CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218591Orig1s000, 207620Orig1s025

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 104628

MEETING REQUEST-
WRITTEN RESPONSES

Novartis Pharmaceuticals Corporation
Attention: Emily Burd, PharmD
Global Program Regulatory Manager, Regulatory Affairs
One Health Plaza
Building 337
East Hanover, NJ 07936

Dear Dr. Burd:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for LCZ696 (sacubitril/valsartan).

We also refer to your submission dated February 2, 2023, containing a meeting request. The purpose of the requested meeting was to discuss proposed updates to the United States Prescribing Information to include efficacy and safety data from the completed PANORAMA-HF study, as well as to discuss submission of a New Drug Application for a pediatric formulation.

Further reference is made to our Meeting Granted letter dated February 7, 2023, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your February 2, 2023, background package.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology,
Endocrinology, & Nephrology
Center for Drug Evaluation and Research

Enclosure: Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-NDA

Application Number: 104628

Product Name: LCZ696 (sacubitril/valsartan)

Indication: N/A (No new indication proposed)
Sponsor Name: Novartis Pharmaceuticals Corporation
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Entresto is a combination of sacubitril and valsartan originally approved in 2015 to reduce the risk of cardiovascular (CV) death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF). Pediatric studies were waived under PREA because of the small number of patients, but the Agency issued a Written Request (WR) in March 2017 for clinical study CLCZ696B2319 (PANORAMA-HF). The WR was originally written for a 52-week trial. Due to slow enrollment, the WR was amended to allow for an interim analysis at week 12 using NT-proBNP as a bridging biomarker for pediatric patients from 1 to <18 years of age. A supplement (sNDA) was submitted April 1, 2019, and approved on October 1, 2019, providing for a new indication for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

PANORAMA- HF continued for the 52 weeks comparing LCZ696 to enalapril with patients down to 1 month of age. In September 2021 Novartis requested a Written Response Only meeting to discuss format and content of a planned supplemental New Drug Application (sNDA). A meeting was held in April 2022 to discuss the results of the completed trial. At the time of the meeting, Novartis explained that they did not plan to submit a supplement to expand the age range down to 1 month (b) (4)

The Division suggested that information from the trial be included in the label (b) (4)

(b) (4)

(b) (4)

Novartis requested this meeting to provide an update on the details of the planned sNDA to update the label with pediatric information, and to discuss submission of a new NDA for the pediatric formulation. In addition, they are requesting clarification on FDAs feedback from the September 2021 meeting request in the additional comments section.

2.0 QUESTIONS AND RESPONSES

Question 1: Proposed submission plan
Does the Agency agree with the proposed plan for submissions of a supplemental NDA for clinical data and new NDA to register a new formulation for pediatric use?

FDA response: Your proposal to submit a supplemental NDA (sNDA) to NDA 207620 to incorporate final PANORAMA-HF data into the label is reasonable. We agree with the proposal to submit information supporting the proposed pediatric formulation, film-coated granules, in a new NDA.

Question 2: Labeling
Does the Agency agree with the proposed parallel implementation of labeling?

FDA response: We agree.

Question 3: Overall Content of sNDA and NDA
Does the Agency agree with the proposed content of the sNDA and NDA packages and labeling strategy?

FDA response: You propose to submit clinical overview, summary of clinical efficacy, summary of clinical safety, summary of clinical pharmacology, and final clinical study report under the planned pediatric sNDA 207620 based on PANORAMA-HF. (b) (4)

The proposed format for pediatric sNDA 207620 is reasonable. With regard to the proposed content of the new NDA, the outline of information to be submitted in Module 3.2.P, 3.2.A, and 3.2.R appears reasonable, but no cross-reference for 3.2.S is provided for the drug substance. We remind you to include a cross-reference to either the approved NDA or a drug master file with a letter of authorization to enable review of information to be included in Sections 2.3.S and 3.2.S.

Question 4: Waiver for Safety Update
Does the Agency agree to the proposed safety cut-off date and that the established safety profile of Entresto is adequate and that a waiver for a 120-day safety update as required per 21 CFR 314.50(d)(5)(vi)(b) may be granted?

FDA response: We agree.

Question 5: FDA Additional Comments to Content Format Briefing Book
Does the Agency accept Novartis' responses to the 3 Agency's additional comments related to clinical trial material, quality of the datasets and Kaplan-Meier time to event analysis dataset and code?

FDA response: Based on the information provided in the meeting package we acknowledge your inability to provide sample clinical trial kits with the sNDA. We agree with your plan to submit high quality data and executable code. Please be sure that code in the submission is well commented.

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*.[1] 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.[2]

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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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.

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[1] 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.
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] 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.

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.[5]

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.[6]

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

[5] http://www.fda.gov/ectd
[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]*.* 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.

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

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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/

NORMAN L STOCKBRIDGE
03/15/2023 11:36:54 AM

IND 104628

MEETING REQUEST-
WRITTEN RESPONSES

Novartis Pharmaceuticals Corporation
Attention: Shivani Shah, PharmD
Global Program Regulatory Manager, Regulatory Affairs
One Health Plaza, Building 315
East Hanover, NJ 07936

Dear Dr. Shah:

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

We also refer to your submission dated September 21, 2021, containing a meeting request. The purpose of the requested meeting was to discuss the content and format of the pediatric heart failure supplemental New Drug Application.

Further reference is made to our Meeting Granted letter dated September 24, 2021, wherein we agreed that written responses to your questions would be provided in lieu of a meeting.

The enclosed document constitutes our written responses to the questions contained in your September 21, 2021 background package.

If you have any questions, please call Alexis Childers, Sr. Regulatory Project Manager, at (301) 796-0442.

Sincerely,

{See appended electronic signature page}
Norman Stockbridge, M.D., Ph.D.
Director
Division of Cardiology and Nephrology
Office of Cardiology, Hematology,
Endocrinology, & Nephrology
Center for Drug Evaluation and Research

Enclosure: Written Responses

U.S. FOOD & DRUG ADMINISTRATION

WRITTEN RESPONSES

Meeting Type: B
Meeting Category: Pre-sNDA

Application Number: 104628

Product Name: sacubitril/valsartan
Indication: treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients (b) (4)

Sponsor Name: Novartis Pharmaceuticals Corporation
Regulatory Pathway: 505(b)(1)

1.0 BACKGROUND

Entresto is a combination of sacubitril and valsartan approved in 2015 to reduce the risk of cardiovascular (CV) death and hospitalization for heart failure in patients with chronic heart failure (NYHA Class II-IV) and reduced ejection fraction (HFrEF). Pediatric studies were waived under PREA because of the small number of patients, but the Agency issued a Written Request (WR) in March 2017 for Clinical study CLCZ696B2319 (PANORAMA-HF) to fulfill the WR. The WR was originally written for a 52-week trial. Due to slow enrollment, the WR was amended to allow for an interim analysis at week 12 using NT-proBNP as a bridging biomarker for pediatric patients from 1 to <18 years of age. A supplement (sNDA) was submitted April 1, 2019 and approved on October 1, 2019 providing for a new indication for the treatment of symptomatic heart failure with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. ENTRESTO reduces NT-proBNP and is expected to improve cardiovascular outcomes.

PANORAMA- HF is expected to conclude in Q4 2021 and Novartis plans to submit a sNDA with the completed trial data (b) (4) Novartis has also created a pediatric formulation of granule capsules that will be included in the submission. Novartis plans to request a topline results meeting when data are available.

Novartis requested this meeting to obtain feedback on key aspects of the proposed content and format of the sNDA.

2.0 QUESTIONS AND RESPONSES

1a. Does the Agency agree with the proposal to present efficacy in the planned submission, specifically within the Summary of Clinical Efficacy (SCE; CTD Module 2.7.3) as detailed [in the meeting package]?

FDA response: Yes

1b. Does the Agency agree to the proposed approach to satisfy the requirements for an Integrated Summary of Efficacy?

FDA response: Yes

2a. Does the Agency agree with the proposal to assess safety and associated content in the planned submission, specifically within the Summary of Clinical Safety (SCS; CTD Module 2.7.4) as detailed [in the meeting package]?

FDA response: Yes.

2b. Does the Agency agree to the proposed approach to satisfy the requirements for an Integrated Summary of Safety?

FDA response: Yes.

3. Does the Agency agree with the proposed clinical content of Module 5, including the plan for submission of case report forms, patient narratives, and clinical endpoint adjudication packages?

FDA response: Yes.

4. Does the Agency agree with the proposed plan for submission of datasets and programs for the pediatrics sNDA?

FDA response: Yes.

5. Does the Agency agree with the proposed content of the key elements of the sNDA package?

FDA response: Please submit the following documents under Module 1:

1) Form 3674
2) Debarment Certification
3) FDA Form 3542
4) Financial Disclosure FDA Forms 3454 and 3455

Additional comment: If a new dosage form will be included with these data, then a new NDA will need to be submitted. We suggest you submit the question in a meeting request with more information so that we can further assess the appropriate type of submission.

For the new NDA, please ensure that complete CMC information is included in Module 3 or cross-referenced with supporting Letter(s) of Authorization as appropriate.

Reference is made to your general correspondence submitted on October 28, 2021, in which you informed the Division of an urgent safety measure implemented. According to your letter, the study treatment of all patients remaining in the study will be discontinued by the end of October, two months prior to the scheduled study end. A maximum of 31 patients are affected. You proposed to continue following these patients till the end of study. The total on-treatment follow up time lost is expected to be small. (b) (4) . You should continue including the off-treatment data as originally planned and conduct sensitivity analysis using on-treatment data. Given the impact is small, study conclusion should not be affected.

Additional requests:

1. Please submit the following information at the time of sNDA submission:

   a. Randomization

      1) A dataset that links the subject's randomization number and unique subject ID to the allocated medication kit/box number, medication name, and associated define file.

   b. Protocol and Statistical Analysis Plan (SAP)

      1) All versions of the protocol for PANORAMA-HF and the date when changes were implemented. Include a Summary of Changes for each version.

      2) All versions of the SAP for PANORAMA-HF. Include a summary of changes for each version and the number of subjects enrolled in the trial at the time the change was made.

   c. Clinical Trial Materials

      Case report forms (CRFs) and narratives for all subjects who died, dropped out, discontinued study drug for any reason, experienced a serious adverse event (SAE), or reached an efficacy endpoint. Please note that CRFs must include all clinical documents collected regardless of whether you label them as "CRFs" (Medwatch forms, event fax coversheets, SAE or event worksheets, narrative worksheets, data queries, etc.).

      1) Sample clinical trial kits, from both treatment arms, identical to those used during PANORAMA-HF. Ship them to Alexis Childers' desk address in the same packaging as was used for shipping to investigative sites.

2) All data management plans for PANORAMA-HF. Cite all amendments for each data management plan, including all manual and programmatical checks.

3) All site monitoring plans for PANORAMA-HF. If changes to your site monitoring plans were not documented contemporaneously by formal signed amendments, explain the amendment process.

4) A description of the responsibilities of each academic research organization (ARO) or clinical research organization (CRO) used in PANORAMA-HF.

5) All charters for committees involved in conducting PANORAMA-HF (e.g., Data Safety Monitoring Board [DSMB], Steering Committee, etc.)

6) All meeting minutes of all groups with any responsibility for the management of the trial, e.g., Executive Committee, Clinical Endpoint Committee, Steering Committee and DSMB. Include agendas and all data/slides presented to the Committee. Indicate whether the meeting was opened or closed. Ensure that these packages include a table of contents and are bookmarked by date.

7) All newsletters and all other communications to investigational sites and national coordinators from the groups responsible for the conduct of PANORAMA-HF. Please bookmark the communication by date.

d. General Data and Analyses

1) All code and datasets used to create your analyses found in the main sections of your Summary of Clinical Efficacy, Summary of Clinical Safety, and Phase 3 trial clinical study report.

2) Footnote the tables and figures featured in the main clinical efficacy and safety sections of the sNDA with the name of the script used to create the table or figure.

3) List of datasets that you assert are of high quality for review. Explain how you assessed the quality of your datasets and what you did to ensure your datasets are suitable for an sNDA review. Submit code that was used to create or clean up your analysis datasets.

4) Kaplan-Meier time to event analysis datasets and code (both safety and efficacy) censoring subjects without an event at the date of last known information about the event of interest (not vital status check at the end of the study). Indicate how censoring was determined (e.g., by a patient visit or by telephone call). This dataset should allow one to analyze by intent-to-treat (ITT) as well as on-treatment. The events should include all adjudicated

events, any important composite endpoints, important adverse events, and laboratory parameter changes of interest.

5) Subject ID variable for all open label extension study datasets that links the subject to the ID used in the pivotal trial datasets.

6) Dataset that contains all subjects that were unblinded. Include the unique subject ID, the treatment received, who requested unblinding, date of unblinding, and the reason for unblinding.

7) Dataset that contains a list of all subjects for whom you submitted a CRF, narrative, or adjudication packages. The dataset should contain four variables with an indicator for whether each item was submitted.

8) A table set up similarly to the dataset requested in above, but with a hyperlink to the respective document. The table could be further organized by reason for narrative submission (subjects with cardiovascular events of interest, subjects with hepatic laboratory anomalies of interest, etc.).

9) One table which includes the following information for PANORAMA-HF:
   - Dates of first patient and last patient visits
   - Date of data lock
   - Dates for each interim analysis
   - Dates of all versions of the SAP (with a hyperlink to each SAP)
   - Dates of the initial protocol and all revisions. (with a hyperlink to the protocol and each revision).

e. Important Endpoints

1) An adjudication dataset for PANORAMA-HF that contains one line per event. The columns in the dataset should include the study number, unique subject id, randomized treatment, actual treatment, flag that indicates subject is included in the ITT analysis, flag that indicates the subject is included in the safety analysis, the event type being adjudicated (i.e., stroke, major bleed, death, hospitalization for heart failure, etc.), date of event, what triggered the event for adjudication (i.e., investigator, laboratory result, etc.), the investigator's assessment of the event, each adjudicators' result (in chronological order across the dataset), date of each adjudication, final adjudication result and date.

2) A comprehensive description of the algorithm used to identify potential endpoint events in your final clinical study report. If your algorithm changed, you should also provide detailed information on its evolution, including when and why changes were made.

Other

1) Statement of Good Clinical Practice confirming that all clinical studies were conducted under the supervision of an Institutional Review Board and with adequate informed consent procedures. If you were granted an IRB Waiver during this trial because a specific site or country operated under a Central Ethics Committee (CEC) and/or Local Ethics Committees (EC), please reference the waiver and include the date.

2) Rationale for assuring the applicability of foreign data to U.S. population/practice of medicine in the submission for those phase 3 trials conducted primarily outside of the United States (OUS)

   There are two major pieces to this applicability of foreign data issue as follows:

   - Are the patients the same (US versus rest of the world)?
   - Are the medical systems treating the disease the same way with respect to interventions and background therapy on a region-specific basis?

3) An annotated version of the pre-NDA meeting minutes that include a hyperlink, when applicable, to the analysis and/or documents requested. This document is usually placed in Module 1.

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*.[1] 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.[2]

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[3] and Pregnancy and Lactation Labeling Final Rule[4] 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

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[1] 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.

[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information

[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

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[5] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[6]. 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*.[7]

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

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