

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

208078Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 106263

MEETING MINUTES

Catalyst Pharmaceutical, Inc.
Attention: Gary Ingenito, MD, PhD
Chief Medical Officer and Head of Regulatory Affairs
355 Alhambra Circle, Suite 1250
Coral Gables, FL 33134

Dear Dr. Ingenito:

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

We also refer to the meeting between representatives of your firm and the FDA on January 30, 2018. The purpose of the meeting was to review and discuss the planned contents of an NDA for amifampridine phosphate for the indication of Lambert-Eaton myasthenic syndrome and (b) (4) congenital myasthenic syndromes.

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 Laurie Kelley, Senior Regulatory Project Manager at laurie.kelley@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
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: C
Meeting Category: Guidance

Meeting Date and Time: January 30, 2018
11:00am – 12:00pm EST

Meeting Location: FDA White Oak, Building 22

Application Number: IND 106263
Product Name: amifampridine phosphate

Indication: Lambert-Eaton myasthenic syndrome and congenital myasthenic syndromes

Sponsor/Applicant Name: Catalyst Pharmaceutical, Inc.

Meeting Chair: Billy Dunn, M.D.

FDA ATTENDEES

Division of Neurology Products

Billy Dunn, M.D., Director
Eric Bastings, M.D., Deputy Director
Nick Kozauer, M.D., Associate Director
Teresa Buracchio, M.D., Clinical Team Leader
Rainer Paine, M.D., Clinical Reviewer
David Jones, M.D., Clinical Reviewer
Heather Bullock, RN, BSN, MSHS, Senior Regulator Project Manager
Laurie Kelley, PA-C, Senior Regulatory Project Manager

Office of Pharmaceutical Quality

Martha Heimann, Ph.D., CMC Lead

Controlled Substance Staff

Edward Hawkins, Ph.D., Pharmacologist

SPONSOR ATTENDEES

Catalyst Pharmaceutical, Inc.

Gary Ingenito, MD, PhD, Chief Medical Officer and Head of Regulatory

Anutosh Saha, PhD, Executive Director, Clinical and Regulatory

Patrick McEnany, Chief Executive Officer

Steven Miller, PhD, Chief Scientific Officer

1.0 BACKGROUND

The sponsor is currently developing amifampridine phosphate for the treatment of Lambert-Eaton myasthenic syndrome (LEMS) and congenital myasthenic syndrome (CMS). The purpose of this meeting was to discuss the sponsor's plan to present the abuse liability information, as well as the planned contents of an NDA application for amifampridine phosphate.

2. DISCUSSION

2.1. Clinical

Question 1: Does the Agency agree that the data from the two phase 3 studies is sufficient to file the application?

FDA Response to Question 1:

The data from Studies LMS-002 and LMS-003 appear capable of supporting the filing of your application for LEMS, pending a formal filing review.

Meeting Discussion: None

Question 2: Data from each phase 3 study (LMS-002 and LMS-003) will be presented in full, however it has been previously presented that patients from one site in LMS-002 were dosed incorrectly on Day 14 (primary endpoint) such that they were all assessed 'off medication.' When this site was excluded from the analysis, the p value of the QMG endpoint changed from 0.0452 to 0.0048. This error also resulted in the apparent loss of efficacy between Day 8 and Day 14 of the blinded withdrawal period, for the subset of subjects that were improperly dosed. Knowing this, Catalyst would like to prepare the ISE with and without the aberrant site, to provide better understanding of the true drug effect. Does the Agency agree with this approach?

FDA Response to Question 2:

Yes, we agree with the approach to prepare the integrated summary of effectiveness (ISE) both with and without the aberrant site. Note that the integrated summary of safety (ISS) needs to include all subjects exposed to the drug.

Meeting Discussion: None

2.2. Controlled Substance Staff

Question 4: Catalyst is presenting a proposed overall organization for the summary of abuse-related data to be included in Section 2.7.4, and plans to reference other supportive sections within the NDA submission. Does the Agency agree with the proposed overall plan and organization?"

FDA Response to Question 4:

Your proposed content and organization of the abuse-related data within the NDA appear appropriate. However, a proposal for scheduling will be required as part of your NDA submission, even if that proposal is that the substance not be controlled [21 CFR 314.50(d)(5)(vii)].

Meeting Discussion: None

Question 5: Does the Agency agree that each of the items listed in the abuse liability information to be submitted in the NDA are adequate, and that overall the information is sufficient for the filing and review of an NDA for amifampridine phosphate tablets?

FDA Response to Question 5:

Yes, it appears the proposed abuse liability section will be sufficient for the filing of the NDA. However, as you indicated in the briefing package, complete study reports will need to be included in the NDA submission. Our final determination of the appropriateness of the data to support your NDA will be made at the time of NDA review.

Meeting Discussion: None

2.3. Chemistry, Manufacturing and Controls

Question 6: Does the Agency agree that Catalyst can set an expiration date of 24 months for bottles of 240 tablets manufactured and packaged by (b) (4) in a container-closure system identical to the one used by (b) (4)

FDA Response to Question 6:

Your overall strategy for the tablet batches prepared by (b) (4) in the proposed packaging configurations appear reasonable for Questions 6,7, 9, and 10. This will depend on our confirmation of the comparability between the drug product prepared at (b) (4) product, which will be a matter for review. If not comparable, additional stability data may be required to support the proposed expiration dating period. The blister package information will be reviewed to confirm that the (b) (4) blisters have no significant differences. We remind you that the expiration dating period established during the review will need to be confirmed by real time data as part of the post-approval stability commitment.

Meeting Discussion: None

Question 7: Does the Agency agree that Catalyst can set an expiration date of 24 months for bottles of 60 tablets manufactured and packaged by (b) (4) which are in a container-closure system similar to the one used by (b) (4) for the 240 count bottles?

FDA Response to Question 7:

See response to Question 6.

Meeting Discussion: None

Question 8: (b) (4)

FDA Response to Question 8:

(b) (4)

Meeting Discussion: None

Question 9: Does the Agency agree that expiration dating for the (b) (4) can be used to support 24 months of expiration dating for the (b) (4)

FDA Response to Question 9:

See response to Question 6.

Meeting Discussion: None

Question 10: Does the Agency agree that stability test data for product packaged by [REDACTED] (b) (4) in blister packages can be used to support 24 month expiration dating for blister packages for product manufactured by [REDACTED] (b) (4) and packaged by [REDACTED] (b) (4)

FDA Response to Question 10:

See response to Question 6.

Meeting Discussion: None

Question 11: Does the Agency agree that the release and stability specifications for drug substance are acceptable?

FDA Response to Question 11:

As of January 1, 2018, USP <231> is no longer in effect. Develop and implement a control strategy for elemental impurities as described in USP <232> and <233>, and ICH Q3D for the drug product. We recommend inclusion of a quantitative phosphate counterion test in the drug substance specification to ensure consistent stoichiometry of the drug substance salt.

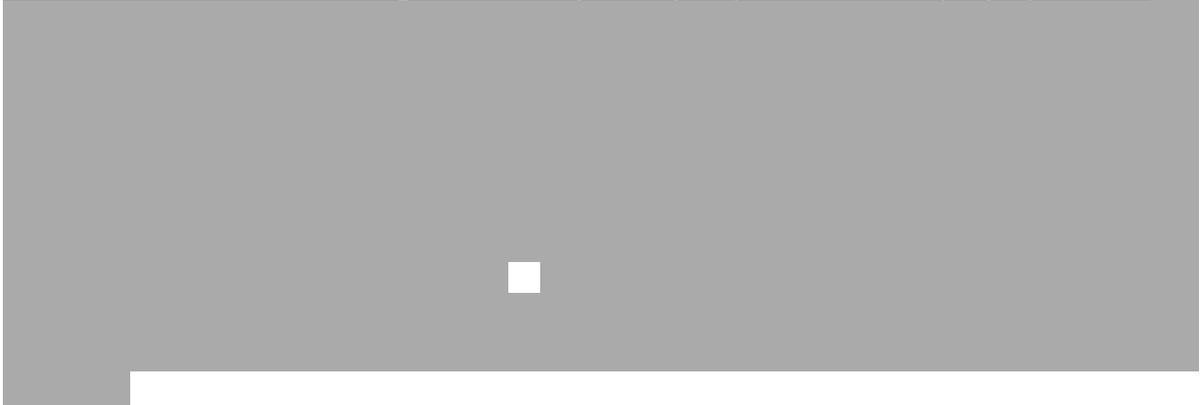
Sponsor Interim Response: Catalyst is aware of the changes in the USP [REDACTED] (b) (4). In response, Catalyst has performed an assessment of the potential of elemental impurities in amifampridine tablets. This assessment will be provided in the NDA as well as proposed actions needed to ensure the drug product complies the new USP specifications and ICH Q3D. Catalyst will also delete test USP <231> as it is now obsolete.

Catalyst has considered your request for a quantitative test for phosphate for amifampridine phosphate and would like to respectfully disagree. In fact, Catalyst considered the inclusion of a quantitative test for phosphate early in product development but decided against it then as it was not practical at the time and did not add anything further that materially further assured the quality of the drug substance. There were several items that were considered regarding the possible inclusion of a quantitative test for phosphate.

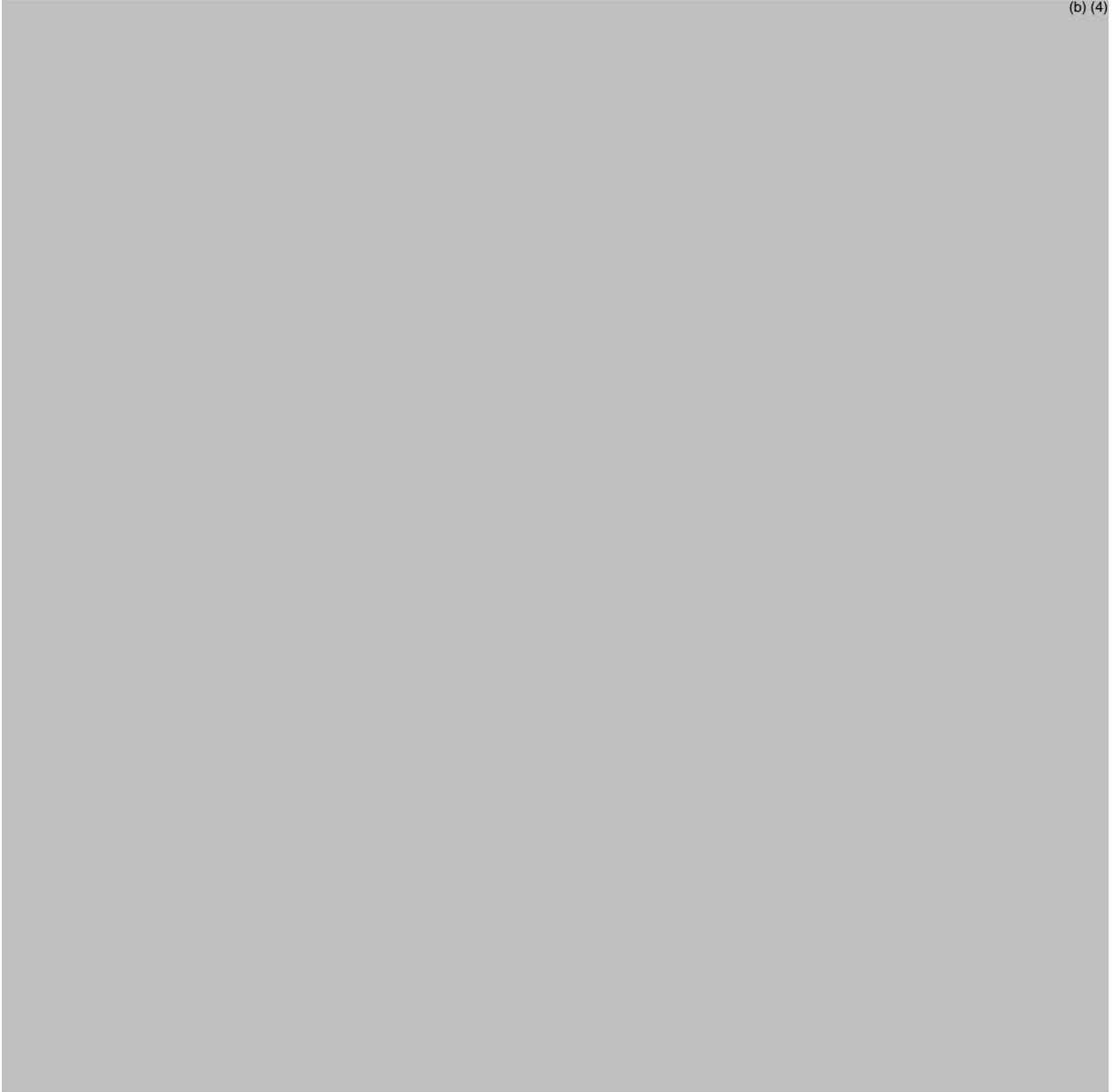
First, phosphate is the counterion to the active moiety (amifampridine) in the drug substance and serves no medicinal purpose (the amifampridine is the active ingredient).
Second, the assay of the active ingredient is a precise HPLC assay that is specific for the amifampridine moiety. This method has already demonstrated adequate accuracy and precision for the intended ranges. As part of the assay, calculations are carried out that take

into account the molecular weight of amifampridine phosphate in the sample preparation.

(b) (4)



(b) (4)



In summary, Catalyst has concluded that the amifampridine phosphate HPLC assay, combined with the phosphate ID testing provide adequate control over the potency of amifampridine phosphate and provide assurance that it is the phosphate salt with the correct stoichiometry. If the Agency wishes to have further discussion of this matter at the meeting, Catalyst would be willing to discuss it.

FDA Response: We concur with this response. We recommend that the justification for excluding a quantitative phosphate counterion test be included in the NDA submission.

Meeting Discussion: None

Question 12: Does the Agency agree that the release and stability specifications for drug product are acceptable?

FDA Response to Question 12:

(b) (4)
This will be a matter for review.

Meeting Discussion: None

2.4. Regulatory

Question 13a: As with the previous submission, will the Agency grant this NDA priority review?

FDA Response to Question 13a:

Determinations regarding review designations are made at the time of filing of the planned application.

Meeting Discussion: None

Question 13b: (b) (4)

FDA Response to Question 13b:

(b) (4)

Meeting Discussion: None

Question 13c: Which box should be checked on the 356H for submission type (original versus resubmission)?

FDA Response to Question 13c:

Because this application is a resubmission [REDACTED] (b) (4) it should be identified as an original submission with the submission sub-type marked as resubmission.

Meeting Discussion: None

Question 13d: Confirm that the Agency has access to all the previously submitted documents from the original NDA submission. If access is present, Catalyst will not resubmit any documents that are unchanged, any revised or updated documents will be ‘replaced’, and new documents will be added as ‘new’ to the resubmission.

FDA Response to Question 13d:

Yes, the Agency has access to all the previously submitted documents from the original NDA submission. Also, from a technical standpoint (not content related) the proposed format for the planned NDA is acceptable. However, please see additional comments below.

- Applicant’s options of cross referencing information submitted to another application (if any), would be to either place a cross reference document under module m1.4.4 (cross reference to other applications), or use cross application links.
 - To use the first option (placing a cross reference document in m1.4.4), a table formatted document can be submitted in section 1.4.4 of the eCTD, detailing previously submitted information (eCTD and/or non- eCTD) that is being referenced by the current application. The information in the document should include (1) the application number, (2) the date of submission (e.g., letter date), (3) the file name, (4) the page number (if necessary), (5) the eCTD sequence number, (6) the eCTD heading location (e.g., m3.2.p.4.1 Control of Excipients – Specifications), (7) the document leaf title and (8) the submission identification (e.g., submission serial number, volume number, electronic folder, file name, etc.) of the referenced document along with a hypertext link to the location of the information, when possible.
 - To use the second option (cross application links), both applications would need to be in eCTD format and reside on the same server. The applications need to include the appropriate prefix in the href links (e.g. nda, ind.). Also, when cross application links are used, it's strongly recommended that a cross reference document be placed in m1.4.4, in case any of the links don't work and in the leaf titles of the documents, it is recommended that the leaf title indicate the word “cross reference” and application number (e.g. Cross Ref to nda123456). The cross-reference information in the leaf title allows the reviewer to know that the document resides in another application and the application number that is being referenced.

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

To submit an eCTD cross application links sample, an applicant would need to request two sample application numbers from the ESUB team - esub@fda.hhs.gov. For more information on eCTD sample, please refer to the Sample Process web page which is located at <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm>

- For archival purposes, an applicant should submit a pdf file of the labeling document submitted in word. Also, when you submit word documents, make sure the leaf title includes "word", so reviewers could quickly identify the word version of the document.
- Please include (b) (4) on the leaf titles of the (b) (4) documents, so reviewers can easily identify the (b) (4) documents from the (b) (4) documents
- Study Tagging Files (STF) are required for submissions to the FDA when providing study information in modules 4 and 5, apart from module 4.3 Literature References, 5.2 Tabular Listing, 5.4 Literature References and 5.3.6 if the Periodic Report is a single PDF document. Each study should have an STF and all components regarding that study should be tagged and placed under the study's STF including case report forms (crfs) and datasets. Case Report Forms need to be referenced in the appropriate study's STF to which they belong, organized by site as per the specifications and tagged as "case report form". Subject Data Listings (16.4) should be file tagged as "data-listing-dataset". For documents with no specific file tags, "study-report-body" or "legacy-clinical-study-report" file tag can be applied. For more information on file tags, please refer to [The eCTD Backbone File Specification for Study Tagging Files 2.6.1 \(PDF - 149KB\) \(6/3/2008\)](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf) - <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM163560.pdf>
- Please do not include the section numbering in the leaf titles of documents (e.g. 16.1.2. Sample Case Report Form)
- Please include "bimo" in the leaf titles of all BIMO documents

Meeting Discussion: None

Question 13e: Catalyst would like to remind the Agency, as previously, that the initial bioavailability study comparing amifampridine phosphate to amifampridine (2003) has only legacy datasets from which partial SDTM format can be reconstructed for submission.

FDA Response to Question 13e:

We agree. You may submit the individual plasma concentration-time data from the relative bioavailability study in legacy format. You should also provide a define file explaining all the variables and their units listed in these datasets.

Meeting Discussion: None

3.0 ADDITIONAL MEETING INFORMATION

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.

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).

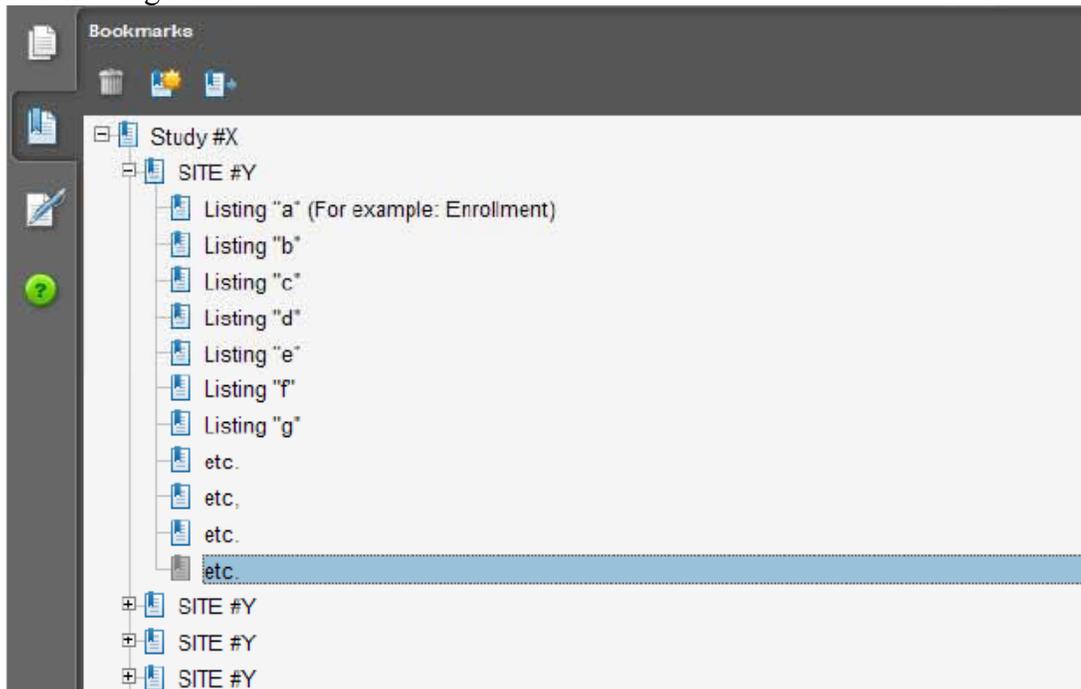
- I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).**

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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

There are no action items.

6.0 ATTACHMENTS AND HANDOUTS

There were no attachments or handouts for the meeting minutes.

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

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

/s/

WILLIAM H Dunn
02/05/2018



NDA 208078

REFUSAL TO FILE

Catalyst Pharmaceutical, Inc.
Attention: M. Douglas Winship
Vice President of Regulatory Operations
355 Alhambra Circle, Suite 1500
Coral Gables, FL 33134

Dear Mr. Winship:

Please refer to your New Drug Application (NDA) dated and received December 16, 2015, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for amifampridine.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

- The published literature that you have provided in support of the Lambert-Eaton myasthenic syndrome (LEMS) indication is inadequate to allow for substantial review. In order for the published literature that you have provided in your application to potentially support the results of Study LMS-002, detailed information would be necessary to allow for a substantive review of the results of these trials (i.e., clinical protocols, statistical analysis plans, and source level data). Sufficiently detailed information was not included in your application. In the absence of this information, you would need to submit positive results from an additional adequate and well-controlled trial with amifampridine in patients with LEMS.

-  (b) (4)

- You will need to submit the raw data sets in .xpt format for the relative bioavailability study (DAPSEL) that compare the bioavailability of the salt and the free base.

Amifampridine is a central nervous system (CNS)-active new molecular entity (NME). Therefore, it is necessary for amifampridine to undergo a full abuse potential assessment to be included in your NDA. Your general approach in assessing the abuse potential of

amifampridine as part of your drug development program should follow the outline provided below. Your abuse potential assessment will allow the Agency's determination of amifampridine's risk of abuse. The FDA draft *Guidance for Industry: Assessment of the Abuse Potential of Drugs* (2010) describes the process of evaluating a drug for abuse potential, which includes the following:

Nonclinical Assessment:

- Chemistry
- Pharmacology
 - i. Safety pharmacology
 - ii. Active metabolites
- Receptor binding at relevant central nervous system sites
- Self-administration studies in animals
- Drug discrimination studies in animals
- Physical dependence studies in animals

Clinical Assessment:

- Human abuse potential studies*
- Clinical safety and efficacy studies (abuse signals):
 - i. Abuse-related adverse events profile
 - ii. Drug withdrawal symptoms
 - iii. Patient narratives, including those related to suspected abuse, misuse, overuse or overdose (intentional or unintentional)
 - iv. Drug accountability during trials to include drug lost, stolen, diverted or missing as well as an accounting of participants who withdraw without returning study medication

* May not be applicable. A human abuse potential study would be necessary if there is a signal for abuse in nonclinical studies. This *Guidance for Industry* is found on the Internet at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

If amifampridine produces abuse potential signals that warrant Controlled Substance Act (CSA) scheduling, you will need to include a proposal for scheduling based on an analysis of the NDA's nonclinical and clinical studies which is consistent with the draft *Guidance for Industry on Assessment of Abuse potential of Drugs* (2010).

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

- **Clinical Deficiencies**

- In Study LMS-002, you should clarify the apparent differences between the body mass index (BMI) in the cohorts of Part 3 (i.e., 28 in subjects on amifampridine, and 24 in subjects on placebo).
- When obtainable, you should provide narratives for all subjects with death as an outcome from LMS-002 and other trials or registries.
- You should provide a categorical breakdown of amifampridine exposure by dose (e.g., x subjects at < 30 mg/day; y subjects at 30-60 mg/day; and z subjects at > 60 mg/day) and by duration (e.g., a subjects at 0-7 days of exposure; b at 8-30 days; c at 31-60 days; d at 61-180 days; e at 181-365 days; and f at > 365 days).
- You should provide narratives for all events of seizures and cardiac disorders, where available.
- In Study LMS-002, clarify if subject [REDACTED] ^{(b) (6)} experienced a return of sick sinus syndrome after resuming amifampridine treatment.
- In Study LMS-002 (or in any other study where obtainable), clarify if a suicidality scale was used. If so, you should provide the results.

- **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. Prior to resubmission of your application, please review these regulations. Also, please ensure your Prescribing Information is in compliance with the formatting requirements of the regulations by completing the “Selected Requirements for Prescribing Information (SRPI)”, which is a checklist of 42 important format items that can be found at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/UCM373025.pdf>.
- In addition, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information website: <http://www.fda.gov/drugs/guidancecompliance/regulatoryinformation/lawsactsandrules/ucm084159.htm>. We recommend you review the following specific labeling guidances found on this website and consider the recommendations contained within these guidances when revising your product labeling for inclusion in a resubmission:
 - Implementing the PLR Content and Format Requirements
 - Dosage and Administration Section of Labeling
 - Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling
 - Adverse Reactions Section of Labeling

- Drug Interaction Studies--Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations (draft)
 - Clinical Studies Section of Labeling
 - Patient Counseling Information Section of Labeling
- We also note that results from your abuse potential assessment may necessitate inclusion of a *Drug Abuse and Dependence* section in the Prescribing Information. If the information obtained with your abuse potential assessment is appropriate and warrants inclusion into labeling as required by 21 CFR 201.57(c)(10), you should develop the language for this section of the Prescribing Information to include in your resubmission.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

PROPOSED PROPRIETARY NAME

If you intend to have a proprietary name for the above-referenced product, submit a new request for review of a proposed proprietary name when you resubmit the application. For questions regarding proprietary name review requests, please contact the OSE Project Management Staff via telephone at 301-796-3414 or via email at OSECONSULTS@cder.fda.gov.'

If you have any questions, contact Laurie Kelley, PA-C, Regulatory Project Manager, at laurie.kelley@fda.hhs.gov.

Sincerely yours,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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

/s/

WILLIAM H Dunn
02/12/2016



IND 106263

MEETING MINUTES

Catalyst Pharmaceutical Partners, Inc.
Attention: M. Douglas Winship
Vice President of Regulatory Operations
355 Alhambra Circle, Suite 1500
Coral Gables, FL 33134

Dear Mr. Winship:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Firdapse (amifampridine, amifampridine phosphate, 3,4-diaminopyridine phosphate) tablets, 10 mg.

We also refer to the meeting between representatives of your firm and the FDA on January 28, 2015. The purpose of the meeting was to discuss your planned New Drug Application for amifampridine phosphate in the treatment of Lambert-Eaton myasthenic syndrome.

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 contact me by phone or email at (301) 796-2899 or fannie.choy@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Billy Dunn, M.D.
Director
Division of Neurology Products
Office of Drug Evaluation I
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: January 28, 2015, 10:00 – 11:00 a.m. EST
Meeting Location: FDA White Oak Campus, Building 22, Rm 1315

Application Number: IND 106263
Product Name: Firdapse (amifampridine phosphate; 3,4-diaminopyridine Phosphate; amifampridine)
Indication: (b) (4) treatment of Lambert-Eaton myasthenic syndrome (LEMS) in adults
Sponsor/Applicant Name: Catalyst Pharmaceutical Partners

Meeting Chair: Billy Dunn, M.D.
Meeting Recorder: Fannie Choy, R.Ph.

FDA ATTENDEES

Office of the Center Director
Robert Temple, MD, Deputy Director for Clinical Science

Office of Drug Evaluation I
Ellis Unger, MD, Director

Division of Neurology Products
Billy Dunn, MD, Director
Eric Bastings, MD, Deputy Director
Ronald Farkas, MD, PhD, Clinical Team Leader
Andrew Sostek, PhD, Clinical Reviewer
Laurie Kelley, PA-C, Regulatory Project Manager
Fannie Choy, RPh, Regulatory Project Manager

Office of New Drug Products
Martha Heimann, PhD, Neurology CMC Lead

Office of Biostatistics
Sharon Yan, PhD, Statistical Reviewer

Office of Clinical Pharmacology

Angela Men, MD, PhD, Clinical Pharmacology Team Leader
Bilal AbuAsal, PhD, Clinical Pharmacology Reviewer

Office of Scientific Investigations

Tony El Hage, PhD, Reviewer, Division of Good Clinical Practice Compliance

Office of Surveillance and Epidemiology

Justine Harris, RPh, Reviewer, Division of Medication Error Prevention and Analysis
Nyedra Booker, PharmD, MPH, Reviewer, Division of Risk Management (via teleconference)
Ermias Zerislassie, PharmD, Regulatory Project Manager

Rare Diseases Program

Jonathan Goldsmith, MD, Medical Officer

EASTERN RESEARCH GROUP REPRESENTATIVE

Christopher Sese, Independent Assessor

SPONSOR ATTENDEES

Catalyst Pharmaceutical Partners

Patrick McEnany, Chairman and CEO
Steven Miller, PhD, COO and CSO
Charles Gorodetzky, MD, PhD, CMO
Douglas Winship, VP of Regulatory Operations
William L. Stahovec, Director of RA
Kevin Barber, PhD

(b) (6)



1.0 BACKGROUND

Catalyst Pharmaceutical Partners (Catalyst) has requested the type B meeting to discuss and reach agreement with the Agency on the overall content of a complete New Drug Application (NDA) for Firdapse (amifampridine, amifampridine phosphate, 3,4-diaminopyridine phosphate).

The sponsor is developing amifampridine phosphate for the treatment of Lambert-Eaton myasthenic syndrome (LEMS). The Agency granted Orphan Drug designation for amifampridine phosphate for the treatment of LEMS on November 12, 2009.

Amifampridine phosphate received Breakthrough Therapy designation for the (b) (4) treatment of LEMS in adults on August 22, 2013. On December 5, 2013, a multidisciplinary comprehensive meeting was held between the Agency and the sponsor to discuss the completed and planned nonclinical and clinical studies, and plans for expediting the manufacturing development strategy.

(b) (4)

The sponsor is targeting an NDA submission for July 2015. The objectives of the pre-NDA meeting are:

1. To reach agreement on suitable container/closure systems for product launch.
2. To reach an agreement on the request for a waiver for Pediatric Study Plan.
3. To reach an agreement on a requested waiver for pooled data for the Integrated Summary of Safety/Integrated Summary of Efficacy (ISS/ISE).
4. To reach agreement that the overall content of the NDA described in this package can be accepted by the Agency as complete for review purposes.
5. (b) (4)

FDA sent Preliminary Comments to (b) (4) on January 26, 2015.

2.0 DISCUSSION

Question 1:

Does the Agency agree that the described plan for packaging, testing, and data analysis for amifampridine tablets, 10 mg packaged in bottles of 240 tablets is sufficient to justify commercial launch of the drug product in bottles with 2-year expiration dating?

[FDA Preliminary Response to Question 1:](#)



(b) (4)

(b) (4) We recommend submission of 12 months long-term stability data in the original NDA. Whether additional stability data submitted as an amendment will be reviewed during the same review cycle will depend on the timing of the amendment and available resources. The expiration dating period will depend on the extent and quality of the data.

Additional CMC Comments:

You indicate that you do not plan to perform (b) (4)

(b) (4) We expect all tests included in the product specification to be performed on every batch at release.

In the NDA submission clarify whether the drug substance and drug product validation batches placed on stability are full commercial scale. If not, the post-approval stability commitments should include placement of the first three commercial batches on stability.

Meeting Discussion:

The NDA may be submitted with the available stability data. The quality review team may request submission of any additional data from ongoing studies during the review cycle. Extension of the expiration dating period based on real-time data obtained under an approved stability protocol is an annual reportable change.

Post Meeting Note:

The applicable guidance is “Guidance for Industry CMC Postapproval Manufacturing Changes To Be Documented in Annual Reports”.

Question 2:

According to 21 CFR 314.55(d), any drug for an indication or indications for which orphan drug designation has been granted under part 21 CFR 316, subpart C are exempt of 21CFR 314.55 “Pediatric use information.” Catalyst’s FirdapseTM has been granted orphan drug designation for the indication of (b) (4) treatment of Lambert-Eaton Myasthenic Syndrome (LEMS) under orphan drug designation 09-2953. In addition, on December 2, 2014, in accordance with 21 CFR 316, subpart C, Catalyst submitted a request for orphan drug designation for FirdapseTM for the indication of the (b) (4) treatment of congenital myasthenic syndromes (CMS). It is our understanding that a Pediatric Study Plan is not required for the indication of (b) (4) treatment of LEMS. Should the Agency grant Catalyst’s request for orphan drug designation for the (b) (4) treatment of CMS, a Pediatric Study Plan will not be required for this indication either.

Does the Agency agree that Pediatric Study Plans will not be required for Firdapse™ for indications that have been granted orphan drug designation status?

FDA Preliminary Response to Question 2:

Yes. See PREA requirements under Section 3.2.

Meeting Discussion: There was no meeting discussion.

Question 3:

Catalyst requests a waiver of the requirement to submit pooled data, and pooled statistical analysis thereof, in an Integrated Summary of Efficacy (ISE), given that only the pivotal Phase III study (LMS-002) was designed to assess therapeutic efficacy of Firdapse™ in LEMS. As required, Catalyst will submit a complete ISE based Study LMS-002 and numerous literature references. A full narrative of the study and all the references will be provided as part of the ISE.

Catalyst also requests a waiver of the requirement to submit pooled data, and pooled statistical analysis thereof, for an Integrated Summary of Safety. The ISS would include many literature references where study designs and dosing regimens differed limiting the utility pooling such data.

Does the Agency agree on the proposal not to pool data in the ISS and ISE?

FDA Preliminary Response to Question 3:

You don't need to pool efficacy data; primary data and results from study LMS-002 and literature studies can be described separately.

For safety, however, you should pool data to the degree that is possible and potentially informative. For example, we'd like your assessment of the incidence of serious adverse events, such as seizures or cardiac arrhythmia, across all exposed patients that you have knowledge of, even though study designs and dosing regimens differ. In contrast, we would not expect you to attempt to derive incidence rates for common nonserious events from pooled data.

Meeting Discussion:

The Division stated that it would append a general guide for safety data submission to the meeting minutes (see attachment).

Question 4:

A summary of the reports, data, and literature to be submitted in the NDA is provided as Attachment 5.

Does the Agency agree that the reports, data, and literature included in the summary would be sufficient for our NDA to be considered complete for filing by the FDA?

FDA Preliminary Response to Question 4:

You have described the contents of the NDA at a very high level, without detail that would enable us to provide feedback about if the specific sections of your NDA are likely to be considered adequate for filing. General advice is available about the format and content of an NDA is available at the following site:

<http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/NewDrugApplicationNDA/>

Clinical Pharmacology:

- Evaluate whether amifampridine is a substrate or an inhibitor of major transporter systems based on the “Clinical pharmacology Guidance for Industry: Drug Interaction Studies: Study Design, Data Analysis, Implications for Dosing, and Labeling Recommendations”.
- Please provide the clinical pharmacology summary as a review aid in your NDA submission (see attached template).
- Please provide a justification for dosing recommendations in specific populations, such as patients with renal impairment, patients with mild hepatic impairment, and different age groups.
- Please provide .xpt data files for the clinical pharmacology study and any PK/PD data.
- You reported that slow acetylators have 3 to 4 times higher plasma drug levels than fast acetylators. Please clarify your dosing strategy for slow and fast acetylators in the NDA submission.

ESUB:

From a technical standpoint (not content related), the proposed format for the planned NDA is acceptable. However, please see additional comments below:

1. The new Comprehensive Table of Contents (CTOC) and Hierarchy (dated:-2/14) should not be utilized until the new m1 is implemented. Instead, please refer to the Comprehensive Table of Contents (CTOC) and Hierarchy (dated:-7/05), located at <http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM315023.pdf>.
2. The tabular listing in module 5.2 and synopsis of individual studies in m2.7.6 should be provided in tabular format and linked to the referenced studies in m5.
3. Both Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE) should reside in m5.3.5.3.

4. Do not include placeholder stating “Not Applicable”, for sections without documents. Only provide eCTD sections that have documents.
5. All blue text should be hyperlinked. Some of the blue texts were not hyperlinked (e.g., attachment 4, 7, etc.).

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

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

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

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

Steps to Rolling Submissions

- The initial US Regional.xml file should be coded as "presubmission".
- Cover letter and form should state “presubmission to rolling submission – part 1 of XXX (depending on how many parts before the final submission).
- The subsequent sequences prior to the final sequence, should also be coded as “presubmission”.

- The US Regional of the final submission that makes everything complete and kicks off the clock, should be coded as the “original-application” to start the clock.
- Cover letter and form of the final submission should state "original application - part XXX of XXX of rolling submission" – this starts the clock for review.

Meeting Discussion:

The lack of detail about the contents of the NDA was discussed in the context of advice

(b) (4)

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Question 5:

(b) (4)

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3.0 FDA ADDITIONAL COMMENTS

3.1. DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. 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.
- 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 risk evaluation and mitigation strategy (REMS) was held. At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology have insufficient information to conclusively determine whether a REMS will be necessary to ensure that the benefits of the drug outweigh the risks. However, based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

3.2. PREA REQUIREMENTS

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

Because this drug product for this indication has an orphan drug designation, you are exempt from these requirements. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

3.3. 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](#). As you develop your proposed PI, we encourage you to review the labeling review resources on the [PLR Requirements for Prescribing Information](#) website including:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products
- Regulations and related guidance documents
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) – a checklist of 42 important format items from labeling regulations and guidances.

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

Post-Meeting Note:

Please also note that on December 4, 2014, the Food and Drug Administration published a Final Rule in the Federal Register [Docket No. FDA-2006-N-0515 (formerly Docket No. 2006N-0467)] regarding the Requirements for Pregnancy and Lactation Labeling. All applications submitted after effective date of the final rule, June 30, 2015, will be required to comply, with a staggered implementation schedule for applications submitted prior to the effective date. You are encouraged to comply with this rule in advance of the effective date if you submit your application prior to June 30, 2015. We encourage you to review the Draft Guidance for Industry, “Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products — Content and Format” located at the following URL: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>.

3.4. 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 draft guidance for industry, “Guidance for Industry Assessment of Abuse Potential of Drugs”, available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>.

3.5. 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.				

Post-Meeting Note:

You may submit manufacturing facility information to the NDA prior to submission of the complete application. Although we are not able to issue formal inspection requests prior to receipt of the NDA, we will work within CDER to facilitate timely inspections once the NDA is received.

When submitting presubmissions, the submission type should be coded "presubmission" in the us-regional.xml file, using sequence 0000. Subsequent presubmissions (if any), should also be coded as "presubmission". The original application will use the next available sequence number depending on how many presubmissions were submitted, prior to submitting the original application.

3.6. 505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999), available at <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm>. In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at <http://www.regulations.gov>).

If you intend to submit a 505(b)(2) application that relies for approval, in part, on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely, in part, on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. trade name(s)).

If you intend to rely, in part, on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If you propose to rely on FDA’s finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA’s consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that relies on FDA’s finding of safety and/or effectiveness for a listed drug(s) or on published literature. In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA’s finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the “bridge” that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying in your annotated labeling the source(s) of information essential to the approval of your proposed drug that is provided by reliance on FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature, we encourage you to also include that information in the cover letter for your marketing application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA’s previous finding of safety and efficacy for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
<i>1. Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>2. Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication X</i>
<i>3. Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section XXX</i>
<i>4.</i>	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

Meeting Discussion:

The sponsor stated that its current plan is to submit a 505(b)(1) application. The Division explained that if literature or other studies for which the applicant has no right of reference provide necessary and acceptable support for approval, then the application would be a 505(b)(2).

3.7. 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).

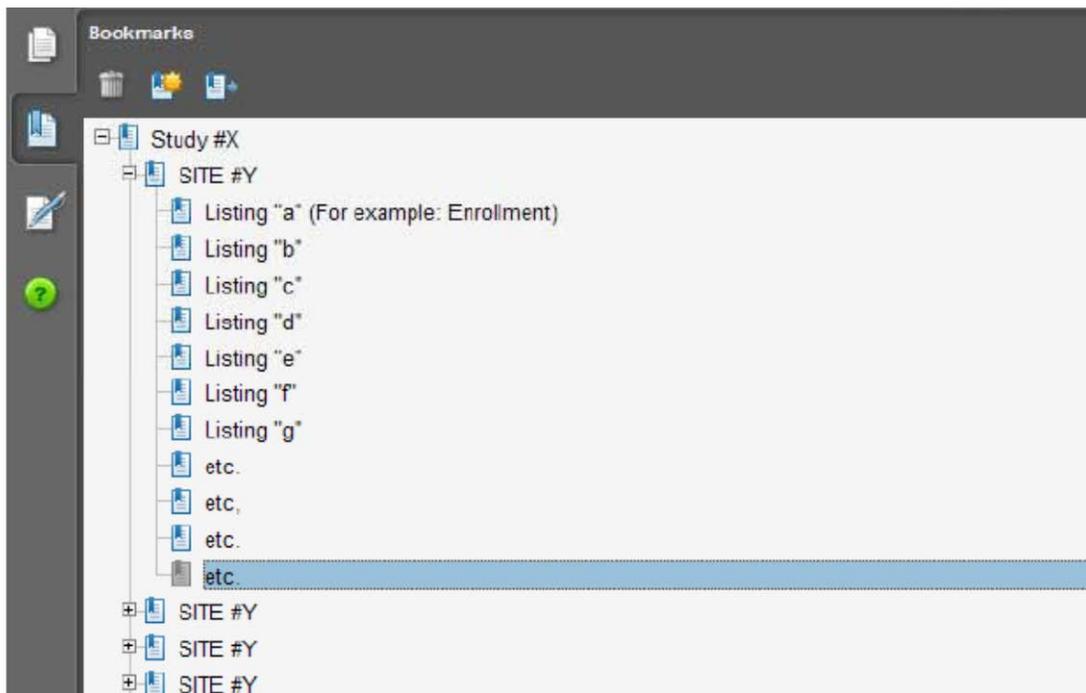
1. Please include the following information in a tabular format in the original NDA for each of the completed pivotal clinical trials:
 - a. Site number
 - b. Principal investigator
 - c. Site Location: Address (e.g. Street, City, State, Country) and contact information (i.e., phone, fax, email)
 - d. 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

3.8. CLINICAL PHARMACOLOGY SUMMARY AID

See attachment.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

- DNP Pre-NDA/Pre-BLA Meetings: General Clinical Safety Requests
- Clinical Pharmacology Summary Aid

DNP Pre-NDA/Pre-BLA Meetings
General Clinical Safety Requests

Electronic Regulatory Submission:

1. Follow the guidance documents and specifications regarding Electronic Common Technical Document (eCTD) submissions located at the following FDA webpage: [eCTD](#)
2. Refer to the following FDA webpage regarding the electronic submission of regulatory information to CDER: [Electronic Regulatory Submission](#)
3. The agency provides a process for submitting an eCTD sample for eCTD validation tests. Further instructions are listed at this FDA webpage: [Sample eCTD Submission](#)
4. Send any questions and general information regarding the preparation of submissions in electronic format to esub@fda.hhs.gov

Datasets:

5. Refer to the following FDA webpage on [Study Data Standards Resources](#)
6. Follow the following Guidance Documents:
 - a. Providing Regulatory Submissions in Electronic Format-Standardized Study Data
 - b. Study Data Technical Conformance Guide – Technical Specifications Document
 - As outlined in Section 2.2, include a Study Data Reviewer’s Guide in the eCTD Module 5 that describes the use of study data standards and their conformance validation (this is in addition to the Reviewer’s Guide in eCTD Module 1 that provides a high level overview of modules 1 through 5 with hyperlinks).
 - As outline in Section 4.1, use SDTM data format specifications for clinical tabulations datasets and ADaM for analysis datasets. Analysis datasets should be traceable to the tabulations datasets.
 - As outlined in Section 4.1.1.2, each individual subject should be assigned a single unique identifier across the entire application (e.g., including open label extensions of the trials).
 - As outlined in Section 4.1.4.5, the data definition file, define.xml, should be included to describe the format and content of the submitted SDTM and ADaM datasets.
 - As outlined in Section 6.3.1, the preparation of the adverse event dataset for the ISS should include MedDRA Preferred Terms from a single version of MedDRA.
 - As outlined in Section 8.3.2, specify whether Legacy data has been converted to SDTM formatting. If this is the case, the rationale, methods, and approach to this conversion process will need to be discussed with our data standards team (eData@fda.hhs.gov). Submit both the original (legacy) and the converted (SDTM) data for these trials. If Legacy data has not been converted to SDTM formatting, provide the rationale.
7. The agency provides a process for submitting sample standardized datasets for validation tests. Further instructions are listed here: [Standardized Data Sample Submission](#)
8. Open CDISC is one possible tool to check for conformance to the CDISC standard.
9. Send any questions regarding the submission or structure of datasets to eData@fda.hhs.gov
10. Submit datasets for all Phase 1, Phase 2, Phase 3 studies (including open label extension studies), including the Phase 2 and 3 studies performed for indications other than the one proposed for this application.
11. Submit all SAS codes used to create your analyses for the ISE and ISS. If a SAS code contains a macro, please also include the macro code.

General Submission Contents:

12. Provide DSMB meeting minutes (including any data/slides presented). For those meetings that were cancelled or meetings where no minutes were taken, please include a place holder

- for that meeting noting such and signed by a member of the clinical team. Please also ensure that these packages come with a table of contents and are bookmarked by date.
13. Include information regarding important regulatory actions in other countries and foreign labeling (translated, if applicable).
 14. Submit an annotated version of the pre-NDA meeting minutes that include hyperlinks, when applicable, to the analysis and/or documents requested.
 15. Include a copy of each clinical study protocol as well as each amended protocol. Provide a list of the inclusion and exclusion criteria for each of the studies, including those introduced as part of protocol amendments. Please submit all versions of the protocols (and Statistical Analysis Plan) and the date when changes were implemented. Please ensure that a Summary of Changes for each version is included.
 16. Include active hyperlinks from the lists of references to the referenced article.
 17. Follow the requirements noted in 21CFR 314.50 (d)(5)(vi), Summary of Safety Information and the [Guideline for the Format and Content of the Clinical and Statistical Sections of an Application](#)
 18. Provide an assessment of safety as per the [FDA Guidance for Industry: Premarketing Risk Assessment](#)
 19. In addition to the comprehensive analyses performed for the pivotal trials, the ISS should also comprehensively integrate safety analyses for all other study group pools for treatment-emergent adverse events (TEAEs), deaths, serious adverse events, discontinuations for TEAEs, TEAEs of special interest, subgroups, and vital sign/laboratory/ECG measurements.
 20. Submit a table detailing all of the tables and figures featured in the clinical efficacy and safety sections of the application. The table should contain the following:
 - a. Title of the table or figure in the application
 - b. A hyperlink to the location of the table or figure with page number
 - c. A hyperlink to the SAS code used to create the table or figure (including information regarding the datasets that were used)
 21. Format the tables of the ISS according to examples in FDA’s [Reviewer Guidance – Conducting a Clinical Safety Review of a New Product Application and Preparing a Report on the Review](#)

Adverse events:

1. Follow the coding rules for MedDRA in the ICH-endorsed “MedDRA Term Selection: Points to Consider” document accessible at [MedDRA](#)
2. For each of the studies, the submitted datasets should contain both the verbatim terms and the MedDRA coding with all levels of the MedDRA hierarchy. For each adverse event, MedDRA coding should be provided for the primary MedDRA path as well as the alternative MedDRA coding paths.
3. Provide a summary table of the original AE coding dictionaries that were used in each of the trials.
4. Ensure that all adverse events are presented, and not only events deemed “drug-related.”
5. Provide a table of treatment-emergent adverse events reported in $\geq 2\%$ of subjects (after rounding) in any drug treated dose group (and greater than placebo) sorted by MedDRA SOC (in alphabetical order) and then by MedDRA Preferred Term.
6. Provide a table which summarizes the outcomes of all pregnancies. Provide a table which summarizes all known adverse events in subject offspring.

Narratives and Case Report Forms (CRFs):

1. Provide narratives and case report forms for deaths, all discontinuations, SAEs, pregnancies, and AEs of special interest. You should be prepared to supply any additional CRFs or narratives with a rapid turnaround upon request.
2. Include a word file (and excel spreadsheet) that indicates those subjects for whom you submitted a case report form and/or narrative. This file should include an indicator for whether each item was submitted and the reason why it was submitted along with hyperlinks to the case report form and/or narrative.
3. Provide reports for any autopsies conducted during any of the studies.
4. Provide a line listing, narrative, and case report form for all subjects who fit the Hy's Law lab criteria.
5. Note that CRFs should include all clinical documents collected about the patient regardless of whether you label them "CRFs", e.g., Medwatch/CIOMS forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.
6. Provide both narratives and CRFs for all discontinuations (including Lost to follow-up, Other, Physician/investigator decision, Patient decision, Withdrew consent). Provide a tabular listing of all subjects with discontinuations, sorted by reason. The table should include columns for study number, treatment group, unique subject ID, primary reason for discontinuation; for reasons including Lost to follow-up, Other, Physician/investigator decision, Withdrew consent, and Patient decision, provide more specific information regarding the discontinuation.
7. Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narratives should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and the adverse event. The following items should be included (but not limited to):
 - Patient age and gender
 - Adverse event onset and stop dates (presented as relative Study Day number)
 - Signs and symptoms related to the adverse event being discussed
 - An assessment of the relationship of exposure duration to the development of the adverse event
 - Pertinent medical history
 - Concomitant medications with start dates relative to the adverse event
 - Pertinent physical exam findings
 - Any abnormal vital sign measurements
 - Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
 - Discussion of the diagnosis as supported by available clinical data
 - For events without a definitive diagnosis, a list of the differential diagnoses
 - Treatment provided
 - Re-challenge results (if performed)
 - Outcomes and follow-up information

Laboratory and Vital Sign Measurements:

1. Refer to the following FDA webpage for the CDER position on use of SI units for lab tests: [SI Units](#)
2. Provide the normal reference ranges for every laboratory value.

3. Clearly list the normal values, as well as the thresholds for analysis of outliers, for outlier analyses of laboratory data, vital signs data and ECG data.
4. When possible, use the latest version of the National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) for toxicity grades and shift analyses.
5. Report the number and percentage of subjects with at least one post-treatment vital sign measurement meeting any of these criteria:
 - Systolic Blood Pressure: <90 mmHg, >140 mmHg, >160 mmHg
 - Diastolic Blood Pressure: <50 mmHg, >90 mmHg, >100 mmHg
 - Pulse Rate: <60 bpm, >100 bpm
 - Body Weight: decrease of $\geq 7\%$ from baseline and increase of $\geq 7\%$ from baseline
 - Temperature: >38.0 °C, <36.0 °C
 - Respiratory rate: <12 breaths/min, > 20 breaths/min
6. Summarize the protocols for collecting ECG data. Summarize the frequency of post-treatment QTc >450 ms, >480 ms, and >500 ms.

CLINICAL PHARMACOLOGY SUMMARY AID

1. Goal

The goal of this Aid is to facilitate the creation of an optimal Clinical Pharmacology Summary that summarizes the relevant Clinical Pharmacology findings and focuses sponsor and reviewer on the critical review issues of a submission. To guide sponsors in creating the Clinical Pharmacology Summary in NDA and BLA submissions the Aid provides a generic questionnaire that covers the entire Clinical Pharmacology realm. The aggregate answers provided by sponsors generate the desired Clinical Pharmacology Summary in NDA and BLA submissions. Where needed instructions are added to the questions to clarify what the answers should address. The questions and instructions included in this guide are not intended to be either inclusive of all or exclusive of any questions that specific reviews will address. A special Section of the Clinical Pharmacology Summary should identify and discuss the critical findings and issues and indicate how the unresolved issues are addressed.

The Clinical Pharmacology Summary generated by sponsors is a **stand-alone document**, i.e. the answers to the questions including supporting evidence should be self-sufficient. Appropriate use of complementary tables and figures should be made. The sponsors' answers to the questions should be annotated with links to the detailed information in the study reports and the raw data located in SAS transport files.

2. Question Based Review

2.1 What are the *in vitro* and *in vivo* Clinical Pharmacology and Biopharmaceutics studies and the clinical studies with PK and/or PD information submitted in the NDA or BLA?

All performed Clinical Pharmacology studies (*in vitro* studies with human biomaterials and *in vivo* studies) and clinical studies with PK and/or PD information along with report numbers should be tabulated. Study titles, objectives, treatments (single or multiple doses, size of the dose/interval), demographics (sex, age, race/ethnicity, body weight, creatinine clearance) and numbers of study participants should be listed. Studies whose results support the label should be marked.

2.2 General Attributes of the Drug

2.2.1 What are the highlights of the chemistry and physical-chemical properties of the drug substance and the formulation of the drug product?

Provide background information on the drug substance (description, chemical name, molecular formula, molecular weight, structure), physical characteristics (Log D, solubility, pKa if applicable). Provide tabular information on the drug products, strengths, quantitative composition of ingredients and lot numbers for all formulations used in all *in vivo* studies and indicate corresponding study report numbers.

2.2.2 What are the proposed mechanism of action and therapeutic indications?

2.2.3 What are the proposed dosages and routes of administration?

2.2.4 What drugs (substances, products) indicated for the same indication are approved in the US?

2.3 General Clinical Pharmacology

2.3.1 What are the design features of the clinical pharmacology and biopharmaceutics studies and the clinical studies used to support dosing or claims?

Provide a tabular description of the designs, methodology and salient findings of the clinical pharmacology-, dose-ranging-, and pivotal studies and other clinical studies with PK and/or PD information in brief for each indication. Indicate duration of study, subjects' demographics, dose regimens, endpoints (clinical/biomarkers) and study report numbers.

2.3.2 What is the basis for selecting the response endpoints and how are they measured in clinical pharmacology studies?

Provide a rationale for the selected clinical endpoints and biomarkers. For biomarkers indicate relationship to effectiveness and safety endpoints.

2.3.3 Are the active moieties in plasma and clinically relevant tissues appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

Indicate circulating active moieties and their plasma and-tissue concentration range after therapeutic doses of the drug of interest. Provide evidence that sensitivity of the assay method(s) used is (are) sufficient to determine apparent terminal $t_{1/2}$ and AUC.

2.4 Exposure-Response

2.4.1 Does the exposure-response relationship support evidence of effectiveness?

Describe briefly the method(s) used to determine the exposure-effectiveness relationship from randomized and well controlled trials (RCT) and other appropriate studies. Provide evidence that the exposure-response analysis supports evidence of effectiveness: e.g. a significant slope in the E-R relationship or a clear separation in effectiveness at different drug levels and placebo.

Indicate whether the selected effectiveness endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-effectiveness relationship. Indicate major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status see also 2.6/2.7) impacting the exposure-effectiveness relationship. If not identifiable by commonly known covariates, evaluate different strategies, for example therapeutic drug monitoring, to maximize effectiveness for patients with a sub-therapeutic exposure.

Provide point estimate as well as a measure of the inter-subject variability for applicable. Indicate minimum and maximum effective dose- and concentration levels (major active moieties). Provide evidence that with the proposed regimens clinically meaningful effectiveness is maintained throughout the entire dose interval or alternatively provide evidence that maintenance of effectiveness during the entire dose interval is not important. Indicate the magnitude of the effect at peak and trough concentrations with the tested dose regimens. Indicate steady-state trough and peak plasma concentrations of the major active moieties with the proposed dose regimens. Indicate whether AUC, C_{max} or C_{min} is more correlated with effectiveness. Show the distribution of the effect size for each dose/concentration level tested.

Justify if an analysis of the exposure-effectiveness relationship was not done.

2.4.2 What are the characteristics of the exposure-response relationships for safety?

Describe briefly the method(s) used to determine the exposure-safety relationship. The analysis should focus on adverse events responsible for discontinuations and other drug related toxicities. Indicate whether the safety endpoints are continuous, categorical or event driven variables. Indicate the number of pooled subjects studied and identify the trials they were enrolled in. Provide the results of the analysis of the dose- and/or concentration-safety relationship. Indicate the major covariates (e.g. age, body weight, sex, race/ethnicity, creatinine clearance, disease severity, genetic factors, hormonal status) impacting the exposure-safety relationship. Provide point estimate as well as a measure of the inter-subject variability for relevant safety endpoints. Indicate magnitude and/or frequency of relevant adverse events at the tested dose/concentration levels. Indicate proportion of subjects with an excessive adverse response. Indicate whether AUC, Cmax or Cmin is more related to clinically relevant adverse effects. Add information on the maximum tolerated single and multiple dose regimens and the corresponding plasma levels [mean (SD) Cmax and AUC] of the circulating major active moieties.

Justify if an analysis of the exposure-safety relationship was not done.

2.4.3 Does this drug prolong QT/QTc Interval?

Provide a brief description of the study design, regimens, population and data analysis used. Indicate whether plasma concentrations of the drug and the relevant metabolites and the positive control were measured. Give a rationale for the chosen supra-therapeutic dose regimen. Report the findings on the relationship between dose/concentration and QTc interval. Indicate point estimate and 95% confidence interval for the increase of the QTc- interval at the supra-therapeutic dose level. Discuss the relevance of the findings for safety. Provide support for the appropriateness of the selected supra-therapeutic dose, if applicable. Indicate whether the pharmacokinetics of the drug of interest at supra-therapeutic levels is different from that at therapeutic levels.

2.4.4 Is the dose and dosing regimen selected consistent with the known E-R relationship?

Provide information on the criteria used to select the dose regimen (doses, dose intervals) used in the RCTs. Indicate the therapeutic dose and/or concentration range for the drug and provide evidence that the proposed dose regimens are optimal given the effectiveness/safety profile of the drug.

2.5 What are the PK characteristics of the drug?

2.5.1 What are the single and multiple dose PK parameters of parent drug and relevant metabolites in healthy adults?

Briefly describe methods (two-stage and/or population approaches, compartment model dependent or-independent methods) in healthy subjects and

in patients with the target disease used to determine the pharmacokinetic parameters of parent drug and relevant metabolites (pharmacologically active or impacting the exposure to parent drug or co-administered drugs). Provide mean, median (SD, CV%) pharmacokinetic parameters of parent drug and relevant metabolites after single doses and multiple doses at steady-state [C_{max} , t_{max} , AUC, $C_{max,ss}$, $C_{min,ss}$, $C_{max,ss}/C_{min,ss}$, $t_{max,ss}$, $AUC_{0-\tau}$, CL/F, V/F and $t_{1/2}$ (half-life determining accumulation factor), accumulation factor, fluctuation, time to steady-state]. Indicate how attainment of steady-state is determined. Provide evidence for attainment of steady-state.

2.5.2 How does the PK of the drug and its relevant metabolites in healthy adults compare to that in patients with the target disease?

Compare the pharmacokinetic parameters of the drug of interest and relevant metabolites in healthy subjects and patients with the target disease. Provide a rationale for observed significant differences between healthy subjects and patients with the target disease.

2.5.3 What is the inter- and intra-subject variability of the PK parameters in volunteers and patients with the target disease?

Provide mean/median (SD, coefficient of variation, range within 5% to 95% confidence interval bracket for concentrations) about mean AUC, C_{max} , C_{min} , CL/F and $t_{1/2}$ of the parent drug and relevant metabolites after single doses and at steady-state.

2.5.4 What are the characteristics of drug absorption?

Indicate absolute and relative bioavailability, lag time, t_{max} , $t_{max,ss}$, C_{max} , $C_{max,ss}$ and extent of systemic absorption of parent drug and relevant metabolites in healthy subjects and patients with the target disease. Indicate mean (SD) for these parameters.

2.5.5 What are the characteristics of drug distribution?

Indicate mean (SD) V/F for the drug of interest in healthy subjects and patients with target disease. Provide mean (SD) blood/ plasma ratio for parent drug in healthy subjects. Briefly describe method and pH- and temperature conditions used for determining plasma protein binding for parent drug and relevant metabolites. Provide mean (SD) values of the plasma protein binding of the drug of interest and relevant metabolites measured over the therapeutic range in healthy subjects and patients with target disease and special populations.

2.5.6 Does the mass balance study suggest renal or hepatic as the major route of elimination?

Present total, renal and fecal recoveries as percent of the administered total radioactivity. Indicate the percentage of radioactivity excreted as unchanged parent drug in urine and feces and the percent of radioactivity excreted as

metabolites in urine and feces.

2.5.7 What is the percentage of total radioactivity in plasma identified as parent drug and metabolites?

Provide identification for $\geq 90\%$ of the circulating total radioactivity (AUC). If multiple small peaks are present whose individual radioactivity is too small to be assignable to individual metabolites provide an estimate for their contribution to circulating total radioactivity.

2.5.8 What are the characteristics of drug metabolism?

Present the metabolic scheme for the drug. Provide an estimate for the contribution of metabolism to the overall elimination of the drug of interest. Indicate mean (SD) values for the non-renal clearance in healthy subjects and patients with the target disease. Indicate whether active metabolites constitute major circulating moieties and if so how much they contribute to effectiveness and/or whether they affect safety.

2.5.9 Is there evidence for excretion of parent drug and/or metabolites into bile?

If appropriate provide *in vitro* and/or *in vivo* evidence suggesting that parent drug and/or metabolites are excreted into bile (*in vitro*: parent drug and/or metabolites are substrates of BCRP, *in vivo*: recovery of unchanged parent drug in mass balance- and absolute bioavailability studies suggest excretion into bile)

2.5.10 Is there evidence for enterohepatic recirculation for parent and/or metabolites?

Indicate whether there are secondary peaks and humps in the plasma concentration profile correlating with food intake.

2.5.11 What are the characteristics of drug excretion in urine?

Provide an estimate of the contribution of renal excretion to the overall elimination of parent drug in healthy volunteers. Present mean values (SD) for the renal clearance (mL/min or mL/min/1.73m²) in healthy subjects and in the target population. Using mean plasma protein binding and renal clearance values in healthy subjects estimate the respective contributions of glomerular filtration and net tubular secretion or re-absorption to renal clearance.

2.5.12 Based on PK parameters, what is the degree of the proportionality

of the dose-concentration relationship?

Briefly describe the statistical methods used to determine the type of pharmacokinetics of the drug and its relevant metabolites (linearity, dose proportionality, non-linearity, time dependency) in healthy subjects and patients with the target disease. Identify the doses tested after single and multiple dose administrations of the drug of interest and the respective dose normalized mean (SD) C_{max} and AUC values in healthy subjects and patients with the target disease. Indicate whether the kinetics of the drug is linear, dose proportionate or nonlinear within the therapeutic range. In case of nonlinear or time dependent pharmacokinetics provide information on the suspected mechanisms involved.

2.5.13 How do the PK parameters change with time following chronic dosing?

Indicate whether the mean ratio of AUC_{0-τ} at steady-state to AUC after the first dose for the circulating major active moieties deviates statistically significantly from 1.0 in healthy subjects and patients with the target disease. Discuss the relevance of the findings and indicate whether an adjustment of the dose regimen is required. If the pharmacokinetics of the drug of interest changes with time provide a rationale for the underlying mechanism.

2.5.14 Is there evidence for a circadian rhythm of the PK?

Indicate whether C_{max} and C_{min} of the parent drug after the morning and evening dose differ significantly. Discuss the relevance of the findings and whether an adjustment of the dose regimen is required for the drug of interest. Provide a rationale for the underlying mechanism for the observed circadian rhythm of the pharmacokinetics of the drug of interest. Indicate whether the dose regimens in the pivotal studies were adjusted for circadian rhythm.

2.6 Intrinsic Factors

2.6.1 What are the major intrinsic factors responsible for the inter-subject variability in exposure (AUC, C_{max}, C_{min}) in patients with the target disease and how much of the variability is explained by the identified covariates?

Provide for all studies investigating the impact of the intrinsic factors (age, sex, body weight, ethnicity/race, renal and hepatic impairment) demographics and number of study subjects, and dose regimens. Provide summaries of the results and indicate intrinsic factors that impact significantly exposure and/or efficacy and safety of the drug of interest. Provide for each major identified covariate an estimate for its contribution to the inter-subject variability and indicate how

much of the inter-subject variability is explained by the identified covariates.

Provide mean (SD) parameters for AUC, C_{max}, clearance, volume of distribution and t_{1/2} for pairs studied (e.g. elderly vs. young, male vs. female, normal body weight vs. obese, race/ethnicity(x) vs. race/ethnicity (y), mild vs. severe target disease)

2.6.2 Based upon what is known about E-R relationships in the target population and their variability, what dosage regimen adjustments are recommended for each group?

Characterize the populations (age, sex, body weight, ethnicity/race) used to determine the impact of each intrinsic factor on variability in exposure and exposure-response. Indicate for each intrinsic factor whether a dose adjustment (change of dose or dose interval or both) is required or not and provide a rationale for either scenario.

2.6.2.1 Severity of Disease State

2.6.2.2 Sex

2.6.2.3 Body Weight

2.6.2.4 Elderly

2.6.2.5 Pediatric Patients

If available provide mean (SD, range) pharmacokinetic parameters, biomarker activity, effectiveness and safety in the pediatric sub-populations (neonates (birth-1 month), infants (1 month- 2 years), children (2-12 years) and adolescents (12- < 16 years) and define the target disease. If no information is available in the pediatric population indicate age groups to be investigated in future studies. Provide a summary stating the rationale for the studies proposed and the endpoints and age groups selected. Include a hyperlink to the development plan of the drug of interest in children.

2.6.2.6 Race/Ethnicity

2.6.2.7 Renal Impairment

Characterize the demographics for each subgroup (normal renal function, mild, moderate and severe renal impairment, on and off dialysis). Indicate mean (SD, range) for creatinine clearance estimated by the Cockcroft-Gault- and MDRD equations for the stages of renal impairment investigated. Provide arithmetic mean (SD) AUC, C_{max} and t_{1/2} of parent drug and relevant metabolites in the different sub-groups assessed by 2-stage or population PK approaches. Show regressions including 90% confidence intervals of AUC, C_{max} and CL/F on

Cl_r for parent drug and relevant metabolites. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of creatinine clearance.

Indicate mean (SD) for total and renal clearance of the drug in the different sub-groups and provide estimates of the contribution of glomerular filtration and net tubular secretion or re-absorption to the renal excretion of the drug of interest. Indicate whether plasma protein binding of the active moieties is significantly altered in renal impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment (dose or dose interval, or both) is required or not for each of the sub-groups of patients with impaired renal function and provide a rationale for either scenario.

2.6.2.8 Hepatic Impairment

Characterize the demographics for each subgroup (normal hepatic function, mild, moderate and severe hepatic impairment based on Child-Pugh scores). Provide information on arithmetic mean (SD) AUC, C_{max}, t_{max} and t_{1/2} of parent drug and relevant metabolites in the different hepatic function sub-groups assessed by two-stage or population PK approaches. Show regressions including 90% confidence intervals of C_{max}, AUC or CL/F on the Child-Pugh score for parent drug and relevant metabolites. Indicate whether plasma protein binding of the active moieties is significantly altered in hepatic impairment and whether the change in the unbound fraction is clinically relevant. Indicate whether a dose adjustment is required or not for each of the subgroups of patients with impaired hepatic function and provide a rationale for either scenario. If a population approach is used provide evidence supporting that statistical power was sufficient to determine impact of Child-Pugh score.

2.6.2.9 What pregnancy and lactation use information is available?

2.6.3 Does genetic variation impact exposure and/or response?

Describe the studies in which DNA samples have been collected. If no DNA samples were collected state so. Include a table with links to the studies in which DNA was analyzed and genomic/genetic information is reported. In the description of these studies include demographics, purpose of DNA analysis (effectiveness, safety, drug metabolism, rule in-out of patients, etc.), rationale for the analysis, procedures for bio-specimen sample collection and DNA isolation, genotyping methods, genotyping results in individual subjects, statistical procedures, genotype-phenotype association analysis and results, interpretation of results, conclusions. If genomic polymorphism impacts either exposure and/or response indicate the measures to be taken to safeguard efficacy and safety of the drug in subjects with varying genotypes. Indicate the contribution of genetic factors to inter-subject variability.

2.6.4 Immunogenicity (NOT applicable to small molecule drugs)

2.6.4.1 What is the incidence (rate) of the formation of the anti-product antibodies (APA), including the rate of pre-existing antibodies, the rate of APA formation during and after the treatment, time profiles and adequacy of the sampling schedule?

2.6.4.2 Does the immunogenicity affect the PK and/or PD of the therapeutic protein?

2.6.4.3 Do the anti-product antibodies have neutralizing activity?

2.6.4.4 What is the impact of anti-product antibodies on clinical efficacy?

2.6.4.5 What is the impact of anti-product antibodies on clinical safety?
Provide information on the incidence of infusion-related reactions, hypersensitivity reactions, and cross-reactivity to endogenous counterparts.

2.7 Extrinsic Factors

2.7.1 Is there an *in vitro* basis to suspect *in vivo* drug-drug interactions?

Summarize the results of the *in vitro* studies performed with the drug of interest as substrate, inhibitor or inducer of relevant CYP and non-CYP enzymes and transporters. Give rationale for why based on the *in vitro* results an interaction study in humans is required or is not required

2.7.2 Is the drug a substrate of CYP enzymes?

Briefly describe the methods used (specific chemicals/antibodies, human recombinant CYP enzymes, human microsomes). Indicate incubate, initial rate conditions, concentration range tested relative to K_m , controls etc. Provide a summary of the results of the *in vitro* studies investigating the drug of interest as a substrate of CYP 450 and non-CYP 450 enzymes. Provide for each of the relevant enzymes a mean estimate for the % contribution to the metabolism of the drug of interest. Discuss the relevance of the *in vitro* findings for the drug of interest as a substrate for deciding which drug-drug interactions should be or need not be performed in humans. For each situation provide supporting evidence.

2.7.3 Is the drug an inhibitor and/or an inducer of enzymes?

Briefly describe the methods used (type and source of liver tissue, concentration

range tested for the drug of interest as substrate, inhibitor and inducer, experimental conditions, pre-incubation, probe substrates, positive/negative controls. Provide summary results of the *in vitro* studies with human liver tissues for the drug of interest as a potential inhibitor or inducer of enzymes. Indicate whether the drug is a reversible inhibitor (competitive, non-competitive or un-competitive) or an irreversible inhibitor (mechanism based) and supportive evidence. Provide mean (SD) values for K_i , IC_{50} and V_{max} for each relevant enzyme and probe substrate. Indicate the anticipated maximum total and unbound concentration of the drug of interest as inhibitor ([I]). Provide the mean (SD) % activity relative to the positive control for the drug of interest as inducer. Discuss the relevance of the *in vitro* findings for the drug of interest as an inhibitor or inducer for deciding which drug-drug interactions should be or need not be performed *in vivo* in humans. If appropriate use the [I]/ K_i ratio as a means to assess the likelihood of an *in vitro* result to be clinically relevant. For each situation provide supporting evidence.

2.7.4 Is the drug a substrate, an inhibitor and/or an inducer of transporter processes?

See 2.7.2.2 and 2.7.2.3. The instructions for the interactions of the drug of interest as substrate, inhibitor or inducer of transporters are analogous to those for enzymes.

2.7.5 Are there other metabolic/transporter pathways that may be important?

2.7.6 What extrinsic factors influence exposure and/or response, and what is the impact of any differences in exposure on effectiveness or safety responses?

Indicate extrinsic factors that impact significantly exposure and/or effectiveness and safety of the drug. Indicate extent of increase or decrease in exposure and/or response caused by extrinsic factors. State whether an adjustment of the dose is or is not required and provide supporting evidence for either case.

2.7.7 What are the drug-drug interactions?

Provide a list of the drug-drug interaction studies (PK or PD based mechanism) performed and give a rationale for conducting the listed studies. Indicate the suspected mechanism responsible for the interaction. For each of the *in vivo* studies performed provide a rationale for the design selected (single or multiple dose regimens, randomized/non-randomized cross-over or parallel design for perpetrator and/or victim).

a) Drug of interest is impacted by co-administered other drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default

interval. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for the drug of interest in the presence and absence of each of the co-administered drugs. Provide a summary statement on the drug interaction liability of the drugs as victim. Indicate whether a dose adjustment is required or not. In either case provide a rationale. Define the required adjusted dose regimens.

b) Drug of interest impacts other co-administered drugs

Provide information on the demographics of populations, number of subjects, dose levels, and design of the studies performed in humans. Justify the magnitude of the equivalence interval selected if it is greater than the default interval. Provide a summary statement on the drug interaction liability of the drug as a perpetrator. Report $t_{1/2}$, point estimates and 90% confidence intervals of the geometric mean ratios of AUC and C_{max} for each of the co-administered drugs in the presence and absence of the drug of interest.

2.7.8 Does the label specify co-administration of another drug?

2.7.9 What other co-medications are likely to be administered to the target population?

2.7.10 Is there a known mechanistic basis for pharmacodynamic drug-drug interactions?

2.8 General Biopharmaceutics

For all *in vivo* studies performed in this section indicate study design, demographics and number of subjects enrolled, and type, composition, strength and lot number of the formulations used. Provide summary results with estimates for mean and inter-subject variability on AUC and C_{max} after single and multiple dose administration and peak to trough fluctuation after multiple dose administration.

IR Product

2.8.1 Based on the biopharmaceutic classification system principles, in what class is this drug and formulation? What solubility, permeability and dissolution data support this classification?

2.8.2 How is the proposed to-be-marketed formulation linked to the

clinical service formulation?

2.8.2.1 What are the safety or effectiveness issues, if any, for BE studies that fail to meet the 90% CI using equivalence limits of 80-125%?

2.8.2.2 If the formulation does not meet the standard criteria for bioequivalence, what clinical pharmacology and/or safety and efficacy data support the approval of the to-be-marketed product?

2.8.3 What is the effect of food on the bioavailability of the drug when administered as solution or as drug product?

Indicate composition and calories of the food administered, and length of the pre-dose fasting period. State whether the impact of food is on the drug substance or the inactive ingredients of the formulation. Indicate the clinical relevance of findings. Indicate the temporal relationship between drug intake and food intake in the pivotal studies.

2.8.4 Was the bioequivalence of the different strengths of the to be marketed formulation tested? If so were the strengths bioequivalent or not?

2.8.5 If unapproved products or altered approved products were used as active controls, how is BE to the to be marketed product demonstrated? What is the link between the unapproved/altered and to be marketed products?

MR product (if an IR is already marketed)

2.8.6 What is the bioavailability of the MR product relative to the approved IR product? How does the plasma concentration time profile of the MR formulation compare to that of the IR formulation after single and multiple doses?

Indicate whether or not the pharmacokinetics of the drug of interest is linear, dose proportional or nonlinear after administration of the MR formulation. Summarize data on C_{max}, AUC and C_{min} of the IR and MR formulations after a single dose and multiple doses at steady-state. Provide information on the fluctuation factor at steady-state.

2.8.7 What is evidence that MR formulation *in vivo* consistently shows claimed MR characteristics?

2.8.8 What is evidence that MR formulation displays less variability in C_{max}, AUC and C_{min} than IR formulation?

2.8.9 Does the MR product show dose dumping *in vivo*?

Describe design, demographics and number of subjects participating in the studies performed to determine whether dose dumping occurs with the MR formulation when given in the fed state or when given together with alcohol. Present summaries of results.

2.8.10 Does ethanol *in vitro* have a dose-dumping effect on the MR product?

Provide the results of the *in vitro* dissolution testing of the various strengths of the ER product in pH 1.2, 4.5 and 6.8 media containing 0, 5, 10, 20 and 40% alcohol. Discuss any dose dumping observed. If an *in vivo* study was performed report the clinical relevance of the findings.

2.8.11 Are the MR and IR products marketed simultaneously?

If the intention is to market both the MR and IR products, indicate how patients are converted from the IR to the MR product and vice versa.

2.8.12 If the NDA is for an MR formulation of an approved IR product without supportive safety and effectiveness studies, what dosing regimen changes are necessary, if any, in the presence or absence of a PKPD relationship?

2.8.13 In the absence of effectiveness and safety data what data support the NDA for a MR formulation of an approved IR product?

2.9 Analytical Section

2.9.1 How are parent drug and relevant metabolites identified and what are the analytical methods used to measure them in plasma and other matrices?

List all assays used and briefly describe the individual methods.

2.9.2 Which metabolites have been selected for analysis and why?

2.9.3 For all moieties measured, is free, bound, or total measured?

Indicate whether free, bound or total (bound+unbound) concentrations of the drug

of interest and relevant metabolites are measured and give a rationale for your selection.

2.9.4 What bioanalytical methods are used to assess concentrations of the measured moieties?

Identify all studies that used a particular assay method. For each assay report indicate the corresponding assay validation report.

2.9.5 What is the range of the standard curve? How does it relate to the requirements for clinical studies? What curve fitting techniques were used?

For each method and analyte provide concentration range of calibration curve and indicate respective concentration range for relevant moieties with therapeutic regimens. Indicate fit type of the calibration curves.

2.9.5.1 What are the lower and upper limits of quantitation?

For each method and analyte indicate LLOD, LLOQ and ULOQ for undiluted and diluted samples.

2.9.5.2 What are the accuracy, precision, and selectivity at these limits?

For each method and analyte indicate inter-day and intra-day precision (CV%) and inter-day and intra-day accuracy (RE%).

2.9.5.3 What is the sample stability under conditions used in the study?

For all studies in which concentrations of the drug of interest and relevant metabolites were measured provide information on initiation date of study, date of last sample analyzed and total sample storage time. For each method and matrix provide information on the stability of the analytes, i.e. number of freeze-thaw cycles, benchtop stability at room temperature and stability during long term storage at $\leq -20^{\circ}$ C.

2.9.5.4 What is the plan for the QC samples and for the reanalysis of the incurred samples?

For each study, method and analyte indicate precision (CV%) and accuracy (%RE) using the QC samples measured alongside samples with unknown concentrations. Indicate the concentrations of the QC and incurred samples used.

2.9.5.5 What evidence is available demonstrating that neither the assay of the drug on interest is impacted by co-administered other drugs and vice versa?

Applicable to therapeutic proteins only

2.9.5.6 What bioanalytical methods are used to assess therapeutic protein

concentrations?

Briefly describe the methods and summarize the assay performance.

2.9.5.7 What bioanalytical methods are used to assess the formation of the anti-product antibodies?

Briefly describe the methods and assay performance including sensitivity, specificity, precision, cut point, interference and matrix, etc.

2.9.5.8 What is the performance of the neutralizing assay(s)?

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/s/

WILLIAM H Dunn
02/25/2015