CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204553Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 064892

MEETING MINUTES

Janssen Research & Development, LLC
Attention: Huy Q. Truong, MS
Associate Director, Global Regulatory Affairs
920 U.S. Highway 202 South, PO Box 300
Raritan, NJ 08869

Dear Mr. Truong:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for rivaroxaban.

We also refer to the meeting between representatives of your firm and the FDA on August 6, 2019. The purpose of the meeting was to discuss the planned New Drug Application submission for two proposed pediatric indications supported by the development program in the treatment and thromboprophylaxis of venous thromboembolism (VTE) and discuss the new pediatric formulation (granule for oral suspension).

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

If you have any questions, contact Katie Chon, Regulatory Project Manager, at katie.chon@fda.hhs.gov or (240) 402-6578.

Sincerely,

{See appended electronic signature page}

Tanya M. Wroblewski, MD
Clinical Team Leader
Division of Hematology Products
Office of Hematology and Oncology Products
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] 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.

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	August 6, 2019 10:00 AM – 11:00 AM EST
Meeting Location:	10903 New Hampshire Avenue White Oak Building 22, Conference Room: 1315 Silver Spring, Maryland 20903
Application Number:	IND 064892
Product Name:	Rivaroxaban tablets
Indication:	Xarelto is indicated for the treatment of venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in children from birth to < 18 years of age following initiation of standard anticoagulation treatment. Xarelto is indicated for the thromboprophylaxis in children 2 years to 8 years of age with congenital heart disease (CHD) who have undergone Fontan procedure.
Sponsor Name:	Janssen Research & Development, LLC (Janssen or JRD)
Meeting Chair:	Tanya Wroblewski, MD
Meeting Recorder:	Katie Chon, PharmD, RPh

FDA ATTENDEES

Office of Hematology and Oncology Products (OHOP)/Division of Hematology Products (DHP)

Ann Farrell, MD, Director
Tanya Wroblewski, MD, Clinical Team Leader
Laurel Menapace, MD, Medical Officer
Lori Ehrlich, MD, Medical Officer
Katie Chon, PharmD, RPh, Regulatory Project Manager

Office of Biostatistics/Division of Biometrics V

Alexei Ionan, PhD, Statistical Reviewer

Office of Clinical Pharmacology(OCP)/Division of Clinical Pharmacology I

Venkateswaran Chithambaram-Pillai, PhD, Clinical Pharmacologist

OCP/Division of Applied Regulatory Science

Jeffry Florian, PhD, General Health Scientist

OCP/Division of Pharmacometrics
Xinyuan Zhang, PhD, Pharmacology reviewer

Office of Pharmaceutical Quality
Ramesh Raghavachari, PhD, Team Leader
Sherita McLamore, PhD, Team Leader
Emily Wu PhD, Product Quality Reviewer

Office of Surveillance and Epidemiology/Division of Medication Error Prevention and Analysis
Mishale Mistry, PharmD, MPH, Associate Director

Office of Device Evaluation/Division of Anesthesiology, General Hospital, Respiratory, Infection Control, and Dental Devices
Rita Lin, MS, RAC, Human Factors Engineer

SPONSOR ATTENDEES
James Buckley, MS, Director, JRD Global CMC Regulatory Affairs
Angela Falzone, PhD, Scientific Director, JRD CMC Leader
Kimberly Nessel, MS, Scientific Director, JRD Cardiovascular and Metabolism
L Miriam Pina, MD, Senior Director, JRD Project Physician
Branden Reid, PhD, Associate Director, JRD Global CMC Regulatory Affairs, Medical Devices and Combination Products
Huy Q Truong, MS, Associate Director, JRD Global Regulatory Affairs

Bayer Pharmaceuticals (Sponsor's collaborator)
Matthew Gale, PhD, Statistical and Programming Lead
Artur Lutfullin, MD, Senior Global Regulatory Strategist
Miriam Tamm, PhD, Senior Statistician, Integrated Analysis Statistics

(Via teleconference):
Penny Zhu, PhD, Associate Scientist Director, JRD Pharmacometrics, Global Clinical Pharmacology

Bayer Pharmaceuticals (Sponsor collaborator):
Dagmar Kubitza, MD, Head Pharmacodynamics Cardiovascular, Clinical Pharmacology Cardiovascular/Hematology
Akos F Pap, PhD, Project Statistician
William Smith, MD, Global Clinical Lead
Thomas Uhlich, PhD, CMC Technical Development Team Leader, Global Chemical and Pharmaceutical Development
Katrin Coboeken, PhD, Scientist Systems Pharmacology (Modelling)
Madhurima Maajumder, PhD, Study Statistician for Einstein Jr Phase 3 study

1.0 BACKGROUND

Rivaroxaban is an oral Factor Xa inhibitor indicated:

- to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation
- for the treatment of deep vein thrombosis (DVT)
- for the treatment of pulmonary embolism (PE)
- for the reduction in the risk of recurrence of DVT and/or PE in patients at continued risk for recurrent DVT and/or PE after completion of initial treatment lasting at least 6 months
- for the prophylaxis of DVT, which may lead to PE in patients undergoing knee or hip replacement surgery
- in combination with aspirin, to reduce the risk of major cardiovascular events (cardiovascular (CV) death, myocardial infarction (MI) and stroke) in patients with chronic coronary artery disease (CAD) or peripheral artery disease (PAD)

The proposed indications the Sponsor is seeking are the following:

- Xarelto is indicated for the treatment of venous thromboembolism (VTE) and the reduction in the risk of recurrent VTE in children from birth to < 18 years of age following initiation of standard anticoagulation treatment.
- Xarelto is indicated for the thromboprophylaxis in children 2 years to (b) (4) with congenital heart disease (CHD) who have undergone Fontan procedure.

On May 29, 2015, Janssen submitted a Proposed Pediatric Study Request (PPSR) for rivaroxaban and on June 8, 2017, the Agency issued a formal Written Request (WR). On March 23, 2018, the Agency issued a WR – Amendment 1.

On May 22, 2019, the Sponsor requested a meeting to discuss their planned New Drug Application (NDA) for two proposed pediatric indications supported by the development program in the treatment and thromboprophylaxis of venous thromboembolism (VTE) and discuss the new pediatric formulation (granule for oral suspension). In addition, the Sponsor seeks guidance on the proposed stability package and testing including the planned assessment in the support of the filing for registration of the commercial product and the oral dosing device, the planned timing and contents of the NDA submission.

FDA sent Preliminary Comments to Janssen on July 31, 2019.

2. DISCUSSION

Preamble: Per the Guidance for Industry – Submitting Separate Marketing Applications and Clinical Data for Purpose of Assessing User Fee[2], you will need to submit a separate NDA for the pediatric formulation, Granule for Oral Suspension.

Discussion: See Question 2 response.

2.1. Clinical Pharmacology

Question 1: *Technical details of the 2 alternatives for an electronic data package of the PBPK model are provided. Does the Agency consider the proposed plan adequate and acceptable?*

FDA Response to Question 1: We recommend you submit your package option B under module 5.3.3. Please convert software specific file extensions (i.e., mat, .pksim, .mbp, etc.) to .txt files. Also provide a script and instruction on converting the files back to the original formats. Submit the figures in .pdf format.

Discussion: Clinical Pharmacology offered several options to the Sponsor depending on the size of the submission. The submission as a physical media is only an option if size is greater than 10GB and would still need to follow eCTD specifications. The Agency recommends submission via Gateway. To facilitate submission, it is not necessary to change file names. To preserve folder hierarchy, we recommend submission of the picture of the structure under Module 5 datasets folder.

It is acceptable to provide .pdf file as part of the report for the submission.

Post meeting note:
The example of the folder hierarchy is provided below.
Example folder hierarchy, where 'Package' is the beginning of the sponsor's proposed project folder hierarchy

NDA123456 › 0001 › m5 › datasets › [study-id] › misc › Package

Adopted from the Data Standards Technical Conformance Guide.[3]

The FDA clarified during the meeting that the report and materials should be linked under Module 5.3.3.5 in the submission.

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submitting-separate-marketing-applications-and-clinical-data-purposes-assessing-user-fees
[3] https://www.fda.gov/media/122913/download

2.2. Chemistry, Manufacturing, and Controls

Question 2: *Sponsor's position that these data constitute a suitable basis for the Agency to assess the NDA shelf-life proposal. Does the Agency agree with the Sponsor's proposal?*

FDA Response to Question 2: We recommend you submit a minimum of twelve months and six months of stability data for the long term and accelerated storage conditions, respectively, for three primary stability batches packaged in the commercial container closure system intended for the U.S. market, since this is a new formulation and dosage form. You may include the stability data generated by your partner in the submission as supporting information. The drug product expiry will be determined by the stability results for the three primary stability batches.

Discussion: The Agency stated the Sponsor will need to submit a separate NDA to support the pediatric formulation complete with all clinical data (efficacy and safety) to support the proposed indication(s). The NDA will need to include appropriate cross-reference to existing NDAs.

The Sponsor proposed 6 month long term and stability data and the Agency did not agree. The Sponsor can submit an alternative proposal. The Agency proposed that the Sponsor could provide 9 month stability data with the application and 12 month data within 30 days after NDA submission.

Question 3: *Does the Agency agree that it is acceptable for the Sponsor to provide 1 representative executed batch record from a primary stability batch that fully represents the proposed commercial formulation, fill, and container closure system (CCS)?*

FDA Response to Question 3: We recommend you provide the executed batch records for all three primary stability batches.

Discussion: There was no discussion.

Question 4: *The Sponsor proposes* (b) (4) [redacted]

FDA Response to Question 4: (b) (4) [redacted]

Human Factors

We note you intend [redacted] (b) (4)

With regards to your planned HF efforts, the comprehensive use-related risk analysis 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. Below are examples of risks and potential errors for your consideration as you develop your product. Please note that these are examples and therefore, are not inclusive of all risks associated with your proposed product:

a. Evaluate the color of the plunger with respect to the readability of the dose markings.
b. It is unclear whether your proposed [redacted] (b) (4) will support accurate measurement of all potential doses (i.e., will some patients require more than 5 mL).
c. It is not clear if the user needs to consider what volume of drug to draw up for a range of patients of different weights within each color group. You state that [redacted] (b) (4)
d. It is not clear if you have considered confusion by your intended users who are color vision deficient (color blind) and not color vision deficient and how that user characteristic may influence user interaction with the proposed product.
e. In your summary of product risk assessment in Table 13 (pg. 33), you state that [redacted] (b) (4)

If models of the same or similar combination products exist, your use-related risk analysis should incorporate applicable information on known use-related problems with those products. Useful information can be obtained from your own experience as well as from public sources such as literature, adverse event reports, and product safety communications (see draft guidance for industry Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development).

Your risk analysis should also discuss risk-mitigation strategies you employed to reduce risks you have identified and the methods you intend to use for validating the risk-

mitigation strategies. This information is needed to ensure that all potential risks involved in using your product have been considered and adequately mitigated and the residual risks are acceptable.

Based on the aforementioned information and data, you should determine whether you need to submit the results of a HF validation study conducted under simulated use conditions with representative users performing necessary tasks to demonstrate safe and effective use of the product.

If you determine you need to submit the results of a HF validation study, the risk analysis can be used to inform the design of a human factors validation study protocol for your product. We recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review is not possible, but this is a decision for your company.

Please refer to our draft guidance titled *"Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications"* for the content of a human factors validation study protocol submission. The guidance is available online at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM621902.pdf

Once complete, the requested information should be submitted to IND 064892 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 can be found online at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM331810.pdf

Note that we recently published two draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling:

Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development can be found online at:

http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM484345.pdf

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

Device Engineering
In addition to the human factors considerations stated above, you have stated that (b) (4) [redacted] The Agency agrees that you should provide dose (syringe) accuracy verification testing to verify that the markings are applied correctly and remain accurate. The Agency also recommends that in addition, drug-device compatibility studies should be conducted to confirm that short contact times do not adversely impact drug quality. Please ensure that you conduct a thorough risk analysis based on the materials, design, and packaging comparison. Please reference design considerations referenced in guidance *Technical Considerations for Pen, Jet, and Related Injectors Intended for Use with Drugs and Biological Products.*[4]

Discussion: The Agency agrees with the Sponsor's proposal on attached slides 12, 14, 15.

2.3. Clinical and Statistical

Question 5:
a) *Does the Agency agree with the plans for the statistical analyses and presentation of results as outlined in the Statistical Analysis Plan, submitted on 21 May 2019 (IND 064892, eCTD Seq.2845) for the Phase 3 clinical study (Study 14372) in EINSTEIN Junior?*

b) *Does the Agency agree with the plans for the statistical analyses and presentation of results as outlined in the Statistical Analysis Plan, Amendment 1, submitted on 21 May 2019 (IND 064892, eCTD Seq.2845) for the UNIVERSE study?*

FDA Response to Question 5:
a) The plans appear acceptable.
b) The plans appear acceptable.

Please ensure that statistical analyses plans and presentations of results are consistent with description and specifications in the Written Request.

[4] https://www.fda.gov/media/76403/download

Discussion: **There was no discussion.**

Question 6: *The Sponsor plans to provide specific pooled analyses of clinical trials in the EINSTEIN Junior program, i.e., treatment of VTE and the reduction in the risk of recurrent VTE in children from birth to <18 years of age as explained. Does the Agency agree with the Sponsor's Plan for pooled analyses?*

FDA Response to Question 6: Yes, the Agency agrees with the presentation of pooled analyses as described in the meeting package.

Discussion: **There was no discussion.**

Question 7: *Post-marketing exposure and cumulative adverse events reports received from worldwide post-marketing surveillance, including spontaneous reports, will also be provided. Does the Agency agree with this proposal?*

FDA Response to Question 7: Yes, the Agency agrees with the proposal.

Discussion: **There was no discussion.**

Question 8: *Each study will provide both the SDTM package for source data and the ADaM package for analysis data. In addition, the Sponsor proposes to submit the ADaM package for the pooled analyses of clinical trials in the EINSTEIN Junior program, i.e., treatment of VTE and the reduction in the risk of recurrent VTE in children from birth to <18 years of age. Datasets of individual studies with the exception of the Phase 3 study 14372 as noted will not be provided with the submission. Does the Agency agree with this proposal?*

FDA Response to Question 8: Yes, the Agency agrees with this proposal.

Discussion: **There was no discussion.**

Question 9: *Executable SAS codes will be provided for primary efficacy and principal safety outputs for the 2 Phase 3 studies EINSTEIN Junior (Study 14372) and UNIVERSE.*

Non-executable SAS codes will be provided for the generation of analysis data sets for the 2 Phase 3 studies EINSTEIN Junior (Study 14372) and UNIVERSE. These are intended to provide reviewers an understanding of analysis algorithms and creation.

Non-executable SAS codes will also be provided for selected key outputs in the 2 Phase 3 studies EINSTEIN Junior (Study 14372) and UNIVERSE. The "table of tables" document in Module 5 in eCTD will be provided to link outputs and corresponding SAS codes.

Executable SAS codes will also be provided for the pooled bleeding event analyses of clinical trials in the EINSTEIN Junior program as described in Section 11.3.2 For all other pooled analyses (ie, adverse events) of clinical trials in the EINSTEIN Junior program as described in Section 11.3.2 non-executable SAS codes will be provided. A "table of tables" document in Module 5 in eCTD will be provided to link pooled analyses of clinical trials in the EINSTEIN Junior program as described in Section 11.3.2 and corresponding SAS codes.

Non-executable SAS codes will be provided for the generation of the pooled analysis data sets (for pool 1, pool 2, pool 3) of clinical trials in the EINSTEIN Junior program as described in Section 11.3.2 These are intended to provide reviewers an understanding of analysis algorithms and creation. Does the Agency agree with this proposal?

FDA Response to Question 9: The approach is acceptable. Please ensure compliance with Study Data Standards and the latest version of the STUDY DATA TECHNICAL CONFORMANCE GUIDE: Technical Specifications Document https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources

Please provide the following in the submission:

- Executable, clearly commented, non-macro programs in ASCII format used to create tables and figures for primary and key secondary efficacy analyses and any additional information included in Section 14 CLINICAL STUDIES of the Prescribing Information, if applicable. Ensure that programs call only data submitted to the Agency and can be easily used to reproduce the results in the CSR. Ensure that variables used in the programs for generating results in the CSR are described clearly in the define file.
- To facilitate the analysis, please include code in programs that explicitly converts submitted .xpt files into the data format used by programs.
- A clear index with descriptions of the programs
- Annotations for each figure and table in the CSR with a list of datasets and variables, as well as a link to the program used to generate results.

Discussion: The Agency agreed to the code in .sas file format, guidance for the executable code and example table of table would be provided in reviewer's guide (ADRG). All results in the USPI Section 14 Clinical Studies including baseline characteristics among others would be provided.

The StatXact 10 procedures compatible with the latest version would be acceptable.

Question 10: *Does the Agency agree with the proposal for providing the narratives in the sNDA?*

FDA Response to Question 10: Yes, the Agency agrees with the proposal for providing narratives in your submissions.

Please see the preamble regarding the need for a separate NDA for pediatric formulation (granule for oral suspension).

Discussion: There was no discussion.

Question 11a: *In accordance with the 2006 FDA guidance document entitled "Adverse Reactions Section of Labeling for Human Prescription Drug and Biological Products – Content and Format", the Sponsor proposes to include only adverse drug reactions in the United States Prescribing Information (USPI) and not all adverse events (AEs) collected during the use of a drug in clinical trial. Does the Agency agree with this approach?*

FDA Response to Question 11a: Your proposed labeling approach for the application is reasonable; however, we cannot agree until review of the adverse event datasets. Please note that we cannot agree to labeling at this time and that labeling negotiations will occur after the filing decision and review of application.

Discussion: There was no discussion.

Question 11b: *Does the Agency agree with the following information proposed to be included in the Adverse Reactions Section (Section 6) of the USPI?*

The Adverse Reactions Section of the USPI will include:

(b) (4)

FDA Response to Question 11b: The content proposed in the Adverse Reactions Section of the USPI will be a review issue once the application is submitted. Labeling negotiations will occur during the review of the supplemental application.

Discussion: There was no discussion.

Question 12: *A submission of a sNDA in 4Q 2020, which will comprise the EINSTEIN Junior study data and analyses package for the proposed indication of treatment of VTE and the reduction in the risk of recurrent VTE in pediatric subjects from birth to <18 years of age AND inclusion of the combined registration stability data package as proposed in Question 2 to assess the market product's shelf-life. A submission of the UNIVERSE study sNDA for the CHD indication in 1Q 2021. Does the Agency concur with the Sponsor's proposed timelines and planned submission of the respective sNDA(s)?*

FDA Response to Question 12: Yes, the Agency agrees with your timelines.

Please see the preamble regarding the need for a separate NDA for pediatric formulation (granule for oral suspension).

Discussion: See response to question 2 regarding submission of separate NDA.

OTHER ADDITIONAL COMMENTS:

1. Please ensure that the application submissions address all the specifics and details in the Written Request.

Discussion: There was no discussion.

Additional Post meeting addendum notes:
For the NDA submission, the Sponsor proposed a cross reference document in m1.4.4 in tabular format containing the application number, date of submission, file name(s), etc. of the cross referenced application (e.g., NDA 022406 and NDA 202439), where applicable, without cross-application hyperlinks to support the pediatric formulation of rivaroxaban.

The Agency agrees with this proposal.

3.0 OTHER IMPORTANT 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-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 Pediatric Study Plans*.[5] 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.[6]

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[7] and Pregnancy and Lactation Labeling Final Rule[8] 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

[5] 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.
[6] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[7] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[8] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

- 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 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.

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)				

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*.[9]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

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

5.0 ACTION ITEMS

The Sponsor would send the Agency the proposal clarifying the cross referencing to the new NDA by August 6, 2019; so that an Agency's response would be included in the meeting minutes and it is included in the additional post meting addendum notes.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached slides to outline the specific issues to address.

25 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

TANYA M WROBLEWSKI
08/09/2019 12:47:23 PM