CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217003Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 147315

MEETING MINUTES

Pharmacyclics LLC
Attention: Xi Tian, PhD
Senior Manager, Regulatory Affairs
995 East Arques Avenue
Sunnyvale, CA 94085-4521

Dear Dr. Tian:[1]

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

We also refer to the teleconference between representatives of your firm and the FDA on May 25, 2021. The purpose of the meeting was to discuss the content of a proposed supplemental new drug application (sNDA) to support inclusion of pediatric data based on Studies PCYC-1146-IM (iMAGINE), PCYC-1140-IM (iNTEGRATE), 54179060LYM3003 (SPARKLE), and PCYC-1129-CA in the IMBRUVICA (ibrutinib) United States Prescribing Information (USPI) and to discuss the proposed concurrent new drug application (NDA) for a new dosage form (oral suspension formulation) of ibrutinib.

A copy of the official minutes of the teleconference 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 Esther Park, Senior Regulatory Health Project Manager, at (301) 796-2811.

Sincerely,

{See appended electronic signature page}

Lori Ehrlich, MD, PhD
Clinical Team Leader
Division of Hematologic Malignancies I
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-sNDA/pre-NDA
Meeting Date and Time:	Tuesday, May 25, 2021; 3:00 – 4:00 PM (ET)
Meeting Location:	Teleconference
Application Number:	IND 147315
Product Name:	ibrutinib
Indication:	treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy
Sponsor Name:	Pharmacyclics LLC
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetics Act
Meeting Chair:	Lori Ehrlich, MD, PhD
Meeting Recorder:	Esther Park, PharmD

FDA ATTENDEES

Office of Oncologic Diseases (OOD)
Gregory Reaman, MD, Acting Associate Director, Pediatric Oncology

OOD/Division of Hematologic Malignancies I (DHMI)
R. Angelo de Claro, MD, Division Director
Lori Ehrlich, MD, PhD, Clinical Team Leader
Kamar Godder, MD, MPH, Clinical Reviewer

OOD/Division of Hematologic Malignancies II (DHMII)
Nicholas Richardson, DO, MPH, Clinical Team Leader
Margret Merino, MD, Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases/Hematologic Malignancies I
Esther Park, PharmD, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Amal Ayyoub, PhD, Acting Clinical Pharmacology Team Leader
Yajun Liu, PhD, Clinical Pharmacology Reviewer
Lian Ma, PhD, Pharmacometrics Team Leader
Ruojing Li, PhD, Pharmacometrics Reviewer

Office of Biostatistics/Division of Biometrics IX
Jonathon Vallejo, PhD, Acting Biometrics Team Leader
Xin Wang, PhD, Biometrics Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products I, Branch II
Sherita McLamore, PhD, Acting Quality Assessment Leader

OPQ/Office of New Drug Products, Division of New Drug API, Branch I
Haripada Sarker, PhD, Quality Assessment Lead

OPQ/Division of Biopharmaceutics
Om Anand, PhD, Acting Biopharmaceutics Lead

OPQ/Office of Pharmaceutical Manufacturing Assessment (OPMA)
Steven Hertz, PE, Consumer Safety Officer

SPONSOR ATTENDEES

Pharmacyclics LLC
Ada Braun, MD, PhD, Regulatory Affairs Therapeutic Area Head
Julie Astanov, BS, Associate Director, Regulatory Affairs
Lori Styles, MD, Senior Medical Director
Justin Wahlstrom, MD, Medical Director
Robert Kahn, MD, Senior Medical Director, Safety Science
Mei Cheng, PhD, Executive Director, Biostatistics
Yihua Lee, PhD, Director, Biostatistics
Harisha Atluri, PhD, Associate Director, Clinical Pharmacology
Juthamas Sukbuntherng, PhD, Head of Clinical Pharmacology and DMPK
Poonam Jethanandani, PhD, Associate Director, RA CMC

AbbVie Inc.
Jayanthy Jayanth, MS, Director, CMC Product Development
Paul Brackemeyer, MS, Principal Research Scientist
Thomas Podsadecki, MD, Vice President, Regulatory Affairs Therapeutic Area
Patrick Marroum, PhD, Senior Director and Senior Research Fellow, Clinical Pharmacology and Pharmacometrics

Janssen R&D, LLC
Alysia Ferro, MS, Senior Director, Regulatory Affairs
Angela Howes, PhD, Vice President, Head of Leukemia Development, Clinical R&D
Sanjay Deshpande, MD, Executive Medical Director, Oncology Therapeutic Area
Rui Qin, PhD, Associate Director, Biostatistics
Italo Poggesi, ChemD, PhD, Scientific Director, Clinical Pharmacology

1.0 BACKGROUND

Imbruvica (ibrutinib) is being co-developed by the Sponsor, Pharmacyclics LLC and Janssen Research & Development, LLC, as an orally administered anticancer agent for the treatment of a variety of B-cell malignancies including mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia (WM), (b) (4) marginal zone lymphoma (MZL) as well as in chronic graft versus host disease (cGVHD). The Sponsor is proposing to update the existing indication in cGVHD to the following: *"IMBRUVICA is a kinase inhibitor indicated for the treatment of adult and pediatric patients age 1 year and older with chronic graft versus host disease (cGVHD) after failure of one or more lines of systemic therapy".*

On March 26, 2021, the Sponsor requested a pre-sNDA/pre-NDA meeting to discuss and reach agreement with the Agency on the content of the proposed sNDA to support updates to the Imbruvica (ibrutinib) USPI based on pediatric data from Studies iMAGINE, iNTEGRATE, and SPARKLE, and final analysis data from Study 1129. In addition, the Sponsor is seeking feedback on the proposal to concurrently submit an NDA for a new dosage form (multi-dose, oral suspension formulation) of ibrutinib for administration in pediatric subjects with cGVHD age ≥ 1 to < 12 years, who are dosed based on BSA.

The Agency sent Preliminary Comments to Pharmacyclics LLC on May 19, 2021.

2.0 DISCUSSION

2.1. Efficacy

Question 1: *Does the Agency agree that efficacy and safety data based on Studies, iMAGINE, iNTEGRATE and 1129 are appropriate to support approval of Imbruvica in pediatric cGVHD: "Imbruvica is indicated for the treatment of adult and pediatric patients age 1 year and older with chronic graft-versus-host disease (cGVHD) after failure of one or more lines of systemic therapy?"*

FDA Response to Question 1:
The proposed clinical studies appear appropriate for submission, but whether the data supports the proposed indication will be a review issue. Approval in the younger age groups will depend on the number of patients treated and whether there were any differences in efficacy or toxicity between the groups.

Discussion:
The Sponsor presented accrual numbers by age cohort and plans to submit information on efficacy and safety across age cohorts (1 to < 6 years; 6 to < 12

years; and 12 to < 18 years) in the sNDA. This plan is acceptable to the Agency.

Question 2: *Does the Agency agree that efficacy data, including the response rate at 24 (or 48) weeks, ORR, sustained response rate for at least 20 (or 32) weeks, DOR, and Lee Symptom Scale improvement, if results are clinically meaningful, are appropriate to support labeling claims in the Clinical Studies section (Section 14) of the USPI?*

FDA Response to Question 2:
The inclusion of particular endpoints in the USPI will be a review issue. For each proposed endpoint, the submission should discuss support for extrapolation from the adult study and the clinical relevance in pediatric patients.

Discussion:
The Sponsor presented an outline of the justification for the applicability of the adult efficacy endpoints to children. The Agency agrees with this approach. The Agency also agrees that the Sponsor may present justification for the value of the pediatric data independent of the adult data.

Question 3: *Pending outcomes from the primary analysis of iMAGINE, assuming a positive benefit-risk evaluation in the subset of subjects with* (b) (4)*, does the Agency agree that data from iMAGINE together with data from iNTEGRATE may support a* (b) (4)

FDA Response to Question 3:
(b) (4)

Discussion:
The Agency reiterated that it is unlikely that data from the frontline treatment of 12 pediatric patients with cGVHD will be sufficient to support a (b) (4)

Question 4: *Does the Agency agree with the below proposed plans for the SCE, and ISE for the sNDA?*

FDA Response to Question 4:
You propose to analyze the efficacy endpoints and perform subgroup analysis for SCE and ISE "per the statistical analysis plan". However, no statistical analysis plan is submitted. Further comments may be provided after the full review of your finalized statistical analysis plan. The proposed dataset pooling appears acceptable.

Discussion:
No discussion occurred.

Question 5: *The Applicant proposes to update the USPI with long-term efficacy data for Study 1129* (b) (4) *including the primary endpoint, best overall cGVHD response rate according to the* (b) (4) *NIH Consensus Panel Response Criteria (with 2 modifications to align with the updated 2014 NIH Consensus Panel Response Criteria), sustained response rate for at least* (b) (4) *weeks, as well as changes in Lee Symptom Scale overall summary score. Does the Agency agree with this proposal?*

FDA Response to Question 5:
The proposal to update the USPI with results of Study 1129 appear acceptable.

Discussion:
No discussion occurred.

2.2. Safety

Question 6: *Does the Agency agree with the overall safety database, including the pooling strategy for the ISS and the proposed plan for the SCS for the sNDA?*

FDA Response to Question 6:
Your general approach to the ISS and SCS appears acceptable. Safety information from the SPARKLE study should be included in the ISS and SCS and can be presented side-by-side and not pooled with GVHD because it is in combination with chemoimmunotherapy.

Discussion:
The Sponsor's plan for presentation of the safety information in the ISS and SCS is acceptable.

2.3. Additional Pediatric Data

Question 7: *The Applicant proposes to include limited safety and clinical pharmacology information from SPARKLE in Section 8.4 (Pediatric Use). Does the Agency agree?*

FDA Response to Question 7:
The adequacy of the proposed labeling based on PK data from Study SPARKLE in Section 8.4 (Pediatric Use) will be a review issue.

Discussion:
No discussion occurred.

2.4. Clinical Pharmacokinetic/Pharmacodynamics

Question 8: *Does the Agency agree with the content of the proposed Clinical Pharmacology package for this sNDA?*

FDA Response to Question 8:
Your general plan for population PK and exposure-response (E-R) analysis appears reasonable. For E-R analyses, we recommend that you conduct multivariate analyses by including baseline demographic characteristics and disease status as covariates to explore potential confounding factors. In addition, you should consider using pooled pediatric data from Studies iMAGINE, iNTEGRATE, and SPARKLE to characterize the exposure-safety profile with a wider exposure range.

We do not agree with your proposal of not conducting a dedicated relative bioavailability study of the commercial multiple-dose suspension formulation compared to the capsule formulation. Based on the limited information submitted, the to-be-marketed formulation (multiple-dose suspension) has not been adequately bridged to the capsule formulation. Provide adequate justification supported by data/information showing that the change in the multiple-dose suspension formulation (total change i.e. (b) (4)) compared to the single-dose suspension formulation is not likely to affect the bioavailability of the multiple-dose suspension. If the provided justification is deemed inadequate, an in vivo relative BA/BE human study and a food effect study may be required.

Discussion:
The Agency stated that additional data/information are needed to demonstrate that the changes in formulation composition between the single-dose and multi-dose suspension formulations are not expected to impact bioavailability. For example, submit comparative drug substance particle size distribution data, viscosity, and pH data.

The Agency also stated that the dissolution data are not acceptable because the dissolution method used is not adequate. The Agency further recommended the Sponsor to develop an optimal dissolution method, with a (b) (4)

demonstrate the discriminating ability and then submit comparative dissolution data.

The Agency acknowledged the Sponsor's response and stated that the acceptability of the new multiple-dose suspension formulation will be a review issue.

2.5. Regulatory

Question 9: *The Applicant intends to apply for priority review for this sNDA and pediatric oral suspension formulation NDA. Does the Agency agree with this request?*

FDA Response to Question 9:
Determination of priority review will be made at the time of sNDA submission. However, pediatric applications are considered priority review designation. Refer to the response to Question 8 regarding the proposed NDA for the pediatric multiple-dose suspension formulation.

Discussion:
No discussion occurred.

Question 10: *The Applicant considers that the planned sNDA and NDA submissions complete the Applicant's commitments under the FDA's pediatric WR for Imbruvica, and the Applicant would therefore like to request pediatric exclusivity determination by the Agency. Does the Agency agree that pediatric exclusivity could be granted based on the planned sNDA to be submitted by Q1 2022?*

FDA Response to Question 10:
The Agency agrees with the plan to request pediatric exclusivity determination. The application will be reviewed by the Pediatric Exclusivity Board. The sNDA submission should include a comparison table of each item in the WR and the information submitted in response.

Discussion:
No discussion occurred.

Question 11: *The Applicant plans to submit an NDA for the pediatric oral suspension formulation concurrently with the sNDA, and to cross-reference relevant sections from the sNDA. Does the Agency agree with this approach?*

FDA Response to Question 11:
The approach to concurrent submission of an NDA for the oral suspension appears acceptable.

Discussion:
The approach to cross-referencing the capsule sNDA presented in Table 17 of the briefing document appears acceptable. The submission should clearly indicate which patients received the capsule versus the oral suspension.

2.6. Chemistry, Manufacturing and Controls (CMC)

Question 12: *The Applicant plans to submit a Type 3 NDA for a new dosage form (oral suspension) of ibrutinib and cross-reference the drug substance Module 3 section (3.2.S) to the approved NDA 205552 for ibrutinib (Imbruvica) capsules. A certificate of analysis for a drug substance lot used to manufacture the suspension will be included. Does the Agency agree with this approach?*

FDA Response to Question 12:
Your plan for referencing the drug substance and submitting the relevant CMC information in the proposed NDA submission appears reasonable. Final determination will be made during the NDA review.

Discussion:
No discussion occurred.

Question 13: *The Applicant plans to provide information for the device (oral dosing syringe) relevant to a Class I, 510(k) exempt, Good Manufacturing Practice (GMP) exempt device in the relevant eCTD sections of the new NDA. Does the Agency agree with this approach?*

FDA Response to Question 13:
The proposal to provide device related information for the oral dosing syringe in the Regional Section (3.2.R-DEVICE) of the NDA submission appears reasonable.

Discussion:
No discussion occurred.

Question 14: *The Applicant plans to include the master batch record (MBR) for commercial production and one EBR for a PSB. The MBR will include manufacturing steps including compounding and filling of the suspension. Does the Agency agree that submission of one EBR for a PSB is adequate?*

FDA Response to Question 14:
No, we do not agree. Per ICH Q1A (R2), at least three primary stability batches of the drug product and 3 executed batch records should be provided in your NDA submission, in addition to the MBR.

Discussion:
No discussion occurred.

ADDITIONAL COMMENTS

Clinical:

1. Please include a custom xpt data file with at least the following variables: study identifier, unique subject identifier, date of last allogeneic HSCT prior to study entry, regimen used for GVHD prophylaxis, date of onset of acute GVHD, date of first treatment for acute GVHD, date of onset of chronic GVHD, date of first treatment of chronic GVHD, date of first exposure to protocol treatment, date of first response, basis of response (investigator assessment vs. IRC assessment), date of best response, date of first new systemic therapy after start of protocol treatment. Please note that an increase in prednisone-equivalents (PE) from < 0.9 PE/kg/day to >= 0.9 PE/kg/day is considered a new systemic therapy.

   Discussion:
   The Agency acknowledges the Sponsor's approach to steroid dose increases not being considered new systemic therapy. The datasets should include any occurrence of increased steroid use to >= 0.9 PE/kg/day. The Agency's evaluation of the steroid data will be a review issue. The Agency agrees with the information regarding acute GVHD treatment and no IRC reads.

2. Ensure that adcm includes a variable for sponsor-adjudicated categorization for drugs used for prevention of GVHD, for treatment of acute GVHD and for treatment of chronic GVHD. Note that drugs for GVHD prophylaxis that continue after start of cGVHD and drugs for treatment of aGVHD that continue after start of cGVHD should not be counted as treatment of cGVHD unless they were previously discontinued and then restarted anew specifically for treatment of cGVHD. Identify each therapy as prophylaxis vs treatment based on the intent at start of the treatment, not based solely on administration date before or after a diagnosis of cGVHD.

   Discussion:
   The Agency acknowledges that the date of treatment for acute GVHD is not available and agrees with the proposed reporting of the start and end date of acute GVHD.

3. Include in adcm a flag to identify the prior therapies for cGVHD. Provide a summary tabulation by treatment arm of the proportion of patients who i) had no prior cGVHD treatments, including no steroids; ii) failed only steroids for treatment of cGVHD, and iii) failed steroids plus additional drugs/ECP for treatment of cGVHD.

   Discussion:
   No discussion occurred.

4. Clarify where in the submission one can find the start and end dates of prior and concurrent use of ECP for each patient.

   Discussion:
   No discussion occurred.

5. Provide a table to identify the data file and variable with the raw data elements listed below for the assessment of cGVHD by the 2014 NIH Consensus Criteria.
   - NIH skin score (0-3)
   - NIH eye score (0-3)
   - Modified OMRS (0-12)
   - Total Bilirubin
   - ALT
   - Alkaline phosphatase
   - FEV-1 (% predicted)
   - NIH joint score (0-3)
   - P-ROM (4-25)
   - NIH lung score (0-3)
   - UGI score (0-3)
   - LGI score (0-3)
   - Esophagus score (0-3)

   Discussion:
   No discussion occurred.

6. Provide a table to identify the data files and variable for the three clinician-assessed global rating scales listed below according to the 2014 NIH Consensus Criteria.
   - Global rating (0-3)
   - Severity score (0-10)
   - Change scale

   Discussion:
   No discussion occurred.

7. Ensure that the Reviewer's Guide includes information on where to find all required elements needed for efficacy analyses as described above.

   Discussion:
   No discussion occurred.

Microbiology:

1. Microbiological specifications for release and corresponding method suitability

test results should be provided in the NDA submission. The specifications, as per USP <1111>, should include Microbial Limits Testing (performed as per USP <61> or equivalent methodology) Absence of *Escherichia coli* (performed per <62> or equivalent methodology) and testing for Absence of *B. cepacia complex* (performed as per USP <60> or equivalent methodology).

2. As the drug product is intended for multi-dose use, data from an Antimicrobial Effectiveness Test (AET) performed according to USP <51> for a Category 3 product or an equivalent method should be provided to demonstrate that at or below the minimum acceptable level of preservative, the preservative system is effective. Results of AET should also be provided to support the in-use period of the drug product. In addition, AET data should be provided (or committed to be performed) for at least one primary batch at the end of shelf-life to demonstrate that the preservative system remains effective throughout the shelf-life of the drug product. See ICH Q1A Stability Testing of New Drug Substances and Products for additional information.

Discussion:
No discussion occurred.

Statistics:

The submission should include following:

1. All raw as well as derived variables in .xpt format. The Agency strongly recommends submission of datasets using CDISC standards.

2. SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, please provide all necessary macro programs.

3. SAS programs for derived datasets and the analyses which are associated with the results presented in the proposed package insert as well as any interim analysis if performed.

4. A define file to show the variables which will be included in the derived datasets for the primary and key secondary efficacy analyses including, but not limited to, the variables for reasons of censoring, dates of IRC determined event or censoring and variables for subgroup analyses, etc. Variables used for sensitivity analysis of the SAP should also be included.

Discussion:
No discussion occurred.

3.0 OTHER IMPORTANT MEETING INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 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 or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) 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.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@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

[2] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[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

human drug and biological products.

- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.

- Regulations and related guidance documents.

- A sample tool illustrating the format for Highlights and Contents, and

- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.

- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

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

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for

INDs not in eCTD format).

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*

[6] https://www.fda.gov/media/84223/download

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]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs,

[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

including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[9]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[10]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response to the Agency's meeting preliminary comments is appended to these minutes.

[9] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[10] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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/s/

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