CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761232Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 135699

MEETING PRELIMINARY COMMENTS

BeiGene USA, Inc.
Attention: Sandra Rivas, M.S., R.A.C.
Director, Regulatory Affairs
1900 Powell Street, Suite 500
Emeryville, CA 94608

Dear Ms. Rivas:[1]

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

We also refer to your March 5, 2021, correspondence, requesting a meeting to reach an agreement with the Agency that the efficacy and safety data from Study BGBA317-302 and supporting studies are sufficient to support the evaluation of tislelizumab for the proposed indication and proposed population, discuss the adequacy of the nonclinical package, scheduling and management of the pre-approval inspection, and the Sponsor's strategy for evaluation and presentation of information regarding the impact of COVID-19 on Study BGB-A317-302.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with 21 CFR 10.65(e) and FDA policy, you may not electronically record the discussion at this meeting. The official record of this meeting will be the FDA-generated 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.

If you have any questions, call me at (240) 402-6376.

Sincerely,

{See appended electronic signature page}

Nataliya Fesenko, Pharm.D.
Senior Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B, Pre-BLA

Meeting Category: Pre-BLA

Meeting Date and Time: April 30, 2021; 10:05 AM – 10:55 AM EST

Meeting Location: Teleconference

Application Number: IND 135699

Product Name: Tislelizumab

Indication: Esophageal squamous cell carcinoma

Sponsor Name: BeiGene USA, Inc

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

FDA ATTENDEES (tentative)
Steven Lemery, M.D., M.H.S., Director (acting), DO3/OOD
Sandra Casak, M.D., Clinical Team Lead, DO3/OOD
Lorraine Pelosof, M.D., Ph.D. Clinical Reviewer, DO3/OOD
Jiaxin Fan, Ph.D., Statistical Reviewer, OB/DBV
Joyce Cheng, Ph.D., Statistical Team Lead, OB/DBV
Safaa Burns, Ph.D., Clinical Pharmacology Reviewer, OCP/DCPI
Jeanne Fourie Zirkelbach, Ph.D., Clinical Pharmacology Team Lead, OCP/DCPI
Emily Place, Ph.D., Nonclinical Reviewer, DHOT/OOD
Matthew Thompson, Ph.D., M.P.H., Nonclinical Team Lead, DHOT/OOD
Pengfei Guo, Ph.D., Product Quality Reviewer, OPQ/OBP
Cyrus Agarabi, Ph.D., Product Quality Team Lead, OPQ/OBP
Virginia Carroll, Ph.D., Senior Pharmaceutical Quality Assessor, OPQ/OPMA
Nataliya Fesenko, Pharm.D., Regulatory Health Project Manager

SPONSOR ATTENDEES
Naveen Babbar, Ph.D., Global Biomarker and Diagnostic Lead, Novartis
Sanjeeve Bala, M.D., M.P.H., Vice President, Regulatory Affairs, BeiGene
Yong (Ben) Ben, M.D., M.B.A., Chief Medical Officer, Immuno-Oncology
Frank Brennan, Ph.D., Preclinical Safety, Novartis
Stephanie Cebe, Ph.D., Global Program Regulatory Director, Novartis
Shao-Chun Chang, M.D., Ph.D., Vice President, Clinical Development, BeiGene
Andrea Chassot Agostinho, M.D., Executive Director, Global Program Clinical Head Novartis

Lisa Erickson, Senior Director, CMC Regulatory Affairs, BeiGene
Diana Francis, Vice President, Quality, BeiGene
Jamie Gillette, M.Sc., Senior Director, Regulatory Affairs, BeiGene
Tomas Haas, Ph.D., Executive Director, Biostatistics, Novartis
Liyun Li, M.D., Director, Clinical Development, BeiGene
Xiaosong Luan, Ph.D., Technical project lead, Novartis
Jennifer Mataraza, Ph.D., Director, Oncology Translational Research, Novartis
Sandra Rivas, M.S., R.A.C., Director, Regulatory Affairs, BeiGene
Anna Rodriguez, M.S., CCRP, Manager, Regulatory Affairs, BeiGene
Edwin Schaart, M.D., Sr. Global Program Safety Lead, CMO-PS, Novartis
James Song, Ph.D., Executive Director, Biostatistics, BeiGene
Karen Stein, M.D., M.P.H., Executive Director, Clinical Development, BeiGene
Aiyang Tao, Ph.D., Director, Biostatistics, BeiGene
Xianbin Tian, Ph.D., Director, PK Sciences, Novartis
Maurizio Voi, M.D., Global Program Head, Novartis
Nicky Wallis, M.D., Executive Director, Global Patient Safety, BeiGene
Hongwei Wang, M.D., Ph.D., Vice President, Global Product Team Lead, BeiGene
Chi-Yuan Wu, Ph.D., Senior Director, Clinical Pharmacology, BeiGene

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for March 12, 2021, 12:00-1:00PM EST between BeiGene and the Division of Oncology 3. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

Background:
On March 5, 2021, FDA received a request for a Type B pre-BLA meeting from BeiGene USA, Inc., (BeiGene) under IND 135699, for tislelizumab for the treatment of patients with unresectable advanced, recurrent, or metastatic esophageal squamous cell carcinoma after prior systemic treatment.

BeiGene identified the following meeting objectives:

- Reach an agreement with the Agency that the efficacy and safety data from Study BGBA317-302 and supporting studies are sufficient to support evaluation of tislelizumab for the proposed indication and proposed population.

- Discuss the adequacy of the nonclinical package to support the review of the proposed BLA.

- Discuss the regulatory path for the tislelizumab BLA application, specifically, whether the Agency will consider the proposed BLA for priority review.

FDA issued the Meeting Granted correspondence on March 21, 2021. The meeting package was submitted on March 31, 2021.

Regulatory
December 12, 2017: IND 135699 was allowed to proceed for the proposed Study BCB-A317-302, entitled "A Randomized, Controlled, Open-label, Global Phase 3 Study Comparing the Efficacy of the anti-PD-1 Antibody BGB-A317 versus Chemotherapy as Second Line Treatment in Patients with Advanced Unresectable/Metastatic Esophageal Squamous Cell Carcinoma."

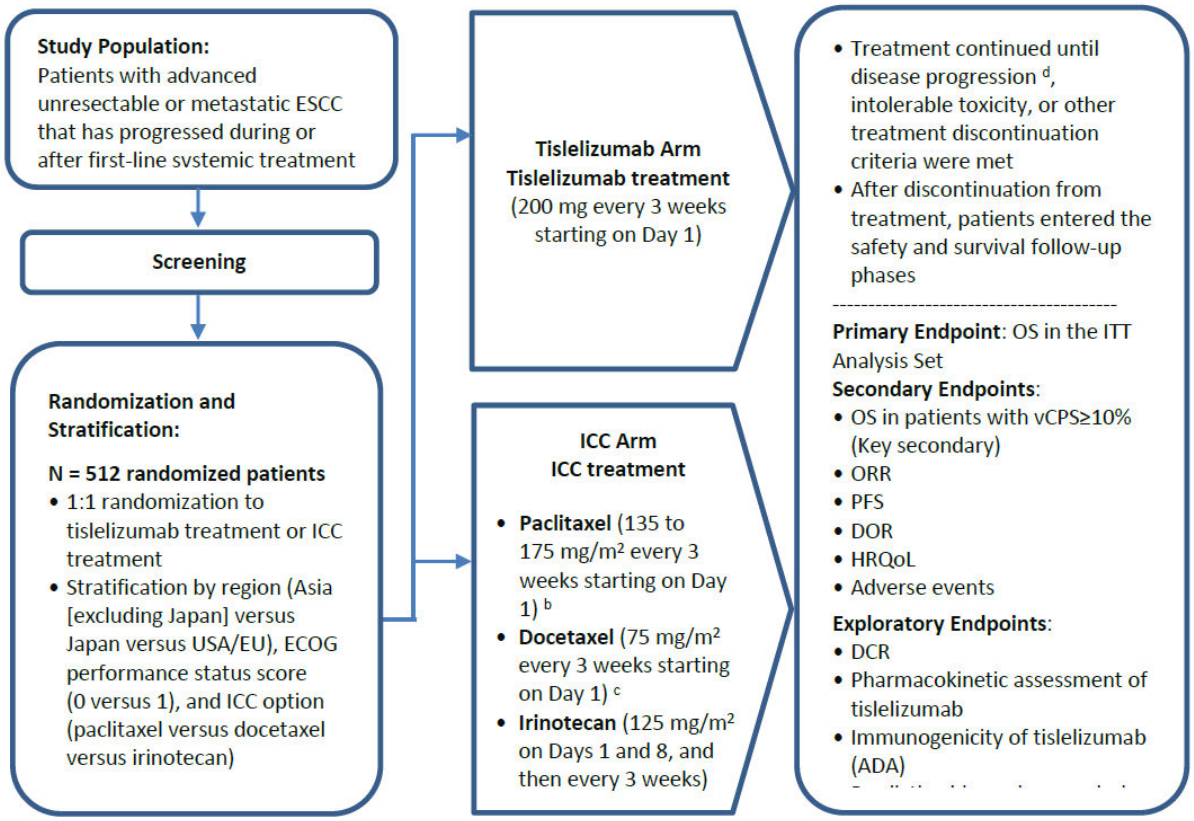
November 6, 2019: Orphan Drug Designation for the treatment of esophageal cancer (ODD #19-7089)

December 10, 2020: Agreed Amended Initial Pediatric Study Plan (b) (4)

Nonclinical
BieGene stated that tislelizumab is an IgG4 anti-PD-1 monoclonal antibody. BieGene's nonclinical package includes pharmacology studies and a 13-week toxicology study in monkeys.

Clinical
Study BGB-A317-302 is an ongoing randomized, open-label, international, active controlled study in patients with advanced, unresectable, or metastatic esophageal squamous cell carcinoma (ESCC) with disease progression during or following first-line treatment. Patients were randomized (1:1) to receive either tislelizumab 200 mg IV Q3W or investigator's choice of chemotherapy (paclitaxel 135-175mg/m^2 IV on Day 1 of each 21-day cycle or docetaxel 75 mg/m^2 IV on Day 1 of each 21-day cycle or irinotecan 125mg/m^2 IV on Days 1and 8 of each 21-day cycle).

Randomization was stratified by region [Asia (excluding Japan) versus Japan versus U.S./E.U.], ECOG performance status (0 versus 1), and investigator choice chemotherapy (paclitaxel versus docetaxel versus irinotecan). The primary objective is to evaluate the overall survival (OS) of tislelizumab compared to investigator choice of chemotherapy. The key secondary endpoint is OS in the PD-L1-high population [defined as patients whose tumor and immune cell score ≥ 10% using VENTANA PD-L1 (SP263) Assay]. Additional secondary endpoints include progression-free survival (PFS), ORR, DoR, and HRQoL.



Based on the assumption that the median OS is 6 months in the control arm, a total of 336 deaths were needed to detect a hazard ratio of 0.73 with 80% power at a 2-sided alpha level of 5%, which required enrollment of 450 patients.

Five hundred and twelve patients were randomized 1:1 to receive tislelizumab (256 patients) or ICC (256 patients: 85 patients received paclitaxel, 53 patients received docetaxel, and 118 patients received irinotecan). The most common reason for treatment discontinuation (70% overall) was disease progression, either radiographic or clinical. The median study follow-up duration was 6.88 months (range 0.0, 31.7). Median age of patients was 62 years old; 84% were men; 80% were Asian and 19% were White; 97% received prior platinum-based prior chemotherapy and 55% and 53% received taxanes and fluoropyrimidines, respectively. A higher proportion of patients in the tislelizumab arm had PD-L1 CPS ≥ 10% (34.8% vs. 26.6%), but nearly 20% of PD-L1 data are missing due to lack of evaluable tumor samples.

As of the data cutoff date of December 1, 2020, a total of 410 deaths had occurred in the ITT population. The median OS was 8.6 months (95% CI: 7.5 to 10.4 months) and 6.3 months (95% CI: 5.3 to 7.0 months) (stratified HR 0.70, 95% CI 0.57, 0.85; p=0.0001) for the tislelizumab arm and the ICC arm, respectively. In the subgroup of patients with tumors PD-L1 CPS ≥ 10%, the median OS was 10.3 months (95% CI: 8.5

to 16.1 months) and 6.8 months (95% CI: 4.1 to 8.3 months) (stratified HR of 0.54; 95% CI 0.36, 0.79) and a p-value of 0.0006) for the tislelizumab arm and the ICC arm, respectively.

The median PFS was 1.6 months (95% CI 1.4, 2.7) in the tislelizumab arm compared to 2.1 months (95% CI 1.5, 2.7) in the ICC arm (HR 0.83; 95% CI 0.67, 1.01). Investigator-assessed ORR was 20.3% and 9.8% in the tislelizumab and ICC arms, respectively.

Median duration of exposure was 2.75 months and 1.5 months in the tislelizumab and ICC arms, respectively. Most patients experienced adverse events (AEs): 46% and 68% patients in the tislelizumab and ICC arms, respectively experienced a Grade ≥ 3 AE. Fatal AEs were reported in 14% and 12% patients in the tislelizumab and ICC arms, respectively. AEs leading to treatment discontinuation were reported in 19% and 27% patients in the tislelizumab and ICC arms, respectively. In the tislelizumab arm, the most frequently reported adverse events were anemia (31%), decreased weight (23%), and cough (17%). Cough (17% vs.12%), increased AST (14.5% vs 5%), increased ALT (13% vs 7.5%), and hypothyroidism (11% vs 0.4%) were reported more frequently (difference ≥ 5%) in the tislelizumab arm than in the ICC arm.

Immune-related AEs (imAEs) were reported in 21% patients receiving tislelizumab. The most frequently reported imAEs were hypothyroidism (9%), pneumonitis (7%), and skin adverse reaction (2%). Most imAEs were Grade 1-2 and 3.5% of patients experienced imAEs there were ≥ Grade 3 in severity.

As discussed in correspondence issued on September 3, 2020, the tislelizumab clinical data package in support of the BLA will comprise 7 studies conducted globally in a broad population of patients with various solid tumor types who received tislelizumab as monotherapy at different dose levels, including 3 clinical studies evaluating the efficacy and safety in the ESCC population (Study 302, and supportive Studies 001 and 102). The tislelizumab safety database consist of 3 datasets:

- Study 302 dataset.
- ESCC dataset: 307 patients with ESCC who received at least 1 dose of tislelizumab monotherapy in Studies 302, 001, and 102.
- All Doses All Indications dataset:1972 patients treated with at least 1 dose of tislelizumab monotherapy (at any dose) for any malignancy, which includes patients in Studies 302, 001, 102, 203, 204, 208, and 303.

BeiGene states an internal committee to evaluate the impact of COVID-19 on BeiGene clinical studies was convened. Alternative means of complying with protocol-defined procedures and assessments were permitted for certain cases after getting approval from the site or central Ethics Committee/IRBs. Scheduled visits were allowed to be conducted remotely. On-site monitoring was restricted due to local COVID-19 impact

within a few countries. There was no impact of COVID-19 on patients' enrollment of Study 302 (enrollment completed on March 4, 2020). There was one COVID-19-related AE and 2 COVID-19 related deaths reported as of the data cut-off date for the final analysis. Throughout the period of the COVID-19 pandemic as of the data cutoff date, 11 patients in the tislelizumab arm and 1 patient in the ICC arm had at least one dose delay of study drug administration due to COVID-19. No important protocol deviations related to COVID-19 were identified in this study; 18 patients in the tislelizumab arm and 6 patients in the ICC arm had protocol deviations related to schedule and procedure or tests. BeiGene states that in general, the number of missed visits, procedures or tests was very small and thus their impact on the efficacy and safety evaluation was considered minimal.

BeiGene intends to submit the BLA for tislelizumab in the second quarter of 2021.

SPONSOR QUESTIONS AND FDA RESPONSES

Clinical

1. Tislelizumab demonstrated statistically significant and clinically meaningful OS benefit in study BGB-A317-302. Does the Agency agree that the clinical package provides sufficient, efficacy and safety data to support a BLA in the proposed indication?

   FDA Response: FDA agrees that the results of Study BGB-A317-302 and the proposed clinical package may support a regulatory submission; however, the relevance of the proposed indication is not clear given the March 22, 2021, approval of pembrolizumab and April 16, 2021, approval of nivolumab in the first-line esophageal cancer setting (both in combination with a platinum and fluoropyrimidine). If approved, the indication statement may need to identify that the treatment would be for patients in the second-line setting who are PD-1 inhibitor naïve.

Nonclinical

2. Does the Agency agree that the nonclinical package is acceptable to support submission and review of a BLA for tislelizumab?

   FDA Response: The nonclinical package appears sufficient to support a BLA submission. A final determination of the adequacy of the nonclinical studies will be a review issue.

Regulatory

3. Priority review of this new BLA will be sought given the OS benefit observed with tislelizumab in study BGB-A317-302. Does the Agency agree that these results support a priority review request?

   FDA Response: Determination of priority status will be made upon submission of the BLA. Priority review designations are not based on a treatment effect alone but based on the demonstration of the potential to be a significant improvement in safety or effectiveness.

Impact of Covid-19 on Pivotal Study (A317-302)

4. Does the Agency agree with the Sponsor's plan of evaluation and presentation of information regarding the impact of COVID-19 on Study BGB-A317-302?

   FDA Response: FDA agrees with BeiGene's plan for evaluation of the impact of COVID-19 on Study BGB-A317-302.

   FDA Oncology requests that applicants submitting data to support BLA submissions to add flags to datasets to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted in the COVID-19 pandemic that permitted some aspects of trial conduct to be performed remote from trial sites to reduce potential COVID exposure. The FDA hopes to learn more about the opportunities and challenges of these REMOTE modifications to foster use of "decentralized" aspects of clinical trials prospectively in the post-COVID era.

Orientation Meeting

5. Does the Agency agree with the proposal for an Application Orientation Meeting in support of the BLA for tislelizumab to occur shortly after the submission?

   FDA Response: FDA will assess the need for an Application Orientation Meeting upon receipt of the BLA.

Manufacturing Facilities and Pre-Approval Inspection

6. As the manufacturing and testing sites for tislelizumab are in China and international travel restrictions may be in place due to COVID-19, can the Agency provide feedback regarding the scheduling and management of the Pre-Approval inspection?

   FDA Response: The FDA will determine the need for Pre-Approval inspections upon receipt of the BLA. The Agency is utilizing alternative approaches to

inspections, where possible, to mitigate the need of inspections during the COVID-19 pandemic. The alternative tools described in FDA's guidance for industry regarding 'Manufacturing, Supply Chain, and Drug and Biological Inspections During COVID-19 Public Health Emergency Questions and Answers' are used to facilitate remote assessments of facilities if an inspection cannot be conducted. In some cases, these alternatives may not provide enough information to mitigate the need for an inspection. At this time, we do not have additional information on when safe travel may resume, and we are actively working to define an approach for scheduling inspections. We will continue to monitor the public health situation as well as travel restrictions.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-other-stakeholders.

Additional Comments:

7. To facilitate review of the application, FDA recommends submission of an Assessment Aid. If an Assessment Aid is submitted, FDA recommends that the document not include promotional statements.

   Refer to the additional comments below. Additionally, submission of the Assessment Aid is voluntary.

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our March 24, 2021 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the

time of original submission.

In addition, we remind you that the application is expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities.

Information on the Program is available at FDA.gov.[2]

In addition, we note that a CMC only pre-submission meeting was held on November 24, 2020, under IND 126875. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm

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.[3]

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.[4]

[3] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[4] 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[5] and Pregnancy and Lactation Labeling Final Rule[6] 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

[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

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	Email address

			number	
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[7] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[8]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

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*.[9]

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

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

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

- RTOR[10]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[11]

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

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/s/

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