CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215814Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 127313

MEETING MINUTES

Forma Therapeutics, Inc.
Attention: Nikole Shpilfogel, PharmD
Senior Manager, Regulatory Affairs
500 Arsenal Street, Suite 100
Watertown, MA 02472

Dear Dr. Shpilfogel:[1]

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

We also refer to the teleconference between representatives of your firm and the FDA on May 13, 2021. The purpose of the meeting was to discuss the content and structure of the NDA and the subsequent safety follow-up for olutasidenib for relapsed/refractory acute myeloid leukemia (AML) planned for submission in 4Q 2021.

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.

If you have any questions, contact Kris Kolibab, Senior Regulatory Project Manager, at (240) 402-0277.

Sincerely,

{See appended electronic signature page}

Kelly Norsworthy, MD
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:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	May 13, 2021; 8:00AM – 9:00AM (ET)
Meeting Location:	Teleconference
Application Number:	IND 127313
Product Name:	Olutasidenib
Indication:	Treatment of adult patients with relapsed or refractory (R/R) acute myeloid leukemia (AML) with an isocitrate dehydrogenase-1 (IDH1) mutation as detected by an FDA-approved test
Sponsor Name:	Forma Therapeutics, Inc.
Regulatory Pathway:	505(b)(1) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Kelly Norsworthy, MD
Meeting Recorder:	Kris Kolibab, PhD

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies I (DHMI)

R. Angelo de Claro, MD, Division Director
Kelly Norsworthy, MD, Clinical Team Leader
Ashley Woods, MD, Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases

Kris Kolibab, PhD, Senior Regulatory Project Manager
Saumya Nathan, MSc, MS, Regulatory Project Manager

Office of Clinical Pharmacology/Division of Cancer Pharmacology I

Amal Ayyoub, PhD, Acting Clinical Pharmacology Team Leader
Vicky Hsu, PhD, Clinical Pharmacology Reviewer

OOD/Division of Hematology, Oncology, Toxicology

Brenda Gehrke, PhD, Acting Pharmacology/Toxicology Team Leader

Office of Biostatistics/Division of Biometrics IX

Lisa Rodriguez, PhD, Biometrics Team Leader
Xin Wang, PhD, Biometrics Reviewer

SPONSOR ATTENDEES

Emma Barrett, MD, Olutasidenib Medical Monitor Executive Director, Pharmacovigilance
Scott Boyle, PhD, Olutasidenib Development Team Leader VP, Business and Corporate Development
Charity Aitken, Senior Director, Regulatory Affairs CMC
Julie Brevard, MPH, Senior Director, Biometrics
Sanjeev Forsyth, PhD, Senior Director, Clinical Pharmacology
Sylvie Guichard, PharmD, PhD, Executive Director, Translational Science
Brooke Harrison, PhD, Senior Director, Medical Writing
Ann Howell, PharmD, MS Executive Director, Regulatory Affairs
Patrick Kelly, MD, Senior VP & Chief Medical Officer
(b) (4) Consultant, Clinical Development
Kate Lipford, BA, Associate Director, Clinical Operations
Olga Polyanskaya, MS, Principal Biostatistician
Nikole Shpilfogel, PharmD, Senior Manager, Regulatory Affairs
Jennifer Sweeney, BS, Senior Director, Clinical Science

1.0 BACKGROUND

Olutasidenib is a potent, selective, orally bioavailable, small-molecule inhibitor of mutated isocitrate dehydrogenase 1 (mIDH1) being developed by Forma Therapeutics, Inc. and is intended for use as an anticancer therapeutic in patients with acute myeloid leukemia (AML) or myelodysplastic syndrome (MDS), solid tumor and gliomas, where the isocitrate dehydrogenase 1-R132x (IDH1) mutation plays an important pathologic role.

On March 19, 2021, Forma Therapeutics, Inc. requested a type B meeting with FDA to discuss the content and format of a planned NDA to support the proposed indication of relapsed/refractory AML.

FDA sent Preliminary Comments to Forma Therapeutics, Inc. on May 5, 2021.

2.0 DISCUSSION

2.1. Questions

Question 1:

Does the Agency agree that the efficacy results from the pivotal relapsed/refractory AML cohort of single agent olutasidenib from the 2102-HEM-101 study are sufficient to support submission and review of an NDA for olutasidenib for R/R AML indication?

FDA Response to Question 1:

The results appear to support submission of an NDA for olutasidenib. Filing and approval will be a review issue. Whether the results are clinically meaningful will be assessed after you submit your data to the agency during the review.

Discussion:

No discussion occurred.

Question 2:

Does the Agency agree that the safety database is sufficient to support submission and review of an NDA for olutasidenib for R/R AML?

FDA Response to Question 2:

No. Please add all studies with safety data, including healthy volunteer studies, to the ISS dataset. Mixing patient study data and volunteer study data in a single data set may be challenging, but you may submit a separate pooled analysis data set for the volunteer studies in an HV subfolder of the ISS MISC folder. The MISC folder is at the same level as the ANALYSIS and TABULATIONS folders. For additional information about the MISC folder, please see Figure 1 and Table 2 in the Study Data Technical Conformance Guide: Technical Specifications Document for further information on technical specifications, at https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Discussion:

In the attached slides, the Sponsor proposed to submit the pooled healthy volunteer data with the safety update instead of the original submission. The Agency conveyed that all safety data must be provided in the initial submission. However, the Agency agreed to late submission of the healthy volunteer data set within the first 30 days of the submission.

The Sponsor proposed to submit a written summary of healthy volunteer safety data by study, without providing pooled summary tables and listings and a pooled written summary. The Agency noted that this was acceptable.

Question 3:

Does the Agency continue to agree with the plans to use the continuous ECGs collected following a single dose and at steady-state in the sub-study in 2102-HEM-101 and concentration-QT modeling to classify the risk of QTc prolongation?

FDA Response to Question 3:

Overall, the proposed study appears acceptable to characterize the large QT effects (i.e., 20 msec) of your product. Whether these data exclude a 20-msec mean QTc effect at the therapeutic exposures will be a review issue when the data are submitted.

For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "*Scientific white paper on concentration-QTc modeling"* (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "*Correction to: Scientific white paper on concentration-QTc modeling*" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6).

When you submit your QT evaluation report, please include a completed version of the "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safetystudies-formerly-qt-irt).

Discussion:

No discussion occurred.

Question 4:

Should waveforms from the ECG substudy in 2102-HEM-101 be submitted to both the ECG Warehouse and through the Gateway? If not, could the Agency provide guidance on how to submit waveforms considering the ongoing transition of the submission procedures?

FDA Response to Question 4:

Submit the related digital ECGs with annotations in electronic format (XML) following the HL7 annotated ECG (aECG) standard to the FDA Electronic Submission Gateway (ESG) only. Scan paper ECGs into PDF and submit to FDA only if digital ones are not available, preferably organized by site, subject or similar to reduce individual file size. When submitting through the ESG, we recommend placing the ECGs in an aecg folder under the misc folder (e.g., m5 -> datasets -> [study-id] -> misc -> aecg). For scanned/digitized paper (e.g. PDF) submissions: analysis datasets to support QT evaluation should include the automatic ECG measurements (i.e., as automatically generated by the ECG device in the clinical site without any adjustment).

Discussion:

No discussion occurred.

Question 5:

Does the Agency agree with the general content and structure of the NDA?

FDA Response to Question 5:

No. You did not propose a complete eCTD Table of Contents, so we are unable to comment on the general content and structure of the NDA. However, we have the following comments:

Clinical:

a. We expect that you will include efficacy data from all cohorts of Study 2102-HEM-101 in the NDA submission, not just the pivotal Cohort 1, in order to fully characterize the efficacy of olutasidenib in patients with myeloid malignancies.

b. We note that you have a rather low response rate for a targeted therapy. Given that you plan to use an SCE in lieu of an ISE in your NDA, please ensure that the SCE includes a discussion of the potential mechanisms of resistance, a summary of the data demonstrating sensitivity of all R132 mutations to your drug, and whether there are mutations in other genes that might prohibit the efficacy of your drug. If you do have mutational analyses for multiple genes for the patients in the clinical trial, the results should also be submitted in the NDA.

c. We remind you that the Clinical Summary text (Modules 2.7.1 through 2.7.4) should not exceed 400 pages.

d. Given the number of protocols in your submission, it would facilitate review if Module 2.7.6 included the actual protocol synopses rather than just a mapping document. The synopses can be submitted as individual documents or combined into a single pdf with bookmarks to identify page 1 of each synopsis.

e. Please include a copy of the proposed labeling in Word in 1.14.1.3.

f. Include in Module 5.3.5 the protocols and amendments for all studies. Submission of just narratives, data sets and CRFs is not sufficient.

g. Ensure that each text file has a unique and descriptive name. Do not include files with the same name within the same folder.

h. Module 5.3.5 should have at least 2 indication folders - one for the AML indication and one for an “Other” indication (or a named indication according to

your overall development plan). Study 2102-ONC-102 should be in 5.3.5.1 of the "Other" folder.

Nonclinical:
The proposed content and structure for module 4 of the eCTD appears acceptable. The eCTD guidance describes the recommended content and format for module 2 (https://www.fda.gov/media/71628/download).

Statistics:
The upcoming NDA submission should include following:

a. All raw as well as derived variables in .xpt format. FDA strongly recommends submission of datasets using CDISC standards.

b. 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.

c. 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.

d. A mock-up 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 event or censoring and variables, etc. Variables used for sensitivity analysis of the SAP should also be included.

Clinical Pharmacology:
Refer to Additional Clinical Pharmacology comments (below) regarding general clinical pharmacology expectations for your NDA submission.

Discussion:

In the slides attached, the Sponsor clarified that safety and efficacy for Cohorts 2-8 (non-pivotal cohorts) are part of the dataset and associated listings and figures for safety and efficacy, which will be submitted with 2102-HEM-101 CSR. The Agency noted that the Sponsor's proposal was acceptable.

The Agency furthermore acknowledged the Sponsor's clarification that data from Cohorts 2-8 would be "snapshots," meaning queries and other information could change the data.

The Agency clarified that the mock-up define file is the same as standard define.xml file.

The Sponsor asked whether the additional files requested by the Agency in the AML guidance could be submitted as excel data sets. The Agency clarified that they would expect these files to be submitted as SAS transport files. However, these files would be custom data sets, and therefore, would not need to fully conform to CDISC standards.

Question 6:

Does the Agency agree with the cut date and scope of the Safety Update?

FDA Response to Question 6:

No. We have the following comments:

a. We have no objection to the cutoff date you suggested pending review of the data submitted.

b. We request that you submit the planned update by 90 days from submission of the NDA rather than 120 days.

c. Include in the safety update all new safety data for all study subjects across all protocols as included in the ISS data set. In general, this is accomplished by updating the ISS data set. If you choose to do so, you may update the Study 2102-HEM-101 data set as well. Updating an individual study data set is not usually required for the safety update, but since you will be updating the efficacy data, if it is easier for you, then it would be acceptable to us if you updated the whole Study 2102-HEM-101 data set.

d. When submitting updated data files, please use the Replace operator rather than Append or Amend. If you are adding new domains, or if you are adding new variables in a replacement file, please also submit a revised define file. For additional information, see Section 7.1 of the most recent Study Data Technical Conformance Guide at: https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Discussion:

No discussion occurred.

Question 7:

Does the Agency agree with providing duration of response and response endpoints, along with OS, with the Safety Update?

FDA Response to Question 7:

Your proposal to provide updated safety and efficacy results appears to be reasonable. We have the following comments:

a. Please ensure that the efficacy update includes remission data, MRD data, and transfusion data.

b. If you submit updated efficacy data, the update should include all patients on Study 2102-HEM-101 as in the original submission rather than just the subset of patients on Phase 2 Cohort 1.

c. The summary of the updated efficacy data can be submitted as an addendum to the SCE (Module 2.7.4). However, the safety update is a free-standing document and must include the same kinds of information (from clinical studies, animal studies, and other sources) and follow the same format as the ISS (21 CFR 314.50(d)(5)(vi)(b)). Place the safety update report in the ISS folder.

d. When submitting updated data files, please use the Replace operator rather than Append or Amend. If you are adding new domains, or if you are adding new variables in a replacement file, please also submit a revised define file. For additional information, see Section 7.1 of the most recent Study Data Technical Conformance Guide at: https://www.fda.gov/downloads/ForIndustry/DataStandards/StudyDataStandards/UCM384744.pdf

Discussion:

The Sponsor clarified that they have not developed an MRD assay and have not collected any MRD data. Therefore, MRD data will not be expected with the efficacy update.

Question 8:

Does the Agency agree that for BIMO planning, datasets and other associated information requested in the BIMO guidances can be provided for 2102-HEM-101 Phase 2 / Cohort 1 only?

FDA Response to Question 8:

Your proposal appears to be reasonable.

To facilitate the selection of clinical sites for inspection, submit a dataset (1 site per row) with the following information from phase 2 cohort 1 of Study 2102-HEM-101. Submit this information as a SAS transport file and include a define.pdf file.

a. Site number
b. Principal investigator
c. Location: Address, City, State, Country
d. Contact Information: Name, Phone, Fax, Email
e. Number of subjects screened
f. Number of subjects enrolled
g. Number of subjects who received olutasidenib
h. Number of subjects who achieved CR or CRh
i. Number of subjects who achieved CR
j. Number of major protocol violations
k. Number of deaths
l. Number of subjects who experienced serious adverse events (SAEs)

Discussion:

No discussion occurred.

Question 9:

Would the Agency comment on the potential of the olutasidenib NDA to be eligible for priority review?

FDA Response to Question 9:

No. We cannot comment on eligibility for priority review at this time.

Discussion:

No discussion occurred.

Additional Clinical Comments:

1. Please see FDA's Guidance for Industry *Acute Myeloid Leukemia: Developing Drugs and Biological Products for Treatment* at https://www.fda.gov/media/140821/download. Section IV.B. of the guidance under "Marketing Applications" describes additional efficacy and safety data files that the agency will expect in your submission to confirm assessments of efficacy and safety.

2. If you have not already done so, please revise Study 2102-HEM-101 to allow follow-up for at least 3 years.

3. Ensure that flags for each analysis population (EE, SAF, etc.) are included consistently in each data file. Include a flag to identify patients determined to be IDH1 mutation positive using the proposed companion diagnostic.

4. Provide the timeline for NDA submission to CDER and companion diagnostic submission to CDRH.

5. Include in the subject level data files the specific IDH1 mutation (e.g., R132C) for each subject.

6. Submit a data file in the NDA with all results of IDH1 mutation testing. For each result, specify the sample type, date of sample, assay used and assay result.

7. Provide in the NDA submission the following information about the MRD assay:

    a. a statement of intended use;
    b. the specific test method (including instruments, reagents, and specimen handling);
    c. confirmation that the lab has a process in place for reagent control;
    d. a discussion of how the test method was analytically validated for each specimen type, and the results of the validation;
    e. a statement of the performance obtained for accuracy and analytical sensitivity.

8. Include all results of MRD testing in a data file in the NDA submission. For each result, specify the sample type, date of sample, assay used and assay result.

Additional Statistical Comments:

1. Please note that the exploratory endpoint health-related quality of life (QOL) will not be used for efficacy claims due to potential bias issues in an open label trial design.

Additional Clinical Pharmacology Comments:

Regarding your dose selection:

You previously stated that dose- and exposure-response analyses for safety and efficacy will be conducted to support your recommended Phase 2 dose (RP2D) selection of 150 mg BID (under SDN 94). To justify your RP2D, provide the following information prior to the proposed NDA submission for FDA assessment:

1. Results of your exposure-safety and exposure-efficacy analyses that were performed including 1) the pooled nonclinical pharmacology, and 2) an assessment of clinical PK, PD (e.g., target engagement), 3) an integrated exposure-response analyses using the preliminary and emerging efficacy and safety data. Your response should include the following by olutasidenib dose level:
    - Summary of baseline demographics and patient characteristics
    - Summary of exposure

- Summary tabulation of DLTs
- Summary of all-grade treatment and grade 3-4 treatment emergent adverse reactions
- Summary of serious adverse reactions, including fatal adverse reactions
- Adverse reactions leading to dose interruptions, dose reductions and discontinuation
- Summary of dose intensity (indicating how many patients tolerated at least 80% of the intended dose per cycle)
- Summary of PK parameters
- Summary of pharmacodynamic parameters
- Summary of efficacy response

Discussion:

The Sponsor clarified that exposure-response analyses for safety and efficacy are currently underway and will be included in the NDA. The Sponsor offered to provide a summary of data to the IND supporting selection of the RP2D prior to NDA submission.

The Agency agreed with the Sponsor's proposal to provide a summary of data supporting the RP2D prior to NDA submission, and if possible, recommend that the Sponsor also include exposure-response analyses results in the summary. If exposure-response analyses results are not submitted prior the NDA, the adequacy of the exposure-response analyses and overall dose justification to support the recommended dosing will be a review issue at the time of NDA review.

Regarding your DDI plan for olutasidenib:

1. Your in vitro studies indicate that olutasidenib may be a perpetrator of DDIs (i.e., inducer of CYP3A4, 2B6, 1A2, 2C8, 2C9; inhibitor of BCRP, OATP1B1/3, OCT2, OAT1/3). To determine whether in vivo clinical DDI studies are needed for these interactions, refer to the following FDA Guidances—

   - *In Vitro Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry*
   - *Clinical Drug Interaction Studies – Cytochrome P450 Enzyme- and Transporter-Mediated Drug Interactions Guidance for Industry*

Regarding your preparation of a new NDA for olutasidenib:

Apply the following advice in preparing the clinical pharmacology sections of the labeling:

1. 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 olutasidenib on the QT/QTc interval?
4. What are the characteristics of absorption, distribution, and elimination (metabolism and excretion)?
5. What are the effects of food on the bioavailability? What are the dosing recommendations with regard to meals or meal types? Provide justification for recommendation with regard to meals or meal types.
6. 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?

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 and biopharmaceutics 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 and biopharmaceutics 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. Submitted 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 toxicity) relationships in the targeted patient population. Refer to Guidance for Industry at http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf for population PK, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf for exposure-response relationships, and http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm for pharmacometric data and models submission guidelines.

3.0 OTHER MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  The Agency was able to agree with the Clinical, Statistical, Clinical Pharmacology, and Non-clinical components of the NDA submission.

- 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. It was concluded that a need for the REMS will be made during the review of the application and the Agency will notify the sponsor once a determination for a need for a REMS occurs.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. We agreed that the following minor application components may be submitted within 30 calendar days after the submission of the original application: Pooled healthy volunteer safety dataset.

In addition, we note that a chemistry pre-submission meeting is scheduled for June 24, 2021. A summary of agreements reached at that meeting will be documented in the respective meeting minutes.

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]

[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

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 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*.

[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

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[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

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided the attached slide deck for the meeting.

14 Pages have been Withheld in Full as B4(CCI/TS)
Immediately Following this Page

[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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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/

KELLY J NORSWORTHY
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