CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

208746Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PNDA 208746

MEETING MINUTES

Hospira, a Pfizer Company
Attention: Rustin Dirk Jones
Senior Associate, Global Regulatory Affairs
600 North Field Drive; Building H2-2
Lake Forest, IL 60045

Dear Mr. Jones:

Please refer to your Pre-New Drug Application (pNDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for "Pemetrexed" (as ditromethamine) for Injection, 100 mg/vial, 500 mg/vial, 1 g/vial.

We also refer to the teleconference between representatives of your firm and the FDA on November 30, 2015. The purpose of the meeting was to discuss the type of additional data necessary to support use of pemetrexed ditromethamine in the proposed drug product as a modification in active pharmaceutical ingredient (API) salt form from the reference listed drug (RLD).

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

If you have any questions, call me at (240) 402-4998.

Sincerely,

{See appended electronic signature page}

Rebecca Cohen, R.N., M.P.H., O.C.N.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA (teleconference)
Meeting Date and Time:	November 30, 2015, 12:00-1:00 PM (EST)
Application Number:	208746
Product Name:	Pemetrexed (as ditromethamine)-
Indication:	In alignment with Alimta: Nonsquamous NSCLC in Combination with Cisplatin, Mesothelioma
Sponsor/Applicant Name:	Hospira, a Pfizer Company
Meeting Chair:	Jeffery Summers, Deputy Director for Safety
Meeting Recorder:	Rebecca Cohen, Regulatory Health Project Manager

FDA ATTENDEES

Jeffery Summers	Deputy Director for Safety, DOP2/OHOP
Barbara Scepura	Clinical Reviewer, DOP2/OHOP
Whitney Helms	Nonclinical Team Lead, DHOT/OHOP
Sachia Khasar	Nonclinical Reviewer, DHOT/OHOP
Olen Stephens	CMC Team Lead, ONDP/OPQ
Amit Mitra	CMC Reviewer, ONDP/OPQ
Hong Zhao	Clinical Pharmacology Team Lead, DCPV
Okpo Eradiri	Biopharmaceutics Team Leader (acting), DB/ONDP/OPQ
Norma Griffin	Lead Regulatory Health Project Manager, DOP2/OHOP
Rebecca Cohen	Regulatory Health Project Manager, DOP2/OHOP

SPONSOR ATTENDEES

Laurie Wojtko	Associate Director, US Regulatory Affairs
Rustin Jones	Senior Associate, US Regulatory Affairs
Clare McAleer	Associate Director, Global Regulatory Affairs
Scott Allan	Product Manager, Global Regulatory Affairs
Gary Brownlee	Associate R&D Fellow, APAC / Australia
Tanya Mercier	R&D Technical Leader (Formulation & Development)
Hsuan-Ming Yao	Manager Clinical Pharmacology
Amelia Trethowan	Global Program Manager
Lisa Zboril	VP Global Regulatory Affairs, Pharmaceuticals
Darryl Whittaker	VP Development (Australia and India)

Teresa Smolarek Sr. Director, Preclinical Development, Global Established Pharmaceuticals. PharmSci R&D

BACKGROUND

Regulatory
September 30, 2015, Hospira submitted a Type B, 505(b)(2), Pre-NDA meeting request. Hospira states they intend to file an application for the proposed Pemetrexed (as ditromethamine) for Injection product via a 505(b)(2) NDA pathway with reliance on the previous FDA finding of safety and effectiveness for pemetrexed through reference to the listed drug, ALIMTA.

Chemistry Manufacturing and Controls
Hospira is developing a new pemetrexed formulation that will refer to the safety and efficacy of ALIMTA, the listed drug. The listed drug is formulated with a disodium salt of pemetrexed, whereas, Hospira's formulation utilizes the ditromethamine pemetrexed salt. The formulations both use mannitol (b) (4) and will be reconstituted to the same concentration in the same diluent. Hospira proposes a 1 g/vial configuration, which is not available from the listed product. The meeting package provides physicochemical data to support a biowaiver request, which will be submitted to the forthcoming NDA.

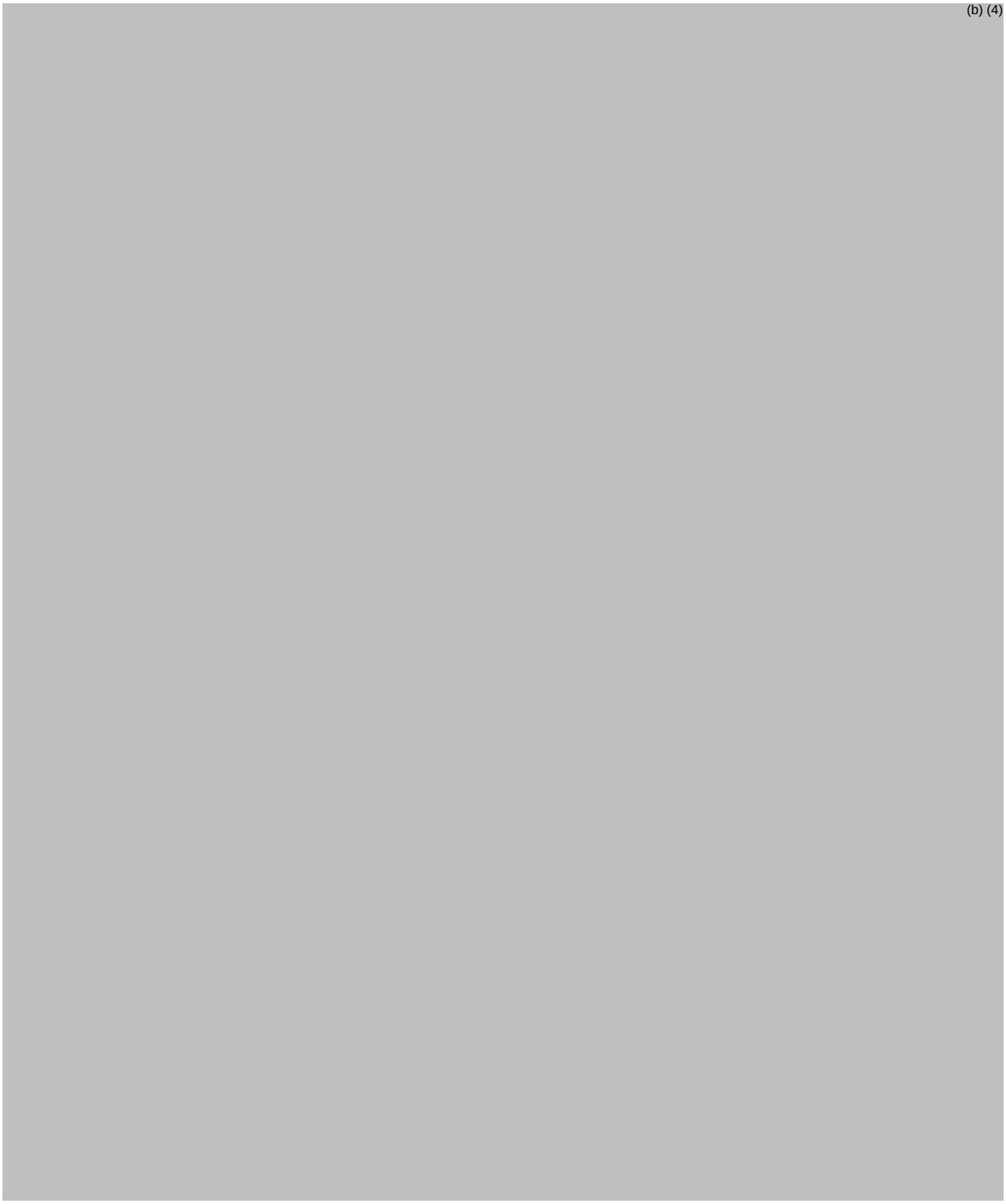
Non-Clinical
In the course of developing a generic version, pemetrexed (as ditromethamine) of the approved drug ALIMTA (pemetrexed; RLD), Hospira identified high levels of 3 degradation impurities (RRT (b) (4), RRT (b) (4), and RRT (b) (4)) during the forced degradation test [60ºC/75% relative humidity (RH)] that were not present in the RLD. Hospira has assessed the potential mutagenicity of the impurities through (quantitative) Structure-Activity Relationships (Q)SAR using DEREK and Leadscope Model Applier. Based on the results presented in the meeting package, these impurities are unlikely to be mutagenic. Although the levels of these 3 impurities do not exceed qualification threshold under the recommended storage conditions (25ºC/60%RH) for 6 months, Hospira has proposed a single dose toxicity study in dogs, depending upon the outcome of the ongoing long time stability test at 25ºC/60%RH.

Clinical
The proposed Hospira drug product, Pemetrexed (as ditromethamine) for Injection will have the same concentration of pemetrexed and inactive ingredients (mannitol) as the RLD. Hospira's product will have the same indications, dosing, and route of administration as the RLD, ALIMTA. Hospira intends to rely on previous findings of safety and efficacy of the RLD, ALIMTA, approved as a different salt form to the proposed drug. Hospira will request a pediatric waiver.

SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

Chemistry, Manufacturing, and Controls

1. (b) (4)



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(b) (4)

Non-clinical

4. See Context and Purpose of Question 4 on pages 43-44 in briefing package.

Hospira would like to obtain the Agency's concurrence that no further *in vitro* testing is required to assess mutagenic concern of potential degradation products specific to Pemetrexed (as ditromethamine) for Injection ((b) (4)) following absence of absence of any structural alerts from the two complementary (Q)SAR methodologies?

FDA Response to Question 4:

Based on the results of the DEREK and Leadscope Model Applier methodologies reported in the meeting package, no further in vitro testing is required to assess mutagenic concern of the 3 potential degradation products specific to Pemetrexed (as ditromethamine) for Injection.

Hospira 11/24/2015 Email Response:

Hospira acknowledged FDA's response and no further discussion was required.

5. See Context and Purpose of Question 5 on pages 43-44 in briefing package.

Hospira would like to confirm with the Agency that no further identification or qualification of the potential degradation products specific to Pemetrexed (as ditromethamine) for Injection (RRT (b) (4)) would be required provided levels remain below the identification and qualification thresholds for new drug products (0.2%) in accordance with ICH Q3B(R2) under real time storage?

FDA Response to Question 5:

If the specifications for the potential degradants remain below the 0.2% threshold described in ICH Q3B(R2), then no additional nonclinical studies to qualify these impurities would be required.

Hospira 11/24/2015 Email Response:

Hospira acknowledged FDA's response and no further discussion was required.

6. See Context and Purpose of Question 6 on pages 45-47 in briefing package.

Does the Agency agree that for the potential impurities specific to Pemetrexed (as ditromethamine) for Injection (RRT (b) (4), RRT (b) (4), and RRT (b) (4)

(b) (4)

FDA Response to Question 6:

No, FDA does not agree. (b) (4)

(b) (4)

7. See Context and Purpose of Question 7 on page 47 in briefing package.

If (b) (4), Hospira proposes a single dose toxicity study in beagle dog with a two week recovery period comparing potential toxicity, toxicokinetics, and pharmacodynamics (clinical hematology) with ALIMTA.

Does the Agency agree with the Animal model –The Beagle dog?

FDA Response to Question 7:

FDA has no objection to the use of the Beagle dog.

Hospira 11/24/2015 Email Response:

Hospira acknowledged FDA's response and no further discussion was required.

8. See Context and Purpose of Question 8 on page 47 in briefing package.

If (b) (4), Hospira proposes a single dose toxicity study in beagle dog with a two week recovery period comparing potential toxicity, toxicokinetics, and pharmacodynamics (clinical hematology) with ALIMTA.

Does the Agency agree the proposed study design, including the proposed dose level of the impurity as outlined in the low and high-dose treatment groups?

FDA Response to Question 8

The design of the toxicology study to qualify the potential degradation impurities, outlined in the meeting package appears sufficient. Please increase the high dose of the impurities to levels high enough to meet or exceed the amount that humans will be exposed to at the maximum recommended dose with the requested specification.

Hospira 11/30/2015 email response:

With reference to FDAs written response (in Q8) to increase the impurities in the high-dose group, Hospira would like to confirm that the current high-dose group in the single-dose Beagle dog toxicity study represents a clinical exposure of (b) (4)X the level that a patient would be exposed to in receiving the recommended maximum dose of 500 mg/m2 (as per Alimta product insert) in Pemetrexed (as ditromethamine) at the provisional NMT spec of (b) (4)%.

Does the agency consider the selection of the dose level in the high-dose group treatment group for the impurity (represents (b) (4) times the clinical exposure level) sufficient for the purposes of qualifying the (b) (4) impurity at the provisional specification of NMT (b) (4)%?

Discussion During 11/30/2015 Teleconference for Question 8:

Yes. FDA reminds Hospira that dose levels that results in death are typically not used to support impurity qualification.

Chemistry, Manufacturing, and Controls

9. (b) (4)

10. (b) (4)

Chemistry, Manufacturing, and Controls & Non-Clinical

11. See Context and Purpose of Question 11 on pages 49 in briefing package.

Hospira would like to confirm with the agency whether the proposed package of comparative CMC and non-clinical studies is considered appropriate and provides an adequate basis to demonstrate a comparable safety and efficacy profile to the listed drug approved as a different salt form, such that a scientific bridge to the RLD can be established in support of a 505(b)(2) application.67 Context and Purpose of

FDA Response to Question 11:

In general, the proposed package appears reasonable to support a 505(b)(2) application. See FDA responses to questions 1-10.

Hospira 11/24/2015 Email Response:

Hospira acknowledged FDA's response and no further discussion was required.

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, you should submit the initial PSP as early as practicable but before the initiation of any phase 3 studies, or any combined phase 2 and phase 3 study, of the drug that is the subject of the initial PSP. If a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, the sponsor should submit the initial PSP no later than 210 calendar days before the marketing application is submitted. 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.

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 *PLLR Requirements for Prescribing Information* websites including:

- 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 in 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 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.

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

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 *PLLR Requirements for Prescribing Information* websites including:

- 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 in 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 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.

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

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog (Catalog) (See http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm).

On December 17, 2014, FDA issued final guidance, *Providing Electronic Submissions in Electronic Format--- Standardized Study Data* (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM292334.pdf). This guidance describes the submission types, the standardized study data requirements, and when standardized study data will be required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide (Conformance Guide) (See http://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pd

f), as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data will be required in marketing application submissions for clinical and nonclinical studies that start on or after December 17, 2016. Standardized study data will be required in commercial IND application submissions for clinical and nonclinical studies that start on or after December 17, 2017. CDER has produced a *Study Data Standards Resources* web page that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that start before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

Additional information can be found at
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm248635.htm

For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, CDER encourages sponsors to use Standards for the Exchange of Nonclinical Data (SEND) and submit sample or test data sets before implementation becomes required. CDER will provide feedback to sponsors on the suitability of these test data sets. Information about submitting a test submission can be found here:
http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/ucm174459.htm

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled, Study Data Standards Resources and the CDER/CBER Position on Use of SI Units for Lab Tests website found at http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/ucm372553.htm.

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.

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. 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.				

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)**
1. Example: Published literature	*Nonclinical toxicology*
2. Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication X*
3. Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section XXX*
4.	

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.

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

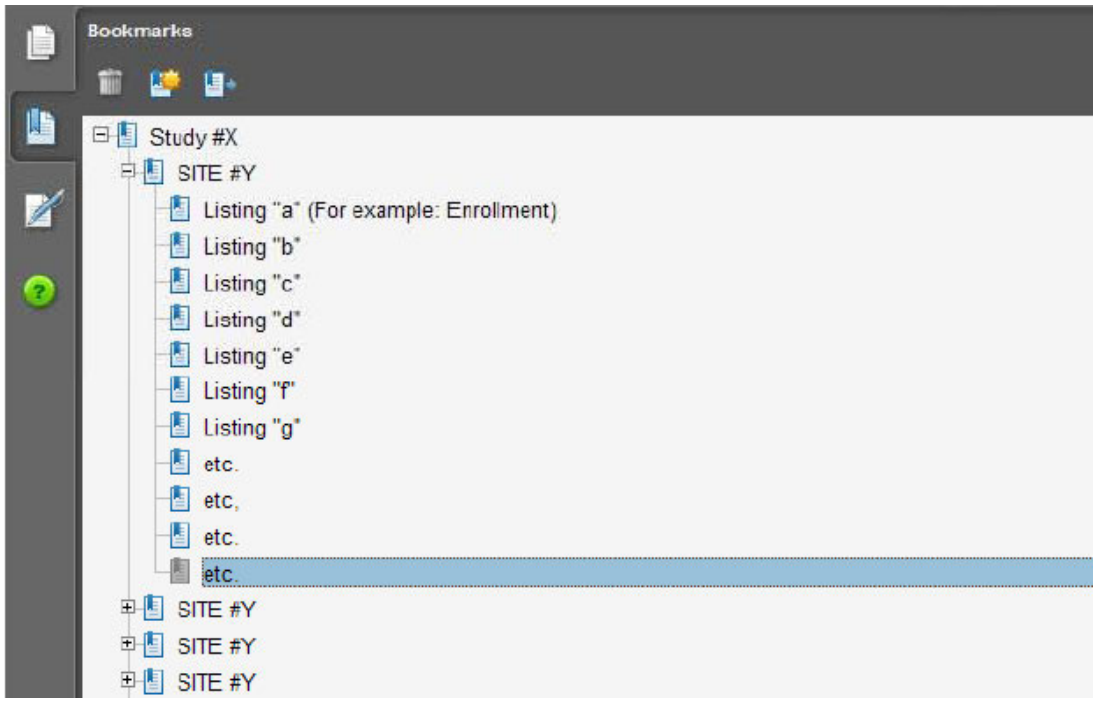
b. Name, address and contact information of all Contract Research Organization (CROs) used in the conduct of the clinical trials and brief statement of trial related functions transferred to them. If this information has been submitted in eCTD format previously (e.g., as an addendum to a Form FDA 1571, 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:

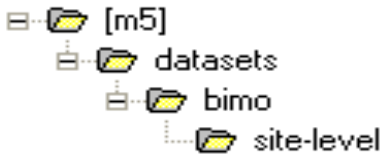
OSI is piloting a risk based model for site selection. Voluntary electronic submission of site level datasets is intended to facilitate the timely selection of appropriate clinical sites for FDA inspection as part of the application and/or supplement review process. If you wish to voluntarily provide 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

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

/s/

REBECCA L COHEN
12/10/2015