CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761432Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 130097

MEETING MINUTES

Merck Sharp & Dohme LLC
a subsidiary of Merck & Co., Inc.
Attention: Sandra Lynn Wood
Senior Director, Global Regulatory Affairs
351 North Sumneytown Pike, P. O. Box 1000
Mailstop: UG2CD48
North Wales, PA, 07065

Dear Sandra Lynn Wood:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for MK-1654.

We also refer to the video conference between representatives of your firm and the FDA on August 23, 2024. The purpose of the meeting was to gain FDA alignment on key elements of the MK-1654 BLA to support the indication of prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season.

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

[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.

If you have any questions, call me, at 301-348-3926 or london.harrison@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

London Harrison, MBEE
Regulatory Health Project Manager
Antivirals Group
Division of Regulatory Operations for Infectious Diseases
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B,
Meeting Category: Pre-BLA

Meeting Date and Time: August 23, 2024, 9:30-11:00 AM (EST)
Meeting Location: Virtual

Application Number: IND 130097

Product Name: MK-1654

Indication: Prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants born during or entering their first RSV season

Sponsor Name: Merck Sharp & Dohme LLC (Merck)

Regulatory Pathway: 351(a) of the Public Health Service

FDA ATTENDEES

Office of New Drug (OND)/Office of Infectious Diseases (OID)

- John Farley, MD, MPH, Director
- Adam Sherwat, MD, Deputy Director

OND/OID/Division of Antivirals (DAV)

- Wendy Carter, DO, Acting Director
- Poonam Mishra, MD, MPH, Deputy Director of Safety
- Aimee Hodowanec, MD, Medical Team Leader
- Melisse Baylor, MD, Medical Officer
- Yugenia Hong-Nguyen, MD, Medical Officer
- Julian O'Rear, PhD, Clinical Virology Team Leader
- Michael Thomson, PhD, Clinical Virology Reviewer
- Eric Donaldson, PhD, Clinical Virology Reviewer

OND/OID/Division of Pharmacology/Toxicology for Infectious Diseases (DPT-ID)

- Hanan Ghantous, PhD, DABT, DPT-ID Director
- Christopher Ellis, PhD, Lead Interdisciplinary Scientist (Team leader)
- David McMillan, PhD, DABT, Pharmacology/Toxicology Reviewer
- Maocheng Yang, PhD, Pharmacology/Toxicology Reviewer

OND/Office of Regulatory Operations/Division of Regulatory Operations for Infectious Diseases, Antivirals Group (DRO-ID)

- Maureen Dillon-Parker, Director, Project Management Staff
- Karen Winestock, Chief, Project Management Staff
- London Harrison, MBEE, Regulatory Project Manager

OND/Office of Translational Sciences (OTS)/ Office of Clinical Pharmacology/Division of Infectious Disease Pharmacology

- Vikram Arya, PhD, Associate Director
- Su-Young Choi, PhD, PharmD, Clinical Pharmacology Team Leader
- Yi Zhang, PhD, Clinical Pharmacology Reviewer

OND/OTS/Office of Biostatistics/Division of Biometrics IV

- Wen Zeng, PhD, Acting Statistics Team Leader
- Yanming Yin, PhD, Statistics Reviewer

OND/Office of Pharmaceutical Quality (OPQ)/Office of Pharmaceutical Quality Assessment III (OPQAIII)/Division of Product Quality Assessment XV (DPQAXV)

- Hailin (Sheena) Wang, PhD, Product Quality Team Lead
- Joao Pedras-Vasconcelos, PhD, Product Quality Reviewer
- Deyun Wang, PhD, Product Quality Reviewer

OND/Office of Surveillance and Epidemiology (OSE)

- Matthew Barlow RN, BSN, Human Factors Team Leader
- Danyal Chaudhry, MPH, Senior Safety Project Manager

SPONSOR ATTENDEES

- Xiaowei Zang, PhD, Associate Director, Quantitative Pharmacology & Pharmacometrics
- Ferdous Gheyas, PhD, Executive Director, Quantitative Pharmacology & Pharmacometrics
- Kiki Cunningham-Bussel, MD, Senior Principal Scientist, Translational Pharmacology
- Debora Rausch, MD, Senior Principal Scientist, Drug Safety
- Shrita Patel, MD, MSCE, Distinguished Scientist, Drug Safety
- Susan Kaplan, MD, MHS, Associate Vice President, Drug Safety
- Janette Gambale, MS, Principal Scientist, Clinical Operations
- Jeannine Lutkiewicz, BS, Principal Scientist, Clinical Operations
- Andrea Krick, PhD, Associate Principal Scientist, Clinical Operations
- Carmen Sofia Arriola Velezmoro, DVM, PhD, Principal Scientist, Epidemiology
- Anushua Sinha, MD, MPH, Senior Principal Scientist, Clinical Research
- Luis Castagnini, MD, MPH, Senior Principal Scientist, Clinical Research
- Andrea Guerra, MD, Principal Scientist, Clinical Research
- Macaya Douoguih, MD, MPH, Vice President, Clinical Research

- Kevin Russell, MD, MTM&H, Associate Vice President, Clinical Research
- Paula Annunziato, MD, Senior Vice President, Clinical Research
- Radha Railkar, PhD, Senior Director, Biostatistics
- Jonathan Hartzel, PhD, Associate Vice President, Biostatistics
- Ying Zhang, PhD, Associate Principal Scientist, Biostatistics
- Ziqiang Chen, PhD, Associate Principal Scientist, Biostatistics
- Kalpit Vora, PhD, Distinguished Scientist, Discovery
- Islam Hussein, PhD, Principal Scientist, Discovery
- David Gutsch, MD, Vice President, Global Regulatory Affairs
- Anita Shaw, PhD, Associate Vice President, Global Regulatory Affairs
- Sandra Wood, PhD, Senior Director, Global Regulatory Affairs
- Shona Mehta, PhD, Director, Global Regulatory Affairs

1.0 BACKGROUND

MK-1654 (clesrovimab) is a fully human IgG1 mAb RB-1, derived from human memory B-cells, with three substitutions YTE (M252Y/S254T/T256E) in the Fc region of RB-1 (RB-1YTE) to increase the half-life. Merck is developing MK-1654 to provide protection against respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. MK-1654 is proposed to be administered at 105 mg (150 mg/mL) via a single, intramuscular (IM) dose of 0.7 mL once prior to or at the beginning of the first RSV season.

On July 5, 2018, Merck submitted a Fast Track Designation request for MK-1654 for the prevention of RSV in infants. The request was granted on August 27, 2018, for the prevention of RSV in infants as it met the criteria for Fast Tract Designation.

Merck submitted a Type C, Guidance meeting request on April 16, 2019, to discuss the clinical development plan for MK-1654 including the proposed endpoints for the phase 2b/3 studies and the determination of anti-drug antibody (ADA) assay cut point in infant serum. The FDA provided written responses to Merck's questions in lieu of a meeting on June 12, 2019.

Another Type C meeting was requested by Merck on January 27, 2020, to gain additional feedback on the revised Late-Stage Clinical Trial Program, including key design elements of the re-designed Phase 2b/3 program and to seek clarification from the Agency regarding prior feedback received in June 2019.

Merck requested a Type C meeting on July 14, 2021, to discuss a proposed MK-1654 dose in the second season in PN007, regarding collection of samples to assess ADA data, and to discuss whether the 100 mg dose administered in PN002 can contribute to the safety database, as well as the duration of safety follow-up in PN004 and PN007.

On August 29, 2023, Merck requested a subsequent follow-up meeting to discuss the proposed nonclinical, chemistry, manufacturing, and controls (CMC), clinical, and statistical development plans to support an original BLA filing in the 2nd quarter of 2024.

Merck submitted a Pre-BLA meeting request on June 13, 2024, to discuss key elements of the MK-1654 BLA to support the indication of prevention of respiratory syncytial virus (RSV) lower respiratory tract disease in neonates and infants who are born during or entering their first RSV season. The meeting request was granted by the Division on July 3, 2024, as a Type B Pre-BLA virtual teleconference scheduled for August 23, 2024. FDA sent Preliminary Comments to Merck on August 20, 2024.

Upon review of the Preliminary Comments, Merck requested that discussions at the teleconference focus on questions 4, 5, and 6 as well as additional virology comments 11, 14, and 18. These discussions are summarized below.

2.0 DISCUSSION

2.1. Clinical Virology

Question 4: Does the FDA agree with the proposed virology assessment, including genotypic analysis and plan for phenotypic analysis?

FDA Response to Question 4: We are not able to make a determination regarding the proposed virology content of a BLA submission without additional information, particularly with respect to phenotyping and assessment of interference by clesrovimab with other commonly used rapid antigen tests. We recommend that mock datasets for genotypic data be provided prior to the BLA submission to ensure the content and format are acceptable for subsequent review of full datasets, and that actual sequence data be provided if available prior to the BLA submission so we can make a determination regarding phenotyping. Details of the information needed prior to a BLA submission are shown in the Additional Comments, along with a number of comments addressing other aspects of the Virology data to be submitted.

Additional Virology Comment # 11: Please respond directly to the following Additional Virology comments sent November 9, 2023:

- [comment 2] […] Please also evaluate polymorphisms which reside adjacent to positions with known resistance-associated substitutions.
- [comment 3] Please state whether variations in the clesrovimab binding site observed in GenBank sequences have been assessed phenotypically. We recommend determining the potential impact of any variations seen at the same amino acid positions in at least two isolates on neutralization activity using reverse genetics, or through assessment of appropriate clinical isolates.
- [comment 6] For resistance data submission, please include a consensus sequence with the percent identify at each amino acid position for RSV A and RSV B

Additional Virology Comment # 14: For determining the potential for cross-resistance with nirsevimab, we recommend assessing the following substitutions, based on ones with ≥100-fold loss of susceptibility to nirsevimab (see the Antiviral Resistance section [in Section 12.4] of the BEYFORTUS™ label):

RSV A: N67I+N208Y
RSV B: I64T, I64T+K68E, K65Q+K68N, K68E, K68N+N201S, K68N+N208S, N201S, N201T, L203I, N208D, N208S

Additional Virology Comment # 18: Regarding your response to Agency Comment 1 in SN 0199, please clarify for the analysis of clinical isolates with ≥5-fold shifts in potency whether one of the sequences assessed was A/HMC-12 or A/BCM-12; (b) (4) comment on the possible impacts of N120S and S255N on glycosylation. Please also evaluate phenotypically the K445R substitution seen in the RSV B isolate.

Discussion:

Additional Virology Comment # 11: Merck presented plans to evaluate clesrovimab-binding site substitutions from breakthrough infections resulting in medically attended acute lower respiratory infections.

FDA asked the sponsor to clarify whether they will be providing genotypic data and FASTQ files prior to the BLA submission to ensure correct format and content. They said they will, and FDA confirmed that they would provide feedback on mock data files prior to BLA submission. FDA also clarified that there is an expectation to provide consensus RSV A and RSV B amino acid sequences based on GenBank data and separately for each breakthrough subject's NGS data, to facilitate identifying substitutions which occur at highly conserved sites.

Regarding resistance-associated substitutions, FDA clarified that we prefer to have cell culture neutralization data; binding data may be helpful but not necessarily predictive. Phenotyping should be prioritized based on substitutions which occur in the clesrovimab binding site in at least one breakthrough infection, followed by any amino acid positions outside the binding site in at least 2 breakthrough infections, though not necessarily substitution with the same amino acid. FDA stated that one of the concerns is that substitutions may be selected following widespread use of clesrovimab, so it is important to identify which may be most likely to be resistance-associated ahead of time.

Additional Virology Comment # 14: FDA indicated that it was preferable to have cell culture neutralization data rather than binding data for nirsevimab cross-resistance assessments. Phenotyping should be prioritized based on whether substitutions occur

within 5 Angstroms of the clesrovimab binding site but that substitutions outside of the binding site may also be important because of allosteric effects.

Merck stated that a majority of the substitutions occur more than 5 Angstroms from the binding site and cross-neutralization of nirsevimab resistance-associated substitutions reported in clinical trials has been investigated. FDA stated that based on review of the cross-resistance and clinical data provided with the BLA, it may be necessary to prioritize substitutions for phenotyping, other than those for which there will be cell culture neutralization data.

Additional Virology Comment # 18: FDA clarified that the context of the comment was based on an analysis the sponsor conducted on sequence data for clinical isolates which showed a >5-fold reduction in susceptibility to clesrovimab, and that there was a discrepancy in the Table and Figure provided showing these data, likely from different reference sequences used. For the RSV A substitutions, it might depend on whether any were seen in clinical trials, as to whether they should be prioritized for phenotyping.

For the RSV B K445R binding site substitution, while it was seen to occur rarely in GenBank, the FDA reiterated that following widespread use of clesrovimab, it may become more prevalent, so it will be important to assess in a cell culture neutralization assay.

Merck agreed to provide phenotypic analysis of K445R substitution but stated the data would not be available at the time of BLA submission.

Merck also confirmed that there were no genotypic data available for study P005 which was a treatment study.

2.2. Regulatory

Question 5: Does the FDA agree with the proposed content and timetable for submission of the Safety Update Report (SUR)?

FDA Response to Question 5:
In general, we agree with your plans for the Safety Update Report (SUR). We have the following additional comments regarding the content of the SUR:

1. Please limit data in the SUR to new data only; do not combine the safety data from the original BLA with the new data presented in the SUR.
2. Please confirm if the SUR will include safety data from Day 241 to Day 365 for all subjects in Trial 004.
3. Please clarify what, if any, data will be available from Day 365 to Day 515 from Trial 004 in the SUR.
4. Please submit the data in the SUR in tabular form with individual tables for each safety parameter. Tables to be provided should include but are not limited to: all

adverse events (AEs), product-related adverse events, rash or skin AEs, serious adverse events (SAEs), adverse events of special interest (AESIs), and deaths.
   a. Please group the tables by study.
   b. Please provide line listings to support each table.
5. Please provide narratives for all SAEs (including deaths) throughout the study, hypersensitivity reactions (AESIs) within 42 days of study drug administration, and study discontinuations due to an AE.

Discussion:
Merck provided an example of the table format to be provided in the SUR. The table included a side-by-side comparison of data provided with the BLA submission, new data available since submission of the BLA (SUR) and updated cumulative data. Merck clarified that P004 SUR tables will include safety data from Days 241 to 365 for all study participants. Data from Day 365 to Day 515 will be available in the BLA.

FDA agreed with the proposed presentation of the sample SUR data table and that no datasets need to be submitted with the SUR.

Question 6: Does the FDA agree with the proposed content and format of the BLA as described in the draft Table of Contents (TOC)?

The proposed content and format of Modules 1-5 is generally acceptable. We have the following comments regarding Modules 2 and 5:

Module 2

1. Please include all clinical trials of clesrovimab, including those conducted in adults, in the Clinical Overview and Summary of Clinical Safety.
2. In addition to summaries of safety for each individual study, a summary of key safety events (e.g., hypersensitivity reactions) across trials should be included in the Clinical Overview and Summary of Clinical Safety.
3. In the Summary of Clinical Safety, please include the following safety analyses:
   - For *all* clinical studies in your development program: overdose, injection site reactions, hypersensitivity reactions including anaphylaxis, rash within 2 weeks of study drug administration, AEs resulting in premature study discontinuation, and deaths.
   - In pediatric trials: an analysis of fever
     - Please include a comprehensive assessment of fever among pediatric participants following receipt of clesrovimab. It is unclear what time frame is most relevant for assessing fever (e.g., within 48 hours vs. 5 days vs. 2 weeks after study drug administration). We therefore encourage you to conduct analyses using multiple time frames and to provide any rationale you may have for favoring a particular time frame for this assessment. Additionally, we

encourage you to identify cases in which fever within 7 days of clesrovimab resulted in a "rule out sepsis" work-up.
- In adult trials: an analysis of use in pregnancy

4. We agree that narratives should be provided for all SAEs (including deaths) throughout the study. In addition, please provide narratives for:
    - All subjects in *any* trial who experienced a hypersensitivity reaction within 6 weeks (42 days) after dosing.
    - All subjects in your pediatric trials who experienced a new-onset rash within 2 weeks after dosing.
    - All subjects in your pediatric trials who discontinued the study due to an AE.
    - All subjects in your pediatric trials who had new onset chronic diseases.

Module 5:

5. Please submit data sets and Clinical Study Reports (CSRs) for *all* clinical trials of clesrovimab, including those conducted in adults.
    - It appears that in Appendix 4, Section 5.3.3.1, when you list study P003MK1654, you are in fact describing Trial PN005. Please confirm if this is correct. Note that we consider Trial PN005 to be part of the clinical development program for clesrovimab. Therefore, please submit the data sets and CSRs for both P003 and PN005 in the original BLA.
6. We acknowledge prior discussions regarding pooling and continue to support your plan not to pool studies for efficacy analyses, given the differences in patient population, comparator, and overall study design. However, we think that analyses of safety across trials could be informative. We strongly encourage you to submit an ISS as well as pooled safety datasets.
7. In the CSR for Trial 007 (RSV Season 1 only) and Trial 004, in addition to standard safety analyses, please include the following safety analyses:
    - An analysis of adverse events by time to onset (i.e., within 24 hours, within one week, and within 42 days of study product administration).
    - All rashes with 14 days of product administration.
    - Analysis of fever (as described above)
    - Hypersensitivity reactions.

Discussion:

Module 2, Comment 2: Merck restated lack of plans to pool or integrate safety data. They noted that it would not be possible to integrate safety data based on the planned BLA submission timeline coinciding with MK-1654 product availability to the public by the start of the 2025-2026 RSV season. To address FDA's request for an analysis of safety across trials, Merck proposed the inclusion of "combined summary tables of key safety events" across the infant populations, to include the following key safety events: hypersensitivity AEs, rash AEs, SAEs/intervention-related SAEs, and deaths.

FDA stated that inclusion of an ISS is required by regulations for submission of an NDA and is recommended for BLAs. FDA requested integrated and pooled infant and adult data with updated coding and dictionary leveling of preferred terms across trials. The FDA advised Merck it will be reviewing the cross-study data of certain adverse events across infant studies and adult studies and encouraged Merck to do the same.

Merck then proposed to provide the following pooled datasets without dictionary "leveling" as part of the BLA submission:

- Pooled infant dataset: P002, P004, P007, and P008
- Pooled adult dataset: P001, P003, and P008

Merck and FDA agreed that the pooled datasets and safety event tables will be included in the ISS section of the original BLA submission and the pooled analysis Reviewer's Guide will be submitted no later than 30 days after submission of the BLA.

FDA agreed to the proposals and requested the inclusion of injection site reaction to the list of key safety events to be provided.

Module 5, Comment 5: Merck acknowledged the error in Appendix 4, Section 5.3.3.1, for study P003MK1654, providing the correct title for P003, and confirmed that P005 was a human challenge study in adults. Merck again proposed to not provide a CSR for P005 as the study was conducted to support internal discussion of a different RSV vaccine program as well as the relationship between viral load and SNA. P005 was not intended to provide information to support additional clinical development of MK-1654. Merck confirmed there was no genotypic data collected for P005.

FDA acknowledged that P005 was not intended to support the clesrovimab development program but noted that any potential safety signals from the trial would be of interest and reiterated request for an overall summary of safety for P005 to confirm that there were no serious adverse events such as hypersensitivity, anaphylaxis, or rash. Merck proposed submission of an abbreviated CSR for P005 with summary primary and secondary endpoint clinical data as well as safety and PK data. The CSR would also include safety summary tables and would be provided in the BLA submission. FDA agreed.

Additional information provided by Merck regarding clesrovimab safety included:

- All hypersensitivity, anaphylaxis, and rash AEs in P004 and P007 were grade 1 or 2, except for one Grade 3 urticaria AE. A dermatology consult report was unavailable.
- No pregnancies were reported among adults in any adult studies.
- Only narratives are available for deaths; autopsy reports are unavailable due to Merck not having ethics committee permission to access autopsy reports.

3.0 ADDITIONAL MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. Merck was informed that the planned original BLA application for MK-1654 under 351(a) of the Public Health Service (PHS) act will be subject to "the Program" under PDUFA VII.

- 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, and it was noted that a REMS is not anticipated to be needed at this time.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: Analysis Reviewer's Guide for the pooled safety datasets.

Prominently identify each submission containing your late component(s) with the following wording in bold capital letters at the top of the first page of the submission:

BLA NUMBER: LATE COMPONENT - CLINICAL

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 guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended 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.

[2] https://www.fda.gov/media/86340/download
[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

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)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[6] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[7]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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,* and the associated conformance guide, *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*.[8]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of

[6] https://www.fda.gov/media/84223/download
[7] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[8] https://www.fda.gov/media/85061/download

meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

Action Item/Description	Owner	Due Date
Submission of sample ADaM datasets, FASTQ file and associated tables for review by FDA.	Sponsor	Prior to BLA submission

6.0 ATTACHMENTS AND HANDOUTS

A copy of the Sponsor's slides that were discussed during this meeting have been attached.

48 Page(s) has 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/

LONDON F HARRISON
09/20/2024 05:00:55 PM