CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217779Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 147027

MEETING MINUTES

Geron Corporation
Attention: Sherrie Pettiford, MS, RAC
Senior Director, Regulatory Affairs
919 E. Hillsdale Blvd., Suite 250
Foster City, CA 94404

Dear Ms. Pettiford:[1]

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

We also refer to the video conference between representatives of your firm and the FDA on March 2, 2023. The purpose of the meeting was to obtain agreement with the Agency on the submission of a New Drug Application (NDA).

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.

If you have any questions, call Tawanna Stokes, Regulatory Information Specialist at (301) 796-2927.

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

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

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	March 2, 2023, 2:00 PM
Meeting Location:	Videoconference
Application Number:	147027
Product Name:	Imetelstat sodium for injection
Indication:	Treatment of adult patients with low to intermediate-1 risk myelodysplastic syndromes (MDS) who are transfusion-dependent and have failed to respond or have lost response or are ineligible for erythropoiesis-stimulating agents (ESA).
Sponsor Name:	Geron Corporation
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Lori Ehrlich, MD, PhD
Meeting Recorder:	Tawanna Stokes

FDA ATTENDEES (tentative)

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies I (DHMI)
R. Angelo de Claro, MD, Division Director
Donna Przepiorka, MD, PhD, Deputy Director (Acting)
Lori Ehrlich, MD, PhD, Clinical Team Leader
E. Dianne Pulte, MD, Clinical Reviewer

Office of Regulatory Operations (ORO)/Division of Regulatory Operations for Oncologic Diseases/Hematologic Malignancies I
Amy Baird, Chief, Project Management Staff
Tawanna Stokes, BA, Regulatory Information Specialist

Office of Pharmaceutical Quality (OPQ)/Office of New Drug Products I, Branch II
Sherita McLamore, PhD, Branch Chief
Tefsit Bekele, PhD, Product Quality Reviewer

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Ruby Leong, PharmD, Clinical Pharmacology Team Leader
Ritu Chadda, PhD, Clinical Pharmacology Reviewer

Office of Biostatistics/Division of Biometrics IX
Jonathon Vallejo, PhD, Biometrics Team Leader

Alexei Ionan, PhD, Biometrics Reviewer

SPONSOR ATTENDEES
Sharon McBain, BSc, Vice President, Global Head of Regulatory Affairs
Sherrie Pettiford, MS, RAC, Senior Director, Regulatory Affairs
Andy Grethlein, PhD, Chief Operating Officer
Faye Feller, MD, Chief Medical Officer
Melissa Behrs, MBA, Chief Alliance Officer
Tymara Berry, MD, Executive Director, Clinical Development
Ying Wan, MD, PhD, Vice President, Biometrics and Data Management
Fei Huang, PhD, Executive Director, Translation Research and Clinical Pharmacology
Chandra Pamulapati, PhD, Senior Director, Clinical Pharmacology
Patrick Murphy, Vice President, Manufacturing
Denise Grippo, Vice President, Quality
(b) (4), Clinical Pharmacology Consultant (b) (4)
(b) (4), Clinical Pharmacology Consultant (b) (4)

1.0 BACKGROUND

The purpose of this meeting obtain agreement with the Agency on the submission of a New Drug Application (NDA), providing for the treatment of adult patients with low to intermediate-1 risk myelodysplastic syndromes (MDS) who are transfusion-dependent and have failed to respond or have lost response or are ineligible for erythropoiesis-stimulating agents (ESA).

The proposed proprietary name, Rytelo, is currently under review with the Agency. In addition, there is a pending Breakthrough Therapy Designation Request for the treatment of adult patients with low to intermediate-1 risk myelodysplastic syndromes (MDS) who are transfusion-dependent and have failed to respond or have lost response or are ineligible for erythropoiesis-stimulating agents. Also, the Agency review of the agreed upon iPSP submitted February 15, 2023, is pending.

Geron received Fast Track Designation on October 27, 2017, for adult patients with transfusion-dependent anemia due to low or intermediate-1 risk myelodysplastic syndrome (MDS) that is not associated with the del(5q) cytogenetic abnormality and who are refractory or resistant to treatment with an erythropoiesis-stimulating agent (ESA). Rolling Review was granted December 9, 2022, with the first submission of the rolling review submitted January 27, 2023, and the final piece expected May 2023.

Geron received orphan drug designation for the treatment of myelodysplastic syndrome on December 23, 2015.

FDA sent Preliminary Comments to Geron Corporation on February 24, 2023.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1: ***Does the Agency agree with the sponsor's plan to submit additional stability data for the primary stability lots during the review of the marketing application, and that the CMC information proposed at the time of NDA submission (end of May 2023), as well as the planned submission of additional real-time stability data during NDA review (end of September 2023), is sufficient to justify an assessment of the proposed shelf life for DS and DP based on both the primary as well as supportive stability data?***

FDA Response to Question 1:

On the surface, we agree with your plan to provide additional drug product stability data at the end of September 2023 and that proposed stability package will enable the review of the proposed drug product expiry. The shelf-life of the drug product will be determined during the NDA review and will be based on the totality of the data submitted in the application.

Discussion:

No discussion occurred.

2.2. Clinical Pharmacology

Question 2: ***Does the Agency agree with the Sponsor's plan to evaluate the effect of renal and hepatic impairment on imetelstat PK by popPK analysis and that formal organ impairment studies are not warranted?***

FDA Response:

Your proposed plan to evaluate the effect of hepatic and renal impairment using a population PK approach instead of conducting dedicated organ impairment studies appears reasonable. Final determination of the adequacy of the results and analyses will be made at the time of NDA review.

Discussion:

No discussion occurred.

Question 3: ***Does the Agency agree that clinical drug-drug interaction studies to evaluate imetelstat as an inhibitor of OATP1B1, OATP1B3, and UGT1A1 are not warranted?***

FDA Response:

No, we do not agree that clinical drug-drug interaction studies are not warranted. You should further evaluate mechanistic model of imetelstat as an inhibitor of OATP1B1, OATP1B3, and UGT1A1. Consider using mechanistic model if feasible or conducting clinical studies to further investigate the in vivo DDI potential of imetelstat as inhibitor of UGT1A1 enzyme and/or OATP1B1/P1B3 transporter given the results from in vitro studies with the R values were greater than 1.01 or 1.1 respectively, imetelstat has the potential to inhibit UGT1A1 and OATP1B1/P1B3 in vivo. Based on further evaluation you may need to conduct additional clinical DDI studies.

Discussion:

No discussion occurred.

Question 4: ***Does the Agency agree with the sponsor's plan to conduct in vitro studies of imetelstat as an inhibitor of the additional transporters post-approval and that in vitro studies to assess imetelstat as a substrate of enzymes and transporters are not warranted?***

FDA Response:

In general, it is the Agency's expectation that the NDA submission should be complete at the time of original NDA submission. For the in vitro studies that cannot be completed prior to NDA submission, you should include justification for lack of these in vitro DDI studies in your NDA submission.

Discussion:

The Agency did not agree with the Sponsor's proposed approach to submitting in vitro transporter studies by the end of September 2023, indicating that, in general, submission of data during the review cycle should be avoided and is subject to extension of the PDUFA clock. The Agency indicated that if the Sponsor commits to submitting the final reports for the studies within 60 days after submission of the NDA application, the in vitro study reports may be reviewed by the Agency.

2.3 Clinical/Safety

Question 5: Does the Agency agree that data from Phase 3 study MDS3001 are adequate to support the submission of the NDA for the proposed indication?

FDA Response:

Please be advised that multiple pivotal trials are generally required for licensure. For a single randomized trial to support an NDA, the trial should be well designed, well conducted, internally consistent, and provide statistically persuasive efficacy findings so that a second trial would be ethically or practically impossible to perform. The data from the phase 3 study may be adequate to support submission of the NDA with supportive evidence provided by the phase 2 portion of the study. However, we note that transfusion independence data should be supported by evidence of clinical benefit (e.g., survival benefit, response, lower rates of progression, improvement in quality of life, or lower rates of use of medical care) in order to demonstrate benefit to the patient.

Discussion:

The Sponsor presented the topline results of the MDS3001 study, including transfusion independence (TI), duration of TI, change in hemoglobin, fatigue, and mutational burden. The Sponsor sought clarification of whether the data from the phase 3 and phase 2 parts of MDS3001 would support approval of imetelstat in the proposed indication. The Agency committed to a comprehensive review of the data to be submitted, but whether the data support approval would be determined during the NDA review.

Question 6: Does the Agency agree that the safety database is sufficient for filing the NDA?

FDA Response:

No. As noted in our comments issued on July 25, 2022, the ISS should include at least a summary of the safety from early phase studies of imetelstat, including combination therapy. In addition, a dataset including all subjects who were treated with imetelstat, including those who received combination therapy and therapy for nonhematological indications, should be included in an integrated safety dataset in order to provide the most complete view of potential safety signals related to use of imetelstat.

The ISS is not a just an overview of the safety results in the pivotal and supporting clinical trials, but a detailed integrated review of all relevant safety data and analyses, including data from nonclinical studies, clinical pharmacology studies, studies in patients, and studies in healthy volunteers. The ISS should show the key results that

contribute to the understanding of the safety of your drug, including analyses across studies, and should not simply reference the study reports.

Discussion:

The Sponsor presented a summary of the planned location of the safety data in the SCS and ISS. The Agency indicated that Module 5.3.5.3 should contain an integrated dataset across all trials using a single MedDRA coding dictionary to allow the Agency to perform an overall safety analysis. The Agency otherwise agreed with the proposal.

Question 7: Does the agency agree that continuous routine post-marketing pharmacovigilance surveillance of the safety profile for imetelstat will adequately assess potential risk in the patient population and that a REMS program is not warranted?

FDA Response:

It is premature to determine whether a REMS will be needed. This will be determined during the NDA review.

Discussion:

No discussion occurred.

2.4 Regulatory

Question 8: Does the agency agree that the overall proposed NDA Table of Contents for Rolling Submission 2 and organization of the 505(b)(1) NDA to be submitted electronically in eCTD format are acceptable?

FDA Response:

From a technical perspective (and not content related), the proposed Table of Contents found in the Attachment Section is acceptable.

As noted in the response to Question 5, supporting evidence for the efficacy and safety of imetelstat in the setting of lower risk MDS should be provided. Therefore, an integrated summary of efficacy should be included to provide an overall view of efficacy. See also Additional Clinical Comments for requested custom datasets.

In addition, you will need to include exposure-response analyses for efficacy, safety, and pharmacodynamics. Refer to Additional Clinical Pharmacology Comments below.

Lastly, ensure that the protocols are placed in disease-specific Module 5.3.5 folders. For example, the lung cancer protocols should not be in the folder for myelodysplastic syndromes.

Discussion:

No discussion occurred.

Question 9: Does the Agency agree with the plans for the presentation of the CMC information in the NDA pertaining to both strengths and manufacturers of the Drug Product?

FDA Response:

Yes, we agree with your proposal to provide information pertaining to the 47 and the 188 mg drug products in two documents (47 mg strength manufactured at Patheon, and the other for the 188 mg strength manufactured at Catalent within one module 3.2.P.

Discussion:

No discussion occurred.

Question 10: Does the Agency agree with our approach to comply with the salt policy?

FDA Response:

Yes, we agree with your approach to comply with the salt policy. Ensure that each protocol report clearly describes how the dose was expressed in the protocol (i.e., as free base or salt). Include in the Clinical Overview and/or Summary of Clinical Safety a table showing the imetelstat doses as free base used in each protocol.

Discussion:

No discussion occurred.

Question 11: Based on the totality of data presented in this Briefing Book and the ongoing application for Breakthrough Designation, does the Agency foresee a potential need for an advisory committee meeting?

FDA Response:

Yes, we consider that an advisory committee meeting may be needed. However, this will be determined during the review of the application.

Discussion:

No discussion occurred.

Additional Clinical Comments

1. Please provide a custom dataset detailing the transfusion independence assessment of patients on trial MDS3001. Data provided should include at minimum unique subject number and demographics, study phase (part 1 or 2), study arm, dose of study medication/placebo at time of transfusion, study and treatment start and end dates and study days, baseline transfusion rate (platelet, RBC, any), date and type of transfusions on study, date of last transfusions (platelet, RBC, any), indication for transfusion, hemoglobin at the time of transfusion (pre- and post-transfusion), and transfusions within 30 days of last dose of study medication/placebo. See the AML guidance for industry (https://www.fda.gov/media/162362/download; Appendix 3) for additional variables that may be included.

2. Provide a response dataset including at minimum unique subject number and demographics, study phase (part 1 or 2), study arm, study and treatment start and end dates, baseline bone marrow results, baseline CBC results, date and type of last platelets and RBC transfusions prior to CBC used to document disease status, date and study day of bone marrow performed as part of study, date and study day of complete blood count and differential obtained within 2 weeks of the marrow for response, and platelet count, ANC, and hemoglobin values used for response.

3. In these datasets, include indicators for missing data as well as reasons for missingness, if known. Describe the variables and their values, including values for missing data, in a define file.

Additional Clinical Pharmacology Comments

The content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application should be consistent with FDA Guidance for Industry, “Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products –Content and Format” (available at: https://www.fda.gov/media/74346/download). Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

Address the following questions in the Summary of Clinical Pharmacology:

1. What is the basis for selecting the doses and dosing regimen used in the trials intended to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

2. What are the exposure-response relationships for efficacy, safety, and biomarkers?
3. What is the effect of your drug on the QT/QTc interval?
4. What are the characteristics of distribution, and elimination (metabolism and excretion)?
5. How do extrinsic (such as drug-drug interactions) and intrinsic factors (such as sex, race, disease, and organ dysfunctions) influence exposure, efficacy, or safety? What dose modifications are recommended?
6. What is the impact of immunogenicity on exposure, efficacy, and safety?

Apply the following advice in preparing the clinical pharmacology sections of the original submission:

1. Submit bioanalytical methods and validation reports for all clinical pharmacology trials.
2. Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with minimum and maximum values as appropriate.
3. Provide complete datasets for clinical pharmacology trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.
   - Provide all concentration-time and derived pharmacokinetic parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
   - Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.
4. Submit the following for the population pharmacokinetic analysis reports:
   - Standard model diagnostic plots.
   - Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.
   - Model parameter names and units in tables.
   - Summary of the report describing the clinical application of modeling results.

   Refer to the following pharmacometric data and models submission guidelines http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm.
5. Submit the following information and data to support the population pharmacokinetic analysis:
   - SAS transport files (*.xpt) for all datasets used for model development and validation
   - A description of each data item provided in a Define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

- Model codes or control streams and output listings for all major model building steps (e.g., base structural model, covariates models, final model, and validation model). Submit these files as ASCII text files with *.txt extension (e.g., myfile_ctl.txt, myfile_out.txt).

6. Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and safety) relationships in the targeted patient population. Refer to Guidance for Industry for population PK and exposure-response relationships.
7. Use the laboratory analysis dataset (adlb.xpt) for the laboratory-based adverse reactions and the adverse event analysis dataset (adae.xpt) for the non-laboratory-based adverse reactions (individual and pooled terms as appropriate) to evaluate the exposure-response relationship for safety and the effect of intrinsic and extrinsic factors on safety based on the maximum toxicity grade compared to baseline.
8. Include a variable that identifies the maximum toxicity grade compared to baseline for laboratory-based adverse reactions in laboratory analysis dataset (adlb.xpt) and for non-laboratory-based adverse reactions (individual or pooled where applicable) in adverse event analysis dataset (adae.xpt) to support these analyses. A description of the pooled non-laboratory-based adverse reactions should be provided in the reviewer guide and consistent with common pooled terms used to inform labeling if applicable.

Additional CMC Comments

1. In compliance with 21 CFR 201.51(g), a gross content specification should be added to the drug product specification to ensure the labeled content is delivered and the residual material is not excessive such as to promote pooling of unused material. Please include a gross content test with upper and lower acceptance criteria reported in mL per vial as a drug product specification. Update 3.2.P.5.1 accordingly. The gross content acceptance criteria (b) (4) (b) (4) Include justification for both your upper and lower gross content limits. The gross content test may be satisfied (b) (4) (b) (4) (b) (4). Please see MAPP 5019.1 (official as of January 28, 2022) for further information.

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The final component of the Submission of Portions of the NDA application is expected May 2023. Final reports of the DDI studies should be submitted by Geron within 60 days of the final component of the NDA application (see FDA response to Question 4). Also, Geron's proposal to provide additional drug product stability data at the end of September 2023, is acceptable (see FDA response to Question 1).

Lastly, the integrated ISS dataset should be submitted within 30 days of the final component of the NDA submission (see FDA response to Question 6).

- 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 concluded that the decision regarding the need for a REMS will be determined during the NDA review (see FDA response to question 7).

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:

NDA/BLA NUMBER: LATE COMPONENT - BIOMETRICS
NDA/BLA NUMBER: LATE COMPONENT - CLINICAL
NDA/BLA NUMBER: LATE COMPONENT - CLINICAL PHARMACOLOGY
NDA/BLA NUMBER: LATE COMPONENT - NONCLINICAL
NDA/BLA NUMBER: LATE COMPONENT - QUALITY

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

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

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 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

[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

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]

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

[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

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, 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]

[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/

LORI A EHRLICH
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