire on August 4, 2017.

DISCUSSION

Quality/CMC

Question 1: *Does the Agency agree to accepting* (b) (4) *stability data in the proposed container closure* (b) (4) *during the NDA review, in order to establish the product shelf life and storage conditions?* (b) (4)

For the blister packaging option, stability data may be included in the NDA submission, to support the approval of the commercialization of the SHP555 product in the USA market.

FDA Response to Question 1: No, we do not agree with your proposal. In accordance with ICH Q1A (R2), at the time of NDA submission you need to provide at least 12 months of long-term and 6 months of accelerated stability data on three drug product registration batches with desiccant. The registration batches must be manufactured by the same manufacturer using the same manufacturing process and packaged in the same container closure system as to-be marketed product.

However, it would be acceptable if you submit during the early NDA review period (i.e., no later than 3 months after the NDA submission) a minimum of 12 months of long-term and 6 months of accelerated stability data on three registration batches with desiccant. The drug product shelf life will be determined at the time of NDA review based on the stability data.

DISCUSSION: The Agency agrees with the sponsor's proposal included in their August 7, 2017 response to the preliminary comments (attached).

Sponsor states (b) (4) **FDA clarified that the sponsor may submit a CBE 0, CBE 30, or annual report with additional stability data for three batches of the drug product with desiccant in the approved container closure system. The shelf-life will be based ONLY on the long-term stability data. The shelf-life will be determined at the time of the supplement review. The sponsor may submit a PAS to get shelf life beyond long term stability testing period.**

Nonclinical

Question 2: *Does the Agency agree that the nonclinical program that includes coronary artery contractility and in vitro platelet aggregation studies (Reports #V6042M-SPD555 and #V6002M-SPD555) conducted recently (at the Agency's request), is adequate to support registration of prucalopride?*

FDA Response to Question 2: Yes, we agree that the nonclinical program appears to be adequate to support submission of the NDA.

Clinical

Question 3: *Does the Agency agree with the sponsor's plan to address the question of 'generalizability' of foreign clinical data to the US population by comparing relevant population and outcome data (eligibility criteria, demographics, efficacy results, safety results) from the Asian, EU and US clinical studies to demonstrate this is reflective of the anticipated US patient population?*

FDA Response to Question 3: The studies RCT SPD 555-302 and RCT PRU-CRC-3001 are proposed as the "pivotal trials" to establish efficacy for a CIC indication in adults. However, these trials were conducted outside the U.S., and Study SPD555-302 enrolled only male patients. Study PRU-CRC-3001 enrolled only an Asian population. Therefore, we are concerned about the generalizability of the safety and efficacy observed in those populations to the U.S. CIC patient population. You will need to provide persuasive justification for relying primarily on these two trials as a basis of approval. For example, is the pathophysiology and natural history of condition the same in non-U.S. population, such as Asian population; are concomitant medications/interventions similar between populations; would differences in pharmacokinetics by sex and/or race be expected to impact safety and efficacy?

Furthermore, it is not clear why you are not relying on the findings of safety and efficacy from trials conducted in the U.S. If this is related to availability of site level source documents from the U.S. sites for FDA Office of Scientific Investigation review, we need to discuss this issue further with you. If it is related to a safety or efficacy issue identified in the US trials, this would raise a significant approvability issue, as it would verify concerns about the generalizability of the non-U.S. trial findings to the U.S. population.

In addition, we are concerned that the primary efficacy endpoint used in the key trials was the percentage of subjects with an average of ≥3 spontaneous complete bowel movements per week over 12 weeks of treatment (or 24 weeks for study SPD 555-401). As discussed in the meetings July 25, 2012 and July 15, 2014, the Division recommended that studies for CIC use the following primary efficacy endpoint:

> ***"Overall 12-week CSBM Responder" defined as a patient who was a CSBM Weekly Responder for ≥ 9 of the 12 weeks of the Treatment Period (3 of which should be in the last 4 weeks of the trial). A CSBM Weekly Responder was a patient who had a CSBM weekly frequency rate that was 3 or greater and increased by 1 or more from baseline. Patients must also have at least 4 days of evaluable response data to be considered a weekly responder."***

This endpoint is referred to as "Alternative Endpoint A" in Background Material Package for July 15, 2014 meeting with FDA. During the July 15, 2014 meeting, we discussed that the proposed "Alternative Endpoint A" will be considered the key sensitivity analysis endpoint since it aligns with current recommendations. You did not present these data in

the meeting package. Does the analysis based on the preferred responder definition support the observed results with the pre-specified primary endpoint analysis?

DISCUSSION: The Agency agrees with the sponsor's proposed approach to addressing generalizability and the proposed comparisons included in their August 7, 2017 response to the preliminary comments (attached).

Regarding the source documentation from previous U.S. studies, it may not be obtainable or available for inspection. The Agency recognizes the issues involved and will still consider the U.S. trials key trials during their review of the NDA.

Shire confirmed that they have conducted the analyses of alternate endpoint A on each of the six studies. They stated the analyses were conducted using logistic regression with multiple sensitivity analyses. The Agency stated that the sponsor would need to include in their NDA submission, CMH analysis of alternative endpoint A, which will be the analysis of interest during the FDA review. In addition, analyses should be presented to evaluate impact of age, sex, race, and region for alternative endpoint A.

The Agency noted the adequacy of population PK analysis evaluating the impact of sex and race on pharmacokinetics will be a review issue.

Question 4: *Does the Agency agree that the data to be presented in the NDA from study SPD555-802 fulfils the requirements of what was requested during these previous meetings and establish with 80% probability an incidence rate ratio (IRR) upper bound of the 95% CI <3 (null hypothesis) under the alternative hypothesis that IRR is 1?*

FDA Response to Question 4: Study SPD555-802, designed to rule out an incidence rate ratio (IRR) of 3 at the NDA stage appears reasonable. Depending on the results of SPD555-802, a post-marketing observational study to rule out an IRR of 2 might be required.

Question 5: *For study SPD555-802, due to country variability, the sponsor plans to present the results as both individual country (UK, Germany, and Sweden) and as pooled analyses (UK and Sweden). Does the Agency agree with the proposed strategy?*

FDA Response to Question 5: The Agency agrees with the proposed strategy to analyze results both as individual country data and pooled data with the exclusion of the German data, due to the age skewness of the German data.

Question 6: *Does the Agency acknowledge that due to the EU data protection directive, while only aggregate data will be available from the SPD555-802 study, and access to limited source data may be possible upon the Agency's requests after necessary data use agreements and/or assurances by the Agency are put into place?*

FDA Response to Question 6: We acknowledge these issues.

Safety

Question 7: *Does the Agency agree that the totality of the safety data provided is sufficient for the Agency to evaluate the benefit-risk profile of prucalopride?*

FDA Response to Question 7: Yes, these safety data appear sufficient to support a submission. We note that there are no controlled trials of 12 months duration in the planned submission. This will be a significant review issue, as the Division has moved towards requiring controlled trials of 12 months duration in a drug class for which there have been cardiovascular safety concerns.

DISCUSSION: The Agency reiterated that the adequacy of the safety database will be a review issue. In addition, the Agency noted that due to the nature of the product class an advisory committee meeting will likely be warranted.

Statistics

Question 8: *Does the Agency agree that submission of these CSRs in their current format is acceptable?*

FDA Response to Question 8: Yes, the Agency agrees that submission of these CSRs in their current format is acceptable.

Question 9: *Does the sponsor need to, additionally, provide the data of these 7 open-label long-term safety studies as separate SDTM data sets?*

FDA Response to Question 9: For all studies included in the submission, you must submit either ADaM or analysis datasets, and either SDTM or CRF tabulation datasets in CDISC standard format. You must also submit reviewer's guides for all submitted datasets.

Regulatory

Question 10: *Does the Agency agree that the eCTD Table of Contents is acceptable?*

FDA Response to Question 10: Yes, the eCTD Table of Contents is acceptable.

CLINICAL PHARMACOLOGY ADDITIONAL COMMENTS

In your NDA submission, please include the following information in addition to what you have proposed in *"Proposed Table of Contents for the New Drug Application 210166"*.

1. **A tabulated summary of in-vitro studies using human biomaterials in Module 5 with hyperlinks to the study reports.**

2. **A summary of in-vitro studies using human biomaterials in the summary of clinical pharmacology in Module 2.**

3. **A tabulated summary of formulations that were used in each clinical trial in Module 3.**

OSI ADDITIONAL COMMENTS

Please refer to the OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS section below. We are aware that you previously submitted these data to the IND. Please re-submit to the NDA and include any updates.

PREA REQUIREMENTS

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

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

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

to: http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm.

PRESCRIBING INFORMATION

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

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

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

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. As of **May 5, 2017,** the following submission types: **NDA, ANDA,** and **BLA** must be submitted in eCTD format. **Commercial IND** and **Master File** submissions must be submitted in eCTD format beginning **May 5, 2018**. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit: http://www.fda.gov/ectd.

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the Guidance for Industry, *Assessment of Abuse Potential of Drugs*, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf.

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.

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA 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), you 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).

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion were noted during the meeting.

ACTION ITEMS

With the exception of any items identified in the responses above, no additional action items were identified.

ATTACHMENTS AND HANDOUTS

The sponsor's reply to the August 7, 2017 preliminary comments letter is attached.

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

/s/

LAWRENCE W ALLAN
09/01/2017