CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214032Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 144421

MEETING MINUTES

FACET LIFE SCIENCES
Attention: Maria Oysaski, MS, MA, RAC
US Agent for Telix Pharmaceuticals
1005 Green Street
Durham, NC 27701-1519

Dear Ms. Oyaski,

Please refer to your Pre-Investigational New Drug Application (PIND) file for Ga-68 PSMA-11 Injection.

We also refer to the meeting between representatives of your firm and the FDA on July 24, 2019. The purpose of the meeting was to receive guidance concerning their clinical development program and potential 505 (b)(2) NDA submission.

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

If you have any questions, call Diane Hanner, Regulatory Project Manager, at (301) 796-4058.

Sincerely,

{See appended electronic signature page}

Libero Marzella, MD, PhD
Director
Division of Medical Imaging Products
Office of Drug Evaluation IV
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-NDA

Meeting Date and Time: July 24, 2019 at 3:00 p.m. (EST)

Meeting Location: White Oak Campus, Building 22, room 1417

Application Number: PIND 144421

Product Name: Ga-68 PSMA-11

Indication: Positron emission tomography (PET) in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels.

Sponsor Name: FACET (US Agent for Telix)

Meeting Chair: August Hofling, MD, PhD.

Meeting Recorder: Diane Hanner. MSW, MPH

FDA ATTENDEES

OFFICE OF DRUG EVALUATION IV

- Charles Ganley, MD, Director, ODEIV
- Lesley-Anne Furlong, MD, Deputy Director, ODEIV
- Jagjit Grewal, MPH, Policy Advisor, OND Policy Staff

OFFICE OF NEW DRUGS / OFFICE OF DRUG EVALUATION IV/ DIVISION OF MEDICAL IMAGING PRODUCTS

- Libero Marzella, MD, PhD. Director, Division of Medical Imaging Products, (DMIP)
- Alex Gorovets, MD, Deputy Director, DMIP
- August Hofling, MD, PhD, Clinical Team Leader, DMIP
- Stephanie Coquia, MD, Medical Officer, DMIP

- Michele Fedowitz, MD, Associate Director for Labeling, DMIP
- CAPT Diane Hanner, MPH, MSW, LSW, Senior Program Management Officer, DMIP

OFFICE OF TRANSLATIONAL SCIENCES / OFFICE OF BIOSTATISTICS / DIVISION OF BIOSTATISTICS I

- Jyoti Zalkikar, Ph.D., Biostatistics Secondary Reviewer, DBI
- Sue Jane Wang, PhD, (Acting) Deputy Division Director, DBI

OFFICE OF NEW DRUG PRODUCTS / DIVISION OF NEW DRUG PRODUCTS (DNDPII)

- Eldon Leutzinger, PhD, CMC Reviewer, DNDPII
- John K. Amartey, PhD, CMC Reviewer, DNDPII

OFFICE OF NEW DRUG PRODUCTS/OFFICE OF PHARMACEUTICAL QUALITY

- Martin Haber, PhD, Chemistry Reviewer
- Laura Wasil, PhD, Chemistry Reviewer

OFFICE OF TRANSLATIONAL SCIENCES/OFFICE OF CLINICAL PHARMACOLOGY/ DIVISION OF CLINICAL PHARMACOLOGY V

- Sam Habet, Ph D, Clinical Pharmacology Reviewer, (DCP V)
- John Christy, Ph D, Clinical Pharmacology team leader, (DCP V)

SPONSOR ATTENDEES

TELIX PHARMACEUTICALS

- Sabrina Greer, Sr. Program Manager, Telix Pharmaceuticals (US) Ltd.
- Bernard Lambert, President and COO, Telix Pharmaceuticals (US) Ltd.

(b) (4)

1.0 BACKGROUND

FACET (US Agent for Telix) requested a Pre-NDA meeting with the Agency on May 21, 2019, for a diagnostic radiopharmaceutical drug: Kit for the Preparation of Ga-68 PSMA-11 injection. The Sponsor intends to use the kit for positron emission tomography (PET) in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment. The meeting was granted on June 4, 2019, and the Sponsor sent in the briefing package on June 21, 2019.

FDA sent Preliminary Comments to FACET on July 18, 2019.

2. DISCUSSION

Question 1:

Does FDA agree that the available efficacy data from the 3 key articles summarized in Table 7 provide adequate pivotal evidence to support the Telix Kit NDA, and that no additional efficacy studies are needed?

FDA Response to Question 1:

No, we do not agree. Primary analysis of the diagnostic performance of ^{68}Ga-PSMA-11 PET should be measured against a reference standard constructed from histologic confirmation whenever possible and conventional imaging and clinical follow-up when histopathology cannot be obtained. (b) (4)

(b) (4)

Due to the issues cited above with the 3 publications, the lack of datasets is a critical limitation of your proposed NDA submission. We recommend that you perform at least one prospective study in the biochemical recurrence population in which primary

analysis of the PPV of ^{68}Ga-PSMA-11 PET is measured against a composite reference standard of histology, imaging, and clinical follow-up for at least three blinded central PET readers.

The published literature on ^{68}Ga-PSMA-11 PET, including the (b) (4) paper, may provide supportive evidence. See response to question 5 on recommended revisions to your literature search. The totality of evidence from prospective evaluation of the diagnostic performance of ^{68}Ga-PSMA-11 PET and the literature may be sufficient to form the basis of NDA submission.

MEETING DISCUSSION TO QUESTION 1:

The Agency stated that published literature could be used as supportive evidence of safety and efficacy, but the sponsor should perform an adequate and well-controlled prospective study to address the gaps in the literature. The Agency explained that its main concern with the published literature is the quality of the data rather than use of different synthesis methods of ^{68}Ga-PSMA-11. The Agency stated that a study must meet many requirements to be considered adequate and well-controlled, such as use of appropriate study populations, endpoints, reference standards, and blinded independent reader assessments. Comparison of the diagnostic performance of ^{68}Ga-PSMA-11 to other imaging tests may be valuable as long as the trials are adequate and well-controlled, but such comparison is not required. The Agency referred the sponsor to the linked Guidance for Industry document (https://www.fda.gov/media/71655/download) for more information regarding clinical evidence of effectiveness. The Agency also stated that meta-analysis of published literature might provide secondary support but would not substitute the need for an adequate and well-controlled study.

The sponsor stated that they will do a new search of the literature to identify adequate and well-controlled studies that assess the diagnostic performance of ^{68}Ga-PSMA-11 against a reference standard of histology and/or clinical and imaging follow-up. The sponsor asked if the Agency would be willing to review the results of the new search. The Agency stated that it would be.

> **Post meeting comment: If the sponsor would like the Agency to review the results of the new literature search, a WRO meeting request should be submitted.**

The sponsor should provide bridging data for different drug formulations, otherwise, the value of specific studies in the published literature may be limited. The bridging data may also come from the published literature. The sponsor stated that it may need to reach out to the PIs of studies in which the formulation was not included or insufficient information was provided in the publications.

The sponsor stated that they are currently working with Endocyte to supply the kit being used in the VISION trial. (b) (4)

(b) (4)

Question 2:

Does FDA agree that the available safety data from the 3 key articles summarized in Table 7 provide adequate pivotal evidence to support the Telix Kit NDA, and that no additional safety studies are needed?

FDA Response to Question 2:

No, we do not agree. The (b) (4) study did not provide any safety information. Safety monitoring should be performed in the prospective trial that we are recommending above to augment the safety information from the literature.

MEETING DISCUSSION TO QUESTION 2:
Please see the Meeting Discussion captured under Question 1.

Question 3:

Does FDA agree that the human biodistribution and dosimetry data on ^{68}Ga-PSMA-11 reported in the public domain are appropriate and sufficient to support the NDA for the Telix Kit?

FDA Response to Question 3:

We recommend that you perform a systematic review of the human dosimetry data available in published literature using ^{68}Ga-PSMA-11 and summarize the results in your next submission.

MEETING DISCUSSION TO QUESTION 3:
No Discussion.

Question 4:

Does FDA agree with the proposed dose of (b) (4) MBq of ^{68}Ga-PSMA-11 resulting from use of the Telix Kit?

FDA Response to Question 4:

The proposed dose of (b) (4) mCi ((b) (4) MBq) of ^{68}Ga-PSMA-11 appears reasonable. Please describe in NDA submission what dose finding studies were conducted and how a dose of (b) (4) mCi was selected.

MEETING DISCUSSION TO QUESTION 4:
No Discussion.

Question 5:

Does the FDA agree that the literature search plan is adequate to support the NDA?

FDA Response to Question 5:

No, we recommend that you revise elements of your proposed PICOS (population, intervention, comparison, outcome, study type) framework that will be used to determine the eligibility of the specific papers for review. Specifically:

P: the patient population should match your desired indication
C: comparison to a reference standard (histology and/or clinical/imaging follow-up) should be a requirement
O: limit to studies using a truth-standard validated performance metric that incorporates true positive and false positive results

The totality of the evidence based on the results of the literature search combined with a new prospective trial may be sufficient for NDA submission as discussed in question 1. Please see clinical comments in 23 for next steps.

MEETING DISCUSSION TO QUESTION 5:
Please see the Meeting Discussion captured under Question 1.

Question 6:

Based on the efficacy and safety results described herein, does FDA agree that the data provided are sufficient to support the indication statement and no additional studies need to be conducted?

FDA Response to Question 6:

Please see responses to question 1 and 2.

MEETING DISCUSSION TO QUESTION 6:
No Discussion.

Question 7:

Does FDA agree with Telix's data package submission plan for this NDA?

FDA Response to Question 7:

Please see responses to question 1 and 2.

MEETING DISCUSSION TO QUESTION 7:
No Discussion.

Question 8:

Are there any other aspects of the clinical development plan or clinical sections of the planned NDA that the FDA would like to comment on or that Telix should take into consideration?

FDA Response to Question 8:

Please see responses to questions 1, 22, and 23.

MEETING DISCUSSION TO QUESTION 8:
No Discussion.

Question 9:

Does FDA have any comments regarding the specification for the drug substance precursor?

FDA Response to Question 9:

The specifications for the drug substance precursor appear reasonable. However, the level (b) (4) is of concern and the applicant is encouraged to lower the limit or (b) (4) In addition, tighten the acceptance criteria, i.e., any unspecified impurity NMT (b) (4) %, total impurities NMT (b) (4) %, assay ≥ (b) (4) %. Final specifications are a review issue dependent on data submitted in the NDA.

MEETING DISCUSSION TO QUESTION 9:
The Agency stated that the drug substance final specifications would be a review issue.

Question 10:

Does FDA have any comments regarding the specification [redacted]?

FDA Response to Question 10:

The bacterial endotoxins and sterility test methods and acceptance criteria appear reasonable. However, please note that the maximum endotoxins patient dose will be determined from the sum of endotoxins exposure from the three vials [redacted] the ^{68}Ga generator eluate, and kit components, [redacted] and sterile 10 mL syringes. The maximum endotoxin patient dose should not exceed 175 EU/dose, per USP <85>.

MEETING DISCUSSION TO QUESTION 10:
No Discussion.

Question 11:

Does FDA have any comments regarding the specification for the sterile acetate vials?

FDA Response to Question 11:

The bacterial endotoxins and sterility test methods and acceptance criteria for the sterile acetate vial appear reasonable.

MEETING DISCUSSION TO QUESTION 11:
No Discussion.

Question 12:

Does FDA agree that release testing to finished product specifications at GRAM will be sufficient to demonstrate comparability of products resulting from the GRAM process versus prior batches manufactured at [redacted]?

FDA Response to Question 12:

The registration batch plan seems reasonable. However, adequacy will be a review issue. Additionally, detailed description of preparation of the cyclotron-produced Ga-68 should be provided in the application. The information should cover all aspects of the process from target preparation to isolation of the final Ga-68 radiochemical. The final drug product injection prepared at multiple clinical sites using different configurations of the kit will be a review issue. Furthermore, we remind you that for NDA applications

cGMP compliant materials should be used including the specific generator being utilized. The final drug product injection from these sites should be pharmaceutically equivalent and should meet the same release specifications.

MEETING DISCUSSION TO QUESTION 12:

The Agency reiterated that since data from the new manufacturing site has not been provided in detail, the preparation of drug product at multiple clinical sites using different configurations of the kit will be a review issue.

Question 13:

Given the scope of manufacturing changes as described between the (b) (4) and the GRAM process, does FDA agree that the registration batch plan as presented is appropriate and sufficient to support an NDA for all 3 configurations of the Telix Kit, including use of the kit configuration A with either the EZAG Gallia Pharm generator or with cyclotron-produced gallium?

FDA Response to Question 13:

FDA disagrees with the plan to support the use of all three buffer configurations and generators for NDA submission. The FDA expects cGMP compliant generators for NDA submission. The generator eluate should be of acceptable quality and attributes such as level of germanium breakthrough (≤0.001% per Ph. Eur. monograph) should be controlled. Additionally, the cyclotron-produced Ga-68 solution should be qualified with the kit. The final drug product injection manufactured with the two sources of Ga-68 (EZAG or cyclotron-produced) should have same specifications and pharmaceutically equivalent. In the context of the cyclotron-produced Ga-68, limits should be set for any potential radionuclidic impurities, and the levels should be controlled with justifications.

MEETING DISCUSSION TO QUESTION 13:

The sponsor indicated that they will be submitting additional data regarding the cyclotron product. The Agency indicated that they were agreeable to reviewing data from cyclotron produced product.

Question 14:

Does FDA agree to accept an NDA filing containing long-term stability data from components produced at the (b) (4) facility (as currently shown in DMF (b) (4) plus additional stability lots as indicated in Table 13 plus limited accelerated stability data from components produced at the GRAM facility?

FDA Response to Question 14:

The FDA may accept stability data generated at the (b) (4) facility (as presented in the cross-referenced DMF (b) (4)) for NDA filing. However, for NDA submission FDA expects 12 months of long-term stability data to be provided in the application (*ICH Q1A(R2)*). The final acceptance of the data will be a review issue.

MEETING DISCUSSION TO QUESTION 14:

The sponsor stated that they can provide the Agency with 2 lots of each kit. However, the lots from GRAM will have only 6-month stability data at the time of filing. The Agency informed the sponsor that this would not be enough. The Agency would have to discuss this matter with the Office of Pharmaceutical Quality management in order to provide the sponsor with any additional guidance.

Question 15:

Does FDA agree with the proposal to submit stability data at the time of NDA submission for registration batches for the drug substance precursor (PSMA-11) as supplied by (b) (4) according to the protocols presented, assuming that the (b) (4) DMF is not fully vetted by FDA at the time of Telix's NDA filing?

FDA Response to Question 15:

The stability protocol as presented in the meeting package (table 17) appears reasonable. The stability data to be provided should support the proposed expiration time, and this would be a review issue. Nonetheless, if you intend to cross-reference an (b) (4) DMF for the drug substance precursor, provide to the FDA the DMF number and a letter of authorization from (b) (4) at the time of filing.

MEETING DISCUSSION TO QUESTION 15:
No Discussion.

Question 16:

Does FDA agree that the stability protocols currently on file in DMF # (b) (4) are appropriate to support marketing of the Telix Kit? Does FDA also agree that the stability protocols as described (b) (4)

appear appropriate to support a marketed product?

FDA Response to Question 16:

The stability protocol in the DMF (b) (4) appears reasonable. However, FDA does not agree (b) (4) Accelerated stability data at 40ºC/75% RH should be for at least 6 months. Additionally, for NDA submission the stability data for 5ºC and 25ºC/ 60% RH test conditions should be for at least 12 months and 6 months respectively (*ICH Q1A(R2)*).

MEETING DISCUSSION TO QUESTION 16:

The Agency noted that the DMF data appears to be acceptable. The Agency noted that they would like to have 12 months of data which is based upon GMP guidance. One lot would not be sufficient, and the sponsor noted that they can produce two lots. The sponsor noted that stability data from both GRAM and (b) (4) may not have a (b) (4)-month expiry date. The Agency noted that this will be a review issue.

Question 17:

Does FDA agree that the in-use stability provided in the DMF are sufficient to support an NDA for the Kit?

FDA Response to Question 17:

The in-use stability data for the [^{68}Ga]-PSMA-11 provided in the DMF appears reasonable, however, adequacy of the additional data to be provided in the NDA application will be a review issue.

MEETING DISCUSSION TO QUESTION 17:
No Discussion.

Question 18:

Does FDA have any other comments regarding the chemistry, manufacturing, and controls for ^{68}Ga-PSMA-11 injection?

FDA Response to Question 18:

FDA cannot make any determination until the amended DMF is reviewed with the inclusion of data for the cyclotron-produced Ga-68.

MEETING DISCUSSION TO QUESTION 18:
No Discussion.

Question 19:

Does FDA agree that there is sufficient evidence to consider the biological activity of ^{68}Ga-PSMA-11 (b) (4) (b) (4)

FDA Response to Question 19:

Although published information indicated (b) (4) the sponsor indicated (b) (4) Clarify this discrepancy in the application.

MEETING DISCUSSION TO QUESTION 19:

The Agency informed the sponsor (b) (4) **The agency also stipulated that a bridging study would be needed to compare the Telix kit to the published clinical studies.**

Question 20:

If Telix is unable to reference (b) (4) will it be possible for FDA to approve (b) (4)

FDA Response to Question 20:

No. The FDA prefers (b) (4)

MEETING DISCUSSION TO QUESTION 20:
No Discussion.

Question 21:

Telix plans to submit a complete update to DMF [redacted] (b) (4) prior to submitting the NDA. Will it be possible for FDA to review this DMF amendment in the context of Telix's plans to cross-reference to the DMF as the CMC information for the NDA to be filed?

FDA Response to Question 21:

The FDA will review the amended DMF for adequacy in support of the application. The final determination will be a review issue.

MEETING DISCUSSION TO QUESTION 21:
No Discussion.

Question 22:

Does FDA have any comments regarding the NDA contents or content locations based on the TOC that has been provided?

FDA Response to Question 22:

We note your outline of the NDA in Appendix 1 does not include an ISS or ISE in Module 5. These are required sections of the NDA. If you intend to use the Module 2 summaries to replace the ISS and ISE, we recommending including cross references to the appropriate summary documents in Module 2 and your rationale for them in the required ISE and ISS sections for Module 5. See FDA guidance, "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document," https://www.fda.gov/regulatory-information/search-fda-guidance-documents/integrated-summaries-effectiveness-and-safety-location-within-common-technical-document.

MEETING DISCUSSION TO QUESTION 22:
No Discussion.

Question 23:

Does FDA have any additional guidance or suggestions on any aspect of the development program or NDA?

FDA Response to Question 23:

For additional information regarding the materials that should be provided in support of an NDA for a sterile drug product, see the following guidances:

- *Guidance for Industry for the Submission Documentation for Sterilization Process*

Validation in Applications for Human and Veterinary Drug Products
- *Guidance for Industry Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice*

As a part of a future meeting request, we recommend that you submit a prospective study protocol and statistical plan as well as a summary of the results of your revised literature search. Your protocol should address the issue of (potential) subject drop off between imaging and PET validation (b) (4)

MEETING DISCUSSION TO QUESTION 23:
No Discussion.

Additional Comments:
We understand that you are planning to use 68Ga-PSMA-11 injection for positron emission tomography (PET) in men with suspected prostate cancer recurrence based on elevated blood prostate specific antigen (PSA) levels following prior treatment. We do not anticipate that a human factors (HF) validation study is needed. However, you have not submitted a comprehensive risk analysis.

We recommend you conduct a proactive risk assessment if you have not already completed one. The proactive risk assessment should include a comprehensive and systematic evaluation of all the steps involved in using your product (e.g., based on a task analysis) the errors that users might commit or the tasks they might fail to perform and the potential negative clinical consequences of use errors and task failures.

It may be useful to conduct comparative analyses such as a labeling comparison, a comparative task analysis, and a physical comparison between your proposed product and the comparator for the purposes of identifying what differences exist between the user interfaces and where the same or similar risks may apply to your proposed product.

Submit your risk analysis, comparative analyses and justification for not conducting a HF validation study for our review. We will notify you if we concur with your determination.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in:
Applying Human Factors and Usability Engineering to Medical Devices, available online at:
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm259760.pdf

Guidance on Safety Considerations for Product Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors and can be found online at:
http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf

Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications can be found online at
https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621902.pdf

3.0 IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our July 18, 2019 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[1]

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. SUMMARIZE DISCUSSION AND AGREEMENTS

- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

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-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP 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 iPSP 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 iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended*

[1] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

Pediatric Study Plans.[2] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 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[4] and Pregnancy and Lactation Labeling Final Rule[5] 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.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant

[2] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information 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*.

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

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

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 guidance for industry *Assessment of Abuse Potential of Drugs*.[8]

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

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[8] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

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).[9] 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-

[9] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

2003-P-0274-0015, available at Regulations.gov.[10]

If you intend to submit a 505(b)(2) application that relies for approval 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 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. by trade name(s)).

If you intend to rely 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 FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

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.

[10] http://www.regulations.gov

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). 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 the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the 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 effectiveness 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 A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(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.

FDA has made a preliminary determination that the application for this product would be reviewed as a new molecular entity (NME) and therefore subject to the Program, under

PDUFA VI. Please note that this is a preliminary determination, based on information available to FDA at this time, and will be re-evaluated at the time your application is submitted. This determination is based on our understanding of the active moiety (21 CFR 314.108(a)) and whether another marketing application containing the same active moiety is approved or marketed. Please also note that the NME determination for an application is distinct from and independent of the new chemical entity (NCE) determination and any related exclusivity determinations, which are made after approval of an NDA.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications* 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 ORA investigators who conduct those inspections. 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.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.[11]

PATIENT-FOCUSED ENDPOINTS

An important component of patient-focused drug development is describing the patient's perspective of treatment benefit in labeling based on data from patient-focused outcome measures [e.g., patient-reported outcome (PRO) measures]. Therefore, early in product development, we encourage sponsors to consider incorporating well-defined and reliable patient-focused outcome measures as key efficacy endpoints in clinical trials, when appropriate, and to discuss those measures with the Agency in advance of confirmatory trials. For additional information, refer to FDA's guidance for industry *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Claims.*

[11] https://www.fda.gov/media/85061/download

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No additional issues requiring further discussion were identified.

5.0 ACTION ITEMS

No action items were identified during the meeting.

6.0 ATTACHMENTS AND HANDOUTS

Attachment I- (below) contains the slides used during the discussion at the meeting.

3 Pages have been Withheld in Full as B4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

ALEXANDER GOROVETS
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