CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209080Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 123532

**MEETING REQUEST-
WRITTEN RESPONSES**

Italfarmaco S.p.A.
Attention: Damaris DeGraft-Johnson, RPh, MSc
US Agent, DJA Global Pharmaceuticals, Inc.
325 Sentry Parkway, Building 5 West, Suite 200
Blue Bell, PA 19422

Dear Ms. DeGraft-Johnson:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act (FDCA) for Teglutik (riluzole) oral (b) (4)

We also refer to your submission dated March 15, 2016, containing a Type C meeting request. The purpose of the requested meeting was to discuss submission of a 505(b)(2) application for Teglutik.

Further reference is made to our Meeting Granted letter dated April 7, 2016, wherein we stated that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your March 15, 2016, background package.

If you have any questions, call Susan Daugherty, Regulatory Project Manager at (301) 796-0878.

Sincerely,

{See appended electronic signature page}

Eric Bastings, MD
Deputy Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure:
Written Responses

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

WRITTEN RESPONSES

Meeting Type:	C
Meeting Category:	WRO
Meeting Date and Time:	May 18, 2016 1:00 pm EDT
Application Number:	IND 123532
Product Name:	Teglutik (riluzole) oral suspension
Indication:	amyotrophic lateral sclerosis (ALS)
Sponsor/Applicant Name:	Italfarmaco S.p.A.

1.0 BACKGROUND

On November 25, 2014, responses for a pre-IND meeting request were sent to Italfarmaco. The purpose of that meeting was to discuss the development of Teglutik (riluzole) oral suspension to treat ALS for submission as a 505(b)(2) application. The sponsor plans to rely on FDA's finding of safety and effectiveness for NDA 020599 for Rilutek (riluzole) tablets.

On October 30, 2015, the sponsor submitted their IND.

On March 15, 2016, the sponsor requested a pre-NDA meeting. A type C meeting was granted because the pivotal PK trial was not complete.

2.0 QUESTIONS AND RESPONSES

REGULATORY QUESTIONS

(b) (4)

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

(b) (4)

[redacted]

NONCLINICAL QUESTIONS:

4. Nonclinical Safety Data Package: Nonclinical Studies; Published literature to support the 505(b)(2) NDA application

4a. Safety of Excipients

In the FDA December 23, 2015 IND Study May Proceed letter, FDA provided the following comment:

You have not documented that the excipient, polyoxyl 20 cetostearyl ether, is present in an FDA-approved oral drug product at a level resulting in a daily dose similar to or higher than that anticipated for ITF2985. Therefore, additional nonclinical data may be needed to support clinical development of ITF2985.

To address this request, ITF is planning to perform a 3-month rat study. The rationale for this proposal and the proposed draft protocol outline with details for this study is provided in Attachment A.

- Does the FDA agree with this study proposal?

- If the outcome of the study justifies the daily dosing of ITF2985, does the FDA agree that this study will fully address the above request to support this NDA?

- Depending on when FDA provides input on this study, ITF proposes to provide the results of this study during the NDA review in accordance with NDA data review timeline requirements. Does the FDA agree?

FDA Response to Question 4a:
A 3-month study in a single species would not be sufficient to support use of polyoxyl 20 ceterostearyl ether in the to-be-marketed product. We refer you to guidance for information on the nonclinical studies of the excipient or a sufficiently similar excipient (b) (4) needed to support chronic oral administration at the proposed daily dose (cf. *Guidance for Industry: Nonclinical Studies for the Safety Evaluation for Pharmaceutical Excipients, May 2005*). Although you have identified published nonclinical studies of polyoxyl 20 cetostearyl ether (b) (4) published literature does not typically provide sufficient detail to allow an independent evaluation of the data.

4b. ITF has completed one nonclinical study, an in-vivo PK study titled, "*Comparative oral bioavailability of Teglutik® oral suspension vs. Rilutek® capsules in rats [Pk1]"*. As proposed above, ITF plans to conduct a second nonclinical study to support safety of the excipient, polyoxyl 20 cetostearyl ether in the drug product. The results for this second study will be included in the NDA. Since there will be only two completed nonclinical study in the NDA, ITF plans to summarize the results from these studies in module 2.4 and provide the study reports in module 4. Thus, ITF does not plan to provide a module 2.6 in the NDA submission.

- Does FDA agree with this approach and not including a Module 2.6 in the NDA?

FDA Response to Question 4b:
A summary of the results of all nonclinical studies conducted to support the NDA should be included in the appropriate locations in Module 2, including those from studies of the excipient(s) in Folder 2.6. (See response to Question 4a.)

5. Published Literature Search to Support 505(b)(2) Submission

To support the Riluzole Oral Suspension NDA application the planned literature searches will be performed in their entirety to provide additional documentation. The literature searches will be performed using two separate databases:

- Medline – this database is managed by the National Library of Medicine and contains citations from 1950 to the present.
- Toxnet – this resource is a cluster of databases covering toxicology, hazardous chemicals, environmental health and related areas and is managed by the National Library of Medicine. Toxnet contains citations from 1965 to the present.

Searches in these databases, using the basic search terms (examples of which are described below), will be performed and number of citations recovered will be presented. ITF plans to search the published literature from three months before the date of the last update (November 2012) of the LD Rilutek product labeling i.e. from July 1st, 2012 through Feb/ March of 2016. All abstracts will be reviewed for new, relevant findings in the areas of clinical efficacy, clinical

safety, pharmacokinetics and toxicology. In addition, within each of these areas, specific search terms will be used to find information on specific topics within the basic citations.

Examples of search terms to be used are as follows:
Riluzole, Rilutek, amyotrophic lateral sclerosis, Teglutik, Cmax, safety, efficacy. "Riluzole/administration and dosage"[MeSH] or "Riluzole/adverse effects"[MeSH] or "Riluzole/antagonists and inhibitors"[MeSH] OR "Riluzole/contraindications"[MeSH] or "Riluzole/pharmacokinetics"[MeSH] or "Riluzole/pharmacology"[MeSH] or "Riluzole/poisoning"[MeSH] OR "Riluzole/therapeutic use"[MeSH] or "Riluzole/toxicity"[MeSH]) or (Riluzole or Rilutek) and (Adverse or Toxic*) or (Side Effect*) or Safety or Safe or Risk or Monitor* or Efficacy or Case or Outcome or Evaluation* or Mechanism or Action)

The general approach will be to include literature citations with new relevant pre-clinical, nonclinical and clinical safety and efficacy information in support of the NDA. Literature will be summarized and presented, and the citations themselves will be submitted hypertext-linked to the evaluated, statistical analyses, adverse events (serious and non-serious), discontinuations, and deaths will be included. Publications will be in a text, not graphic, format in order to facilitate searching and readability.

-Does the FDA agree with our proposal and search terms for the literature search that will support the NDA?

FDA Response to Question 5:
Your approach appears reasonable.

CLINICAL QUESTIONS

6. PK Bridging Study for Efficacy and Safety to Rilutek (LD)
As mentioned above, a US IND pivotal PK study, using US procured Rilutek, and with an assessment of food effect as requested by FDA (see email to DJA dated Aug 17, 2015) is underway. The last patient out (LPO) for this study has been completed. Results from this US IND pivotal trial is expected to be available in May/June 2016. This study is intended to bridge the safety and efficacy of Riluzole Oral Suspension to Rilutek. In the FDA December 23, 2015 IND may proceed letter, FDA provided the following comments and requests regarding this pivotal study. ITF responses to these comments and requests are indicated below in italics.

Clinical Pharmacology:

- The final protocol should specify the number of subjects in each treatment arm, in addition to the total number of subjects in the trial.

ITF Response: *This has been addressed in the protocol Amendment submitted to the IND February 19, 2016.*

(b) (4)

(b) (4)

(b) (4)

- ***Does the FDA agree with this position and/or have any further comments?***

FDA Response to Question 6:
We acknowledge your rationale and justification, and will review the data and supportive information as part of an NDA review.

- For the pharmacokinetic (PK) comparison for the planned 505(b)(2) application, we consider that Cmax would be a primary PK parameter along with AUC0-t and AUC0-inf for the assessment (see the protocol synopsis and page 35 of 38 in the protocol). In the protocol, you should also specify the standard for assessing the food effect. We typically recommend that point estimates of geometric mean ratios and corresponding 90% CVs

applied to these PK parameters for both bioequivalence and food effect evaluation, judging by bioequivalence (BE) acceptance criteria (80-125%).

ITF Response: *The proposed change has been made in the amended protocol listing Cmax as a primary PK parameter together with AUC0-t and AUC0-inf and to specify that the food effect PK parameters would be assessed using the criteria of 80-125%.. The revised protocol amendment has been submitted to the IND on February 19, 2016.*

7. Confirmation of Planned Interpretation of Primary Parameter Results

(b) (4)

(b) (4)

- ***Does the FDA agree with this position and/or have any further comments?***

FDA Response to Question 7:

The main objective of a pivotal PK bridging study for a 505(b)(2) submission is to demonstrate that the proposed formulation will behave sufficiently similarly to the reference listed drug. This is to ensure the reliance of safety and efficacy of the reference listed drug for the labeling of the proposed product.

Please note that the Agency has been recommending the use of traditional BE acceptance criteria for key PK parameters to judge the similarity of two drug products. For 505(b)(2) submissions, in the event that a certain key parameter falls out of the BE acceptance criteria, it is the Applicant's responsibility to provide supportive information along with an adequate

justification for why not meeting BE acceptance criteria will not result in significant differences in clinical outcomes, and safety and efficacy findings for the reference list drug can still be relied upon for the labeling.

8. Statistical Analysis Plan (SAP) – Proposal for FDA input

Provided in Attachment C is the proposed SAP to be used for the U.S. IND Pivotal PK

study. A summary of the key features of the SAP is provided below:

a: Pharmacokinetic Profile

The PK parameters of AUC0-t, AUC0-inf, and Cmax will be the primary parameters. All other PK parameters will be regarded as secondary. The pharmacokinetic population will include all subjects completing at least 2 periods including Treatments A and B for relative bioavailability assessment and those who completed A and C for food effect assessment without major protocol violation, and for whom the pharmacokinetic profile can be adequately characterized. Analysis of Variance (ANOVA) will be performed on untransformed Tmax, Kel and T½ el and on ln- transformed AUC0-t, AUC0-inf, and Cmax at the alpha level of 0.05. Factors incorporated in the model will include: Sequence, Subject(Sequence), Period, and Treatment. The Sequence effect will be tested using the Subject(Sequence) effect as the error term. The Treatment and Period effects will be tested against the residual mean square error. Based on pairwise comparisons of the ln-transformed AUC0-t, AUC0-inf, and Cmax data, the geometric least-squares means for each treatment, the ratios (A/B and C/A) of the geometric least-squares means, calculated according to the formula "e(X-Y) * 100", as well as the corresponding 90% geometric confidence intervals will be determined. The analysis for each comparison (A versus B and C versus A) will be conducted excluding the data from the treatment that is not relevant for the comparison.

We believe these planned PK analyses support the NDA.

-Does the FDA agree with this position and/or have any further comments?

FDA Response to Question 8A:

Your proposed statistical analysis plan appears reasonable.

b: Safety Assessments

The incidence of Treatment-emergent adverse events (TEAEs) will be summarized, attributing the TEAE to the most recent study drug taken. Vital signs will be summarized using descriptive statistics and will be presented overall for Screening and Study Exit, and by the associated current treatment and measurement time for measurements taken prior to dosing and at 1.25 and 24 hours post-dose; changes from baseline will also be presented. Laboratory assessments (biochemistry, hematology, and urinalysis) and clinical signs and symptoms from

physical examination will be summarized overall for Screening and Study Exit. Safety data will be summarized but will not be subjected to inferential analysis.

We believe these planned safety analyses support the NDA.

-Does the FDA agree with this position and/or have any further comments?

FDA Response to Question 8b:

We agree with this proposal.

9. Prospective Assessments of Suicidal Ideation and Behavior in Clinical Protocols

In the FDA December 23, 2015 IND Study May Proceed letter, FDA indicated the following:

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology Products.

ITF Response: The pivotal IND PK study being conducted with Riluzole Oral Suspension does not include a prospective assessment for suicidal ideation and behavior because this study is a single dose trial in healthy volunteers.

- Does FDA agree with this omission?

FDA Response to Question 9:

Yes, we agree.

10. Integrated Summary of Safety (ISS)/Overall Safety Data to Support the NDA

a. ITF plans to utilize reliance on FDA's finding of safety as embodied in the label for the LD Rilutek by bridging Riluzole Oral Suspension to safety information in the Rilutek label via PK data. ITF plans to provide full clinical study reports with data listings for the two pilot and one EU pivotol trials; datasets for these studies are not planned to be submitted. These comparative

studies were conducted to support the EU marketing approvals for Teglutik. Thus, the reference listed drug product used as a comparator was EU approved Rilutek and therefore these studies are considered supportive for the US NDA. ITF also plans to provide a complete clinical study report with data listings and complete SDTM data sets from the US IND pivotal PK study. Because the 3 PK trials conducted in the EU are supportive and there is only one US pivotal PK trial using US sourced Rilutek, ITF does not plan to integrate all 4 studies into an ISS.

ITF also plans to submit a literature search as well as a report that documents a search of the FDA AERS since the last update of the Rilutek product insert labeling that evaluates if any new safety information currently not contained in the Rilutek label exits. This AERS report will cover November 2012 through Feb/March 2016.

Finally, ITF will provide in the NDA our most current periodic safety update report (PSUR) covering the period from Nov 19, 2013 through December 12, 2015 for adverse event reports from the Teglutik product (oral suspension) which is currently being marketed in the EU.

- Does FDA agree that ITF is not required to include an ISS in the NDA and that the proposed overall safety information that will be provided is sufficient to support the 505(b)(2) submission?

FDA Response to Question 10:

We agree with your plans to submit complete safety reports for the 3 European studies, a literature search, and your latest PSUR. We also agree that you do not need to include an ISS in the NDA.

11. Proposed Datasets for the NDA (SDTM/ADaM/CDISC)

Datasets for Pivotal PK Study (Study DSC-15-298) conducted under the IND
For the US IND pivotal PK trial we plan to submit a full clinical study report (CSR) in ICH format including full SDTM data sets. We do not plan to include ADaM datasets for the following reasons:

- The CDISC SDTM datasets, covering all the study data (AE, PK, labs, etc.), will be provided.
- The currently accepted FDA BE standard datasets (actual time and PK concentrations) will also be provided. There are no additional derived data beyond the PK parameters and those are already included in SDTM, so all of the information to reproduce analyses are accessible within SDTM.
- We understand the CDISC data standards (SDTM and ADaM) will be obligatory for FDA submissions starting Q2 2017 onwards.

Supportive EU PK studies
In Module 5, we plan to provide full clinical study reports (CSRs) with data listings for the two EU pilot studies and pivotal PK trials. These comparative studies were conducted to support the EU marketing approvals for Teglutik. Thus, the reference listed drug product

used as a comparator was EU approved Rilutek and therefore these studies are considered supportive in the US. ITF does not plan to provide SDTM and ADaM datasets for these trials.

- Does FDA agree with our plans to provide full study reports for the 3 supportive EU trials and a full clinical study report with SDTM datasets for the US pivotal trial?

FDA Response to Question 11:

We agree that you can provide full study reports from the 3 supportive EU trials, and a full study report for the US pivotal trial with SDTM datasets.

12. Case Report Forms (CRFs) and Tabulations

ITF plans to comply with 21 CFR part 314.50(f)(2). For the EU PK studies, no serious adverse events (SAE) or deaths occurred. For the US PK IND study, CRFs and Tabulations for any subjects who experience death or SAE or withdrew from the study due to any adverse event will be reported. No other case report forms will be provided.

- Does FDA agree?

FDA Response to Question 12:

We agree to this proposal.

13. Adverse Event Data Listings

ITF plans to submit adverse event listings (by subject), frequency of adverse events by body system, by intensity and relationship. Additionally, ITF plans to provide data listings of laboratory and safety measurements for all 3 EU trials and the US IND pivotal PK study by patients?

- Does FDA agree with ITF's plans with regards to safety data?

FDA Response to Question 13:

We agree that the listings you propose should be submitted. In addition, for each study separately, you should submit summary tables that include TEAEs by SOC, including the verbatim terms of all TEAEs, along with the proportion of the TEAEs for each SOC as compared to the overall total for the study; and also the proportion for each verbatim term as a function of the total number of TEAEs in that study.

14. Safety Narratives

ITF plans to provide safety narratives only for subjects who experience a serious adverse event or death during the clinical trial.

- Does FDA agree with ITF's plans?

FDA Response to Question 14:

In addition to narratives for SAEs and deaths, you should also submit narratives for subjects who withdraw due to an adverse event.

15. Coding of Safety Data

ITF plans to provide MedDRA coded adverse events and clinical study reports in the eCTD format. The clinical study reports (CSRs) for all three completed EU studies used MedDRA versions 12.0 &13.1 and the US IND pivotal PK trial will utilize version 15.0 or higher.

- Does FDA agree?

FDA Response to Question 15:

This is an acceptable plan.

16. Integrated Summary of Effectiveness (ISE)

As reflected in the pre-IND meeting briefing package and related FDA written responses dated November 25, 2014, this 505(b)(2) NDA will rely solely on FDA's finding of efficacy for the Rilutek tablets as the LD. Thus, no further efficacy studies were conducted and no ISE is warranted.

- Does FDA agree that no ISE is required?

FDA Response to Question 16:

We agree that no ISE is required.

CMC QUESTIONS

17. Stability Data Package to be provided at the time of NDA Submission

Three batches of drug product have been manufactured at the contract manufacturer, (b) (4) and submitted to ICH long term, intermediate and accelerated stability studies. Stability starting dates were October 14, 2015 for the first lot and January 6, 2016 for the second and the third lots.
Based on ICH Q1C guidance, ITF plans (b) (4)

Does the FDA agree with ITF's strategy to provide stability data?

FDA Response to Question 17:

No, we do not agree. The ICH Q1C guidance recommendations apply to applications for new dosage forms *submitted by the owner of the original application*, after the original submission for new drug substances and products. However, even for the owner of the original application, submission of a reduced stability database should be justified.

We recommend that the initial NDA submission include a minimum of 12 months long-term (25°C/60% R. H.) stability data, plus 6 months accelerated (40°C/75% R. H.) data for three primary batches of the same formulation as the to-be-marketed product in the proposed commercial packaging. The expiration dating period assigned during the review will be commensurate with the extent and quality of the available stability data. Refer to ICH guidance "Q1E Evaluation of Stability Data."

Whether we review information submitted to the NDA subsequent to the original submission will be determined based on the timing of the submission and available Agency resources.

18. Plan being implemented to address FDA's biopharmaceutics comments regarding dissolution test method and acceptance criteria

Reference is made to the FDA's biopharmaceutics comments made in the written responses dated November 25, 2015 regarding dissolution test method and acceptance criteria.

To address this request, ITF is providing the following information:

A dissolution test for Riluzole Oral Suspension has been developed and validated and is intended to be included in drug product specification (release and shelf-life) as routine QC single point performance test similarly to the single point dissolution test included in the current USP monograph of Riluzole tablet.

The dissolution method developed for ITF Riluzole Oral Suspension drug product was based on the dissolution test included in current USP monograph of Riluzole tablet, suitably modified as deemed necessary by the specific dosage form / formulation (i.e. oral suspension instead of tablet). Particularly the effect of different parameters on the oral suspension dissolution behavior, such as pH/type of medium, volume of the dissolution medium and rotation speed, was studied.

The developed dissolution test has been validated by the US manufacturer (i.e.: (b) (4)) which is responsible for the manufacturing and release of both clinical/registration batches and future commercial batches.

Below is a summary of the developed dissolution test conditions:

Sample: 10mL of Riluzole 5mg/mL Oral Suspension (equivalent to 50 mg Riluzole)

USP Apparatus: II (paddle)

Temperature: 37°C

Speed: 35 rpm

Medium: phosphate buffer pH 4.5

Volume: 900 mL (890 mL medium + 10mL Riluzole Oral Suspension)

(b) (4)

Sampling time: (b) (4) minutes (*)

(b) (4)

ITF will provide in the documentation for NDA submission the detailed description of the dissolution method, the development report (including ITF drug product dissolution profile) and the validation report (including validation data supporting dissolution method robustness and analytical method linearity, precision, accuracy, stability etc.).

The method is currently applied during the stability program of the registration stability batches.

(b) (4)

- ***Does FDA agree that the above plan addresses the referenced biopharmaceutics comments?***

FDA Response to Question 18:

We agree that your approach seems to be in line with the general biopharmaceutics comments provided by FDA in the Nov 25, 2015 Written Responses; however, the acceptability of the proposed dissolution method and acceptance criterion for your product will be made during the NDA review based on the dissolution method development data as well as on the totality of the data for clinical and primary stability batches.

19. (b) (4)

Reference is made to the FDA's Microbiology comments made in the written responses dated November 25, 2015, in which the FDA provided comments regarding microbiology information relating to (b) (4)

To address this request, ITF is planning to perform the activities described in Attachment B.

-Does FDA agree with this approach for testing?

FDA Response to Question 19:

No, we do not agree. (b) (4) (b) (4)

As stated in the microbiology comments dated November 25, 2015, we remind you that the pending NDA submission should include a test method and acceptance criterion that demonstrates the drug product is free of (b) (4)

3.0 ADDITIONAL INFORMATION

PREA Requirements

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

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.

Prescribing Information

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

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

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

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

Submission Format Requirements

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. 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.

Manufacturing Facilities

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
1.				
2.				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
1.				
2.				

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

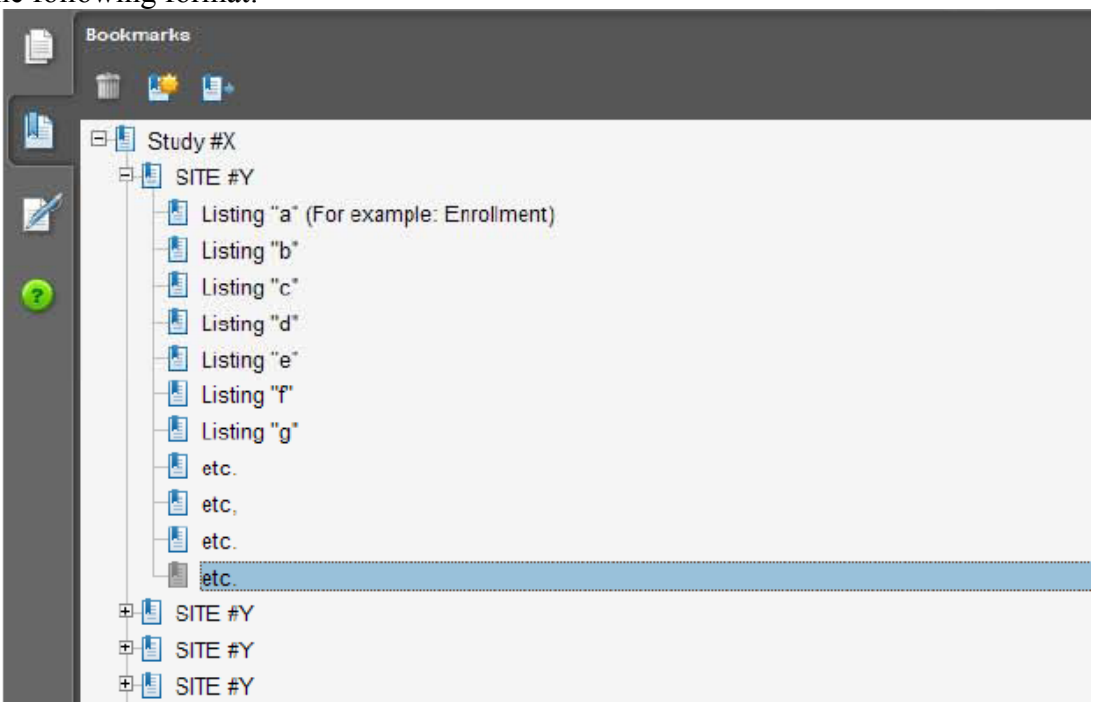
3. Please include the following information in a tabular format in the NDA for each of the completed pivotal clinical trials:
   a. Location at which sponsor trial documentation is maintained (e.g., , monitoring plans and reports, training records, data management plans, drug accountability records, 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/

ERIC P BASTINGS
05/26/2016