CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209472Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 126831

MEETING MINUTES

Eagle Pharmaceuticals, Inc.
Attention: Foma Rashkovsky
Vice President, Regulatory Affairs
50 Tice Boulevard, Suite 315
Woodcliff Lake, NJ 07677

Dear Mr. Rashkovsky:

Please refer to your Pre-Investigational New Drug Application (PIND) file for Pemetrexed Injection, 25 mg/mL.

We also refer to the teleconference between representatives of your firm and the FDA on January 21, 2016. The purpose of the meeting was to discuss the proposed nonclinical study to qualify impurity and degradation products in the ready-to-dilute (RTD) product and the appropriateness to submit a waiver request for in vivo bioavailability studies in the New Drug Application (NDA).

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) 402-6611.

Sincerely,

{See appended electronic signature page}

Leah S. Her, M.S.
Regulatory Health Project Manager
Division of Oncology Products 2
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

Reference ID: 3889966
Reference ID: 4662511

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-IND/Pre-NDA
Meeting Date and Time:	January 21, 2016 / 12:00 – 1:00 PM (EST)
Meeting Location:	Teleconference
Application Number:	126831
Product Name:	Pemetrexed Injection, 25 mg/mL
Indication:	The same indications as approved for listed product Alimta
Sponsor/Applicant Name:	Eagle Pharmaceuticals, Inc.
Meeting Chair:	Suzanne Demko
Meeting Recorder:	Leah Her

FDA ATTENDEES

Joseph Gootenberg	Deputy Director, OHOP/DOP2
Gideon Blumenthal	Clinical Team Lead, OHOP/DOP2
Barbara Scepura	Clinical Reviewer, OHOP/DOP2
Leah Her	Regulatory Project Manager, OHOP/DOP2
Whitney Helms	Nonclinical Supervisor, OHOP/DHOT
Anwar Goheer	Nonclinical Reviewer, OHOP/DHOT
Joyce Crich	CMC Lead (Acting), OPQ/ONDP/DNDPI/NDPBII
Xing Wang	CMC Reviewer, OPQ/ONDP/DNDPI/NDPBII
Om Anand	Biopharmaceutics Reviewer, OPQ/ONDP/DB
Joan Zhao	Biopharmaceutics Reviewer, OPQ/ONDP/DB
Hong Zhao	Clinical Pharmacology Team Lead, OTS/OCP/DCPV
Sriram Subramaniam	Clinical Pharmacology Reviewer, OTS/OCP/DCPV
Tamy Kim	Associate Director of Regulatory Affairs, OHOP

SPONSOR ATTENDEES

Adrian Hepner	E.V.P. of Clinical Research, Medical & Regulatory Affairs
Steven L. Krill	E.V.P. and Chief Scientific Officer
Mark Smith	V.P. of Preclinical Development
Foma Rashkovsky	V.P. of Regulatory Affairs
Feng-Jing Chen	V.P. of Pharmaceutical Development
Brian Chanas	Director Preclinical Development
Todd Jenson	Senior Director, Project Management
Sonal Patel	Senior Director, Project Management

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BACKGROUND

On November 24, 2015, Eagle Pharmaceuticals (Eagle) requested a Type B meeting to discuss their 505(b)(2) development plan for a ready-to-dilute (RTD) pemetrexed product [Pemetrexed Injection for Intravenous Use, 25 mg/mL (500 mg/20 mL multiple-dose vial)] referencing the listed product, Alimta. Specifically, Eagle seeks FDA agreement on the proposed nonclinical study to qualify impurity and degradation products in the RTD product and to obtain feedback on the appropriateness to submit a waiver request for in vivo bioavailability studies in the New Drug Application (NDA). The meeting request was granted on December 8, 2015 as a teleconference meeting.

Chemistry, Manufacturing and Controls
The proposed ready-to-dilute (RTD) pemetrexed product contains drug substance pemetrexed (b) (4) (b) (4) which is different from pemetrexed disodium salt, the drug substance used for the listed drug Alimta. The chemical name for pemetrexed is: N-[4-[2-(2-amino-4,7-dihydro-4-oxo-1H-pyrrolo[2,3-d]pyrimidin-5-yl)ethyl]benzoyl]-L-glutamic acid. (b) (4) with a molecular formula of $C_{20}H_{21}N_5O_6$ and a molecular weight of 427.41. Commercially available Alimta (pemetrexed for injection) is a lyophilized powder which must first be reconstituted with 0.9% Sodium Chloride Injection (to yield a solution concentration of 25 mg/mL). According to the additional information provided by Eagle following the January 21, 2016, teleconference, the proposed liquid formulation contains pemetrexed (25 mg/mL) and the following excipients: propylene glycol (260 mg/mL); tromethamine (16.5-19.9 mg/mL) and hydrochloride acid for adjusting pH (b) (4); and water for injection (b) (4) It is intended to be stored at (b) (4) (2-8°C).

Nonclinical
Eagle proposes to conduct a GLP-compliant 6-week repeat dose IV study of RTD Pemetrexed solution in mice in order to provide toxicology data to support potential differences in the impurity/degradation levels for the proposed product that exceed those in the listed drug. No other nonclinical studies are planned. Eagle intends to rely on data from the listed drug to support other pharmacology/toxicology requirements for this pemetrexed solution application.

Clinical
Eagle's RTD liquid formulation pemetrexed product (b) (4) . Eagle expects that the safety and efficacy profiles of their ready to dilute liquid formulation pemetrexed product will be comparable to the listed drug, Alimta.

Eagle states that the indications and usage for their pemetrexed product are the same as for the listed drug, Alimta:

1. treatment of locally advanced or metastatic nonsquamous non-small cell lung cancer (NSCLC)
    - for initial treatment in combination with cisplatin
    - for maintenance treatment of patients whose disease has not progressed after four cycles of platinum-based first-line chemotherapy

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- after prior chemotherapy as a single-agent

2. treatment of mesothelioma is in combination with cisplatin

DISCUSSION

1. Background: See Company Position on page 6 to 7 of the Briefing Document.

Does the Agency agree that a 6-week repeat dose IV mouse GLP toxicology study is appropriate to qualify impurity/degradation product levels that may be present in RTD Pemetrexed Injection?

FDA Response: Yes, the proposed toxicology study appears sufficient in design to support the qualification of impurity/degradation product levels in RTD pemetrexed; however a final determination of the adequacy of the submitted data will be determined following a full review of the reports included in the original NDA submission. In addition, develop and validate a suitable analytical method to cover the range of impurity/degradant levels in the proposed toxicology study.

Eagle Emailed Response of 1/20/16: An analytical method for the assessment of the drug product has been developed and validated to cover the range of impurity/degradant levels for the product to be used in the proposed toxicology study.

Discussion During the Meeting of 1/21/16: FDA acknowledged Eagle's response. FDA stated that Eagle submit related method and validation report in the NDA submission.

2. Background: See Company Position on page 7 of the Briefing Document.

Does the proposed IV repeat-dose study in mice obviate the need for an independent assessment of local tolerance?

FDA Response: Yes, the design of the proposed IV study in mice is sufficient to obviate the need for an independent local tolerance study.

Eagle Emailed Response of 1/20/16: We agree with your responses to questions 2 and 3 and no further discussion is requested at this time for questions 2 and 3.

Discussion During the Meeting of 1/21/16: None

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3. Background: NA

Eagle anticipates using the 505(b)(2) NDA filing pathway for RTD Pemetrexed Injection. Does Agency agree with this approach?

FDA Response: Yes, based on the information provided in the meeting package, the 505(b)(2) pathway appears to be appropriate. See additional comments under **505(b)(2) REGULATORY PATHWAY** below.

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 Eagle's application is submitted, such that Eagle's 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 Eagle's 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.

Eagle Emailed Response of 1/20/16: We agree with your responses to questions 2 and 3 and no further discussion is requested at this time for questions 2 and 3.

Discussion During the Meeting of 1/21/16: None

4. Background: See Company Position on page 8 of the Briefing Document.

Does Agency agree that it will be appropriate to submit a waiver request for in vivo bioavailability studies in the NDA?

FDA Response: Yes, Eagle may include a biowaiver request in the NDA submission; however, Eagle's proposed drug product contains different APIs ((b) (4) instead of disodium salt) and excipients (propylene glycol and tromethamine instead of mannitol and sodium hydroxide). Difference in APIs and excipients may affect the pharmacological activity of pemetrexed. Therefore, to support a waiver request of the requirement for the submission of in vivo bioavailability (BA) and/or bioequivalence (BE) data, submit sufficient justification and supporting data (e.g., published literature, study data, etc.) demonstrating that the existing difference in the API and excipients used do not affect in any way the pharmacokinetics, efficacy, and safety of the proposed Eagle's RTD Pemetrexed Injection product, as compared to the listed drug product, Alimta.

In support of the biowaiver request, FDA recommends that Eagle include (but not limited to) in the NDA the following information/data demonstrating the comparability of Eagle's proposed RTD Pemetrexed product to Alimta:

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a. Comparative general information:
   i. Qualitative and quantitative composition of the formulations before and after reconstitution or dilution, dosage form, administered volume, labeling, etc., for the proposed drug product and the listed drug in a side-by-side comparison table.

Eagle Emailed Response of 1/20/16: We agree with the Agency to include the comparative general information as recommended by FDA in the NDA in support of the biowaiver request.

Discussion During the Meeting of 1/21/16: None

b. Comparative physico-chemical studies:
   i. Analysis methods confirming chemical structure of proposed API in the RTD product vs. the active moiety in Alimta, after reconstitution/dilution.
   ii. Assessment of comparative dissociation of Eagle's proposed drug product vs. Alimta in an aqueous environment with respect to the ions formed.

Eagle Emailed Response of 1/20/16 for 4(b)(i, ii): The proposed API for Eagle's RTD product, pemetrexed ((b) (4) diacid) is identical to the active moiety in Alimta and its basis of strength per Alimta prescribing information by Eli Lilly and Company, revised in 9/2013.

(b) (4)

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(b) (4)

Table 1. Quantitative Composition and Function of each Component in Eagle's Pemetrexed Injection, 25 mg/mL

Ingredient	mg/mL	Function
Pemetrexed[a]	25	Active
Propylene Glycol, USP/EP	260	(b) (4)
Tromethamine, USP/EP	Adjust pH to (b) (4)	pH Adjustment
Hydrochloric Acid, NF/EP	Adjust pH to	pH Adjustment
Water for Injection, USP		(b) (4)
		(b) (4)

Discussion During the Meeting of 1/21/16 for 4(b)(i, ii): FDA acknowledged that Eagle will not perform the analysis as requested in 4(b)(i). FDA stated that Eagle provide justification in the NDA submission.

With regards to Eagle's response for 4(b)(ii), Eagle agreed to demonstrate that different excipients in the proposed product would not affect the solubility of proposed product as compared to the listed product, Alimta. FDA stated that Eagle provide the data and justification for not pursuing additional studies in the NDA submission.

iii. Similarity with Alimta in terms of physico-chemical characteristics relevant for the safety of drug product: appearance, visible particles, pH, and osmolality for the used proposed drug product and listed drug product. The measurements should be done in triplicate for each lot tested of the proposed product relative to the reconstituted/ diluted Alimta product.

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Eagle Emailed Response of 1/20/16 for 4(b)(iii): We agree to include the comparative physico-chemical information recommended by FDA in the NDA in support of the biowaiver request.

Discussion During the Meeting of 1/21/16 for 4(b)(iii): None

c. Comparative nonclinical studies:
   i. In vitro study to assess the affinity of Eagle's RTD Pemetrexed and Alimta to OAT3 renal receptors and to demonstrate similar elimination profile.
   ii. In vitro study to assess the transport of Eagle's RTD Pemetrexed and Alimta by PCFT and RFC receptors and to demonstrate that both proposed and listed drug products follow the same pharmacological pathways.
   iii. In vitro study to assess the binding of Pemetrexed to human plasma proteins, serum albumin and α1-acid glycoprotein. The similarity in protein binding for both proposed and listed drug products should be demonstrated.

Eagle Emailed Response of 1/20/16 for 4(c): As outlined in our response to 4b (above), at the point of patient exposure, Pemetrexed in the Eagle RTD formulation is identical to that in Alimta, as both drug products are a 'true solution' (b) (4) therefore the results of any comparative in vitro assay would be the same between the Eagle and Alimta 'pemetrexed' drug substances. In terms of potential excipient mediated effects on the transporter/receptor mechanisms noted; all excipients in the Eagle RTD formulation are below the FDA Inactive Ingredient Database (IID) limits (for intravenous administration), and are considered standard excipients consistent with the design of a dosage form for intravenous infusion. It is therefore our position that in vitro characterization of the Eagle RTD product vis-à-vis Alimta (in the nonclinical studies listed in response to 4c-i, iii, and iii) would provide no information further to the understanding of the Eagle RTD product as the comparable nature of any data is self-evident.

Discussion During the Meeting of 1/21/16 for 4(c): Eagle agreed to submit their proposal to address FDA comment 4(c) within 2 weeks of this meeting.

d. Comparative in vivo PK study in an animal model:
   i. To further demonstrate that Eagle's proposed RTD Pemetrexed product and Alimta have similar pharmacokinetic profile, regardless of the differences in the active and inactive ingredients, provide in-vivo bioavailability/ bioequivalence data from a nonclinical pharmacokinetic study conducted in an animal model (i.e., Beagle dogs) following IV administration of the proposed and listed Pemetrexed products. This information will help to further understand the in vivo behavior of Eagle's proposed RTD Pemetrexed product in comparison with the listed drug product, Alimta, and demonstrate similarity.

Eagle Emailed Response of 1/20/16 for 4(d): As outlined in our response to 4b (above), at the point of patient exposure, Pemetrexed in the Eagle RTD formulation is identical to that in Alimta as both drug products are a 'true solution' (b) (4)

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(b) (4) It is therefore self-evident that the pharmacokinetic profile of the Eagle RTD product following intravenous infusion will be the same as Alimta (b) (4). This statement is predicated on all excipients in the Eagle RTD formulation being below the FDA Inactive Ingredient Database (IID) limits (for intravenous administration). It is therefore our position that none of the formulation excipients (in either the Eagle RTD formulation, or in the reconstituted Alimta formulation) have an impact on the pharmacokinetic profile of Pemetrexed.

Discussion During the Meeting of 1/21/16 for 4(d): Eagle agreed to submit their proposal to address FDA comment 4(d) within 2 weeks of this meeting.

Be aware that based on the outcome of the review of the biowaiver supporting information, an additional clinical study(ies) may be necessary for approval.

***Eagle Emailed Response of 2/4/2016 for 4c and 4d**: During the teleconference it was discussed that the recommended in vitro studies (item 4c) are customarily conducted with active pharmaceutical ingredient solubilized in a medium compatible with the mammalian cell culture system being employed. It was agreed that as Eagle will be providing data in the submission demonstrating the comparability of the active pharmaceutical ingredient between the Eagle-RTD product and Alimta, that further characterization of pemetrexed diacid in these in vitro studies is not required.*

Furthermore, the pharmacokinetic profile of the Eagle-RTD product is expected to be comparable to the PK profile of Alimta, as both drug products are 'true solutions' (b) (4). *In order to demonstrate the pharmacokinetic bioequivalence of the Eagle RTD product as compared to Alimta, Eagle proposes to conduct a comparative pharmacokinetic study in (beagle) dogs.*

Does the Agency agree that the demonstration of solubility in final admixture, and pharmacokinetic equivalence in dogs, is sufficient to support a biowaiver request?

***FDA Response**: FDA acknowledges the discussion of the in-vitro tests under Question 4c above during the teleconference on 2/4/2016; however, it is FDA's current thinking that at a minimum, similarity in protein binding for both proposed and listed drug products should be demonstrated. This protein binding study should be conducted with the reconstituted listed drug and the proposed RTD product. In addition to the "determination of solubility in the final admixture", provide the other comparative physicochemical data as previously discussed.*

Upon further evaluation of the proposed pharmacokinetic equivalence study in dogs as well as the proposed study in mice comparing Pemetrexed Injection with the listed drug (which will include toxicokinetic data), FDA has determined that an additional comparative PK study in dogs is not warranted.

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ADDITIONAL COMMENTS

5. Submit an Initial Pediatric Study Plan (iPSP) within 60 days of this meeting or no less than 210 days prior to the submission of an NDA application. Please see additional comments under **PREA REQUIREMENTS** below.

Eagle Emailed Response of 1/20/16: Eagle did not request additional discussion.

Discussion During the Meeting of 1/21/16: None

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 this meeting or no less than 210 days prior to the submission of an NDA application. 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.

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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.

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).

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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.pdf), 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

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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.

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.				

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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.

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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.	

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

/s/

LEAH S HER
02/19/2016

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