

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

215040Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



PIND 130190

MEETING MINUTES

Galephar P.R., Inc.
Attention: Britta Martinez
Project Manager
HC-04 Box 4540
Humacao PR 00791

Dear Ms. Martinez:

Please refer to your Pre-Investigational New Drug Application (PIND) file for N-Acetylcysteine Lysine (NAL) powder for oral administration.

We also refer to the meeting between representatives of your firm and the FDA on May 18, 2016. The purpose of the meeting was to discuss and obtain the Agency's agreement on the content of the NDA submission under the 505(b)(2) pathway.

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

If you have any questions, call me at (301) 796-5016.

Sincerely,

{See appended electronic signature page}

Anissa Davis-Williams, RN, B.S.N., M.P.H., C.P.H.M.
CDR/USPHS
Senior Regulatory Project Manager
Division of Gastroenterology and Inborn Errors
Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: May 18, 2016; 3:00 PM – 4:00 PM (EST)
Meeting Location: FDA White Oak Bldg. 22, Room 1415

Application Number: PIND 130190
Product Name: N-Acetylcysteine Lysine (NAL) powder for oral administration
Indication: **antidote to prevent or lessen hepatic injury which may occur following the ingestion of a potentially hepatotoxic quantity of acetaminophen.**

Sponsor/Applicant Name: Galephar P.R., Inc.

Meeting Chair: Dr. Stephanie Omokaro
Meeting Recorder: CDR Anissa Davis-Williams

FDA ATTENDEES

Andrew E. Mulberg, M.D., F.A.A.P., C.P.I., Deputy Director, Division of Gastroenterology and Inborn Errors Products (DGIEP)
Stephanie O. Omokaro, M.D., Medical Team leader, DGIEP
Lara Dimick-Santos, M.D., Medical Reviewer, DGIEP
Sushanta Chakder, Ph.D., Supervisory Pharmacologist, DGIEP
Tamal Chakraborti, PhD, Nonclinical Reviewer, DGIEP
Elizabeth Shang, Ph.D., Clinical Pharmacology Reviewer, DCPIII
Yeh-Fong Chen, Ph.D., Statistical Team Leader, Division of Biometrics III (DBIII)
Andrejus Parfionovas, Ph.D., Statistical Reviewer, DBIII
Danuta Gromek-Woods, Ph.D., Chemistry Team Leader, Office of Product Quality (OPQ)
Tien-Mien Chen, Ph.D., Acting Biopharmaceutics Lead, OPQ
Hansong Chen, Ph.D., Pharm.D., Biopharmaceutics reviewer, OPQ
LCDR Richard Ishihara, Regulatory Scientist, Office of Drug Evaluation III
Amy Taylor, M.D., Medical Officer, Maternal Health Staff
John Alexander, M.D., M.P.H., Acting Deputy Director, Division of Pediatric and Maternal Health (DPMH)
Charles McQueen, M.D., Medical Officer, DGIEP
Jacqueline Yancy, Ph.D., Regulatory Project Manager (RPM), DPMH
Meshawn Payne, RPM, DPMH
Mishale Mistry, Pharm.D., M.P.H., Team Leader, Division of Medication Error Prevention and Analysis (DMEPA)

Matthew Barlow, RN, B.S.N., Safety Evaluator, DMEPA
Ginneh Stowe, M.S., Safety RPM, Office of Surveillance and Epidemiology

SPONSOR ATTENDEES

Name	Title	Organization
Arthur Deboeck	General Manager	Galephar PR
Ileana L. Diez	Director Scientific Affairs	Galephar PR
Britta Martinez	Project Manager	Galephar PR
Hafid Touam	Business Development	Galephar PR
(b) (4)		

1.0 BACKGROUND

N-Acetylcysteine Lysine (NAL) powder for oral solution is the lysine salt of N-Acetylcysteine (NAL) in a powder form to be dissolved in a liquid such as water, (b) (4) or soda and resultant to form a drinkable solution, that upon administration is a solution like the RLD.

Galephar P.R., Inc. (Galephar) submitted a Type B Pre-NDA meeting request to discuss the contents of their impending New Drug Application utilizing the 505(b)(2) regulatory pathway. Galephar plans to use the (b) (4)

The meeting request was granted and held as a face-to-face meeting.

FDA sent Preliminary Comments to Galephar on May 17, 2016.

2. DISCUSSION

Questions from Galephar are in plain text. Responses from the FDA are in **bold text**. Meeting Discussion is in **bold italics**.

2.1. Regulatory

Question 1: Does the FDA agree that a NDA for Galephar's NAL, a salt of Acetylcysteine can be submitted under 505(b)(2), since Galephar's NAL is a powder for oral solution and the RLD is a solution for oral administration?

FDA Response to Question 1:

Based on the information you have provided, your proposed product would not be a "duplicate" of a listed drug (i.e., different active ingredient and dosage form) and therefore may be submitted as a 505(b)(2) application. However, be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate.

A 505(b)(2) application contains “full reports of investigations” of safety and effectiveness where at least some of the information required for approval comes from studies not conducted by or for you and for which you have not obtained a right of reference or use (e.g., reliance on the FDA’s finding of safety and/or effectiveness for a listed drug or published literature). Therefore, in general, reliance on an approved ANDA ([REDACTED] ^{(b) (4)}) is not acceptable to support a proposed 505(b)(2) application. You need to identify the NDA that was the basis for submission for the ANDA you have incorrectly cited as the listed drug relied upon to support your proposed 505(b)(2) application. You must also provide an appropriate patent certification or statement with respect to each patent listed in FDA’s “Approved Drug Products with Therapeutic Equivalence Evaluations” (the Orange Book) for the listed drug upon which you rely (see 21 CFR 314.54(a)(1)(vi)).

If the listed drug for which you are relying on FDA’s finding of safety and/or effectiveness for is discontinued and we determine that a comparative bioavailability study is necessary to establish a bridge, it is recommended you use the ANDA product designated as the reference listed drug (RLD) in the Orange Book to establish a bridge between your proposed drug product and the specified listed drug(s). Note also that reliance on FDA’s finding of safety and/or effectiveness for a discontinued listed drug(s) is contingent on FDA’s finding that the drug was not discontinued for reasons of safety or effectiveness.

Refer to the 505(b)(2) REGULATORY PATHWAY section below for information about submitting a 505(b)(2) NDA.

Meeting Discussion:

Galephar clarified that they will cite Mucomyst as the listed drug and use the RLD listed in the orange book for bridging purposes. Galephar will contact FDA if they cannot obtain the RLD.

2.2. Clinical

Question 2: [REDACTED] ^{(b) (4)}

FDA Response to Question 2:

[REDACTED] ^{(b) (4)}
[REDACTED] you must conduct a relative bioavailability study to bridge your proposed product to the listed drug for which you intend to rely on FDA’s finding of safety and/or effectiveness.

Please provide physicochemical characteristics of NAL, including dissociation constant, and the justification that the lysine portion of the NAL salt molecule would not affect the safety or efficacy of NAC.

See Guidance for Industry - Bioavailability and Bioequivalence Studies Submitted in NDAs or INDs — General Considerations at:

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM389370.pdf>

Meeting Discussion:

FDA advised Galephar to submit the physicochemical characteristics and dissociation constant for the lysine salt and sodium salt for review prior to the submission of the NDA in order to determination whether bioavailability studies need to be conducted. This information should be submitted as a Written Response Only (WRO) meeting request.

(b) (4)

2.3. CMC

Question 3: Does the FDA agree that Physical and Chemical Characteristics of the resultant solution shall be sufficient for approval under a 505(b)(2)?

FDA Response to Question 3:

(b) (4)

In your NDA, you will need to provide complete characterization and testing of your API to ensure identity, purity, strength and quality. Please refer to the ICH Guideline Q6A, *Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances* available at: http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Quality/Q6A/Step4/Q6Astep4.pdf.

Please also refer to response to Question 2 with regard to request for characterization of the NAL active ingredient.

Meeting Discussion:

The acceptability of the drug substance and drug specification will be determined during the NDA review.

Question 4: Does the FDA want any additional Physical and Chemical Characteristics testing as part of the NDA submission?

FDA Response to Question 4:

Please see response to Question 3.

Meeting Discussion:

No further discussion needed.

Question 5: Galephar's NAL for Oral Solution is intended for oral administration and there is no requirement for oral products to be sterile, as such, (b) (4) is this acceptable?

FDA Response to Question 5:

Yes, provided the drug product is manufactured and tested in accordance with current cGMP guidelines, (b) (4). Include USP <61> microbial limits testing as part of the release specification at the time of NDA submission. Note that the drug product should meet the following release and stability specifications: $\leq 10^3$ cfu/g Total Aerobic Microbial count, absence of *Escherichia coli*, and $\leq 10^2$ cfu/g Total Combined Yeasts and Molds count (see USP <1111> *Microbiological Examination of Non-sterile Products: Acceptance Criteria for Pharmaceutical Preparations and Substances for Pharmaceutical Use*).

Meeting Discussion:

No further discussion needed.

2.4. Pediatric Studies

Question 6: Does the FDA agree that given the use of NAL and the established use in pediatric patients that a waiver of PREA would be granted?

FDA Response to Question 6:

Your product represents a new salt and as such would be considered a new active ingredient. Therefore the Pediatric Research Equity Act (PREA) would apply. The final determination for granting a waiver of studies required under PREA would be made at the time of an approval of your product and would need to be reviewed by the Pediatric Review Committee. At this time, a partial waiver for (b) (4) appears reasonable. If you provide an acceptable bridge to the listed drug that you intend to rely upon, then your product would be considered fully assessed for pediatric patients (b) (4). In addition, you will need to address the safety of the lysine component of NAL in pediatric patients.

Since PREA will be triggered, you will need to submit an Initial Pediatric Study Plan (iPSP). See the PREA Requirements section below.

Meeting Discussion:

FDA reiterated that Galephar must provide an iPSP which should also address the safety of lysine salt in pediatric patients.

2.5. Proprietary Name and Labeling

Question 7: Does the FDA agree that the propriety name can be submitted after NDA submission?

FDA Response to Question 7:

We recommend the proposed proprietary name be submitted at the time of the NDA submission. In your request for proprietary name submission, please submit a cover letter with the following information:

- Cover Letter for proposed proprietary name reviews, include the statement “REQUEST FOR PROPRIETARY NAME REVIEW” (PNR) in bold, capital letters on the first page of the submission.
- Submit all labels and labeling or refer to the date and eCTD sequence where the labels and labeling can be found for the PNR you are submitting.

The PNR review clock will start on the date we receive this new submission. Please refer to the following Guidance for any questions or concerns.

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm075068.pdf>

Meeting Discussion:

No further discussion needed.

Question 8: Galephar understand that the labeled amount should expressed in amount of NAC (e.g. $\frac{(b)}{(4)}$ g of NAC = $\frac{(b)}{(4)}$ g of NAL), does the agency agree?

FDA Response to Question 8:

Yes, we agree that the strength should be expressed in terms of the active moiety (NAC). Please follow the FDA guidance *Naming of Drug Products Containing Salt Drug Substances* available at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm379753.pdf>

Meeting Discussion:

No further discussion needed.

2.6. Fast Track/Priority Review

Question 9: Acetylcysteine is a product that is chronically listed on the FDA drug shortage list. Will the FDA consider reviewing this NDA under a priority review process?

FDA Response to Question 9:

The review designation (i.e., priority or standard) will be determined at the time of NDA filing. See the FDA Guidance for Industry - Expedited Programs for Serious Conditions – Drugs and Biologics at:

<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm358301.pdf>

N-acetylcysteine does not currently appear on the drug shortage list at: <http://www.accessdata.fda.gov/scripts/drugshortages/default.cfm>.

Meeting Discussion:

You may include a request with your NDA for priority review.

Additional Comments:

In Section 4.4.1 of your background package, we note the inclusion of a dosage guide and preparation table. Based on the information provided, we are unclear whether you intend to include the table in your prescribing information. We are concerned with the complexity of the table and recommend that you consider the potential for medication errors when providing dosing information for the labeling. Please note that if we find the dosing information and tables you intend to include difficult to follow, we may recommend you provide additional data (such as a label comprehension study) to ensure that healthcare providers can safely and effectively prescribe and prepare doses of NAL based on the dosage guide and preparation table.

4.0 PREA REQUIREMENTS

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

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

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

5.0 PRESCRIBING INFORMATION

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

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

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

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

6.0 SUBMISSION FORMAT REQUIREMENTS

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

7.0 505(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.

8.0 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).

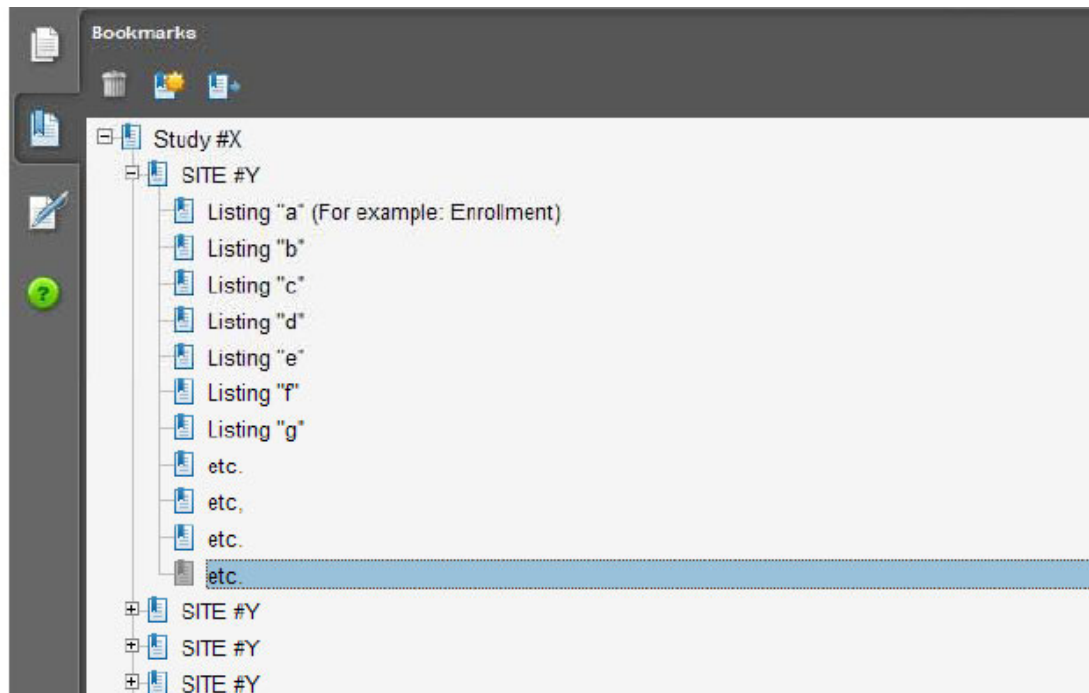
I. Request for general study related information and comprehensive clinical investigator information (if items are provided elsewhere in submission, describe location or provide link to requested information).

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 Item¹	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

8.0 ISSUES REQUIRING FURTHER DISCUSSION

None

9.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
<ul style="list-style-type: none">• See “Meeting Discussion” under #2• iPSP	Sponsor	unknown

10.0 ATTACHMENTS AND HANDOUTS

Galephar’s PowerPoint Presentation slides dated May 18, 2016

19 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

ANISSA A DAVIS
05/19/2016