CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761234Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 136382

MEETING PRELIMINARY COMMENTS

Bristol-Myers Squibb Company
Attention: Cynthia Wojtaszek, MSN
Group Director, US Regulatory Lead
Global Regulatory Strategy & Policy, US Oncology
P.O. Box 5326
Princeton NJ 08543

Dear Ms. Wojtaszek:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for BMS-986213.

We also refer to your March 24, 2021, correspondence, requesting a meeting to discuss the adequacy of data to support review of a marketing authorization and to reach agreement on the Content of a Complete Application.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or 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.

If you have any questions, please call me at 240-402-6571 or email me at Christina.Leach@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Christina Leach, PharmD
Regulatory Health Project Manager
Division of Regulatory Operations-Oncologic Diseases for DO3
Office of Regulatory Operations
Office of New Drugs (OND)
Center for Drug Evaluation and Research (CDER)

ENCLOSURE:
Preliminary Meeting Comments

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: Tuesday May 11, 2021, 1pm to 2pm
Meeting Location: Teleconference

Application Number: IND 136382
Product Name: BMS-986213

Indication: Unresectable or metastatic melanoma
Sponsor Name: Bristol-Myers Squibb Company
Regulatory Pathway: 351(a) of the Public Health Service Act

FDA ATTENDEES (tentative)

'Lola Fashoyin-Aje, MD, MPH	Deputy Division Director, Division of Oncology 3 (DO3)
Preeti Narayan, MD	Clinical Team Lead (acting), DO3
Leslie Doros, MD	Clinical Reviewer, DO3
Matthew Thompson, PhD, MPH	Nonclinical Team Lead (acting), Division of Hematology Oncology Toxicology (DHOT)
Elizabeth Spehalski, PhD	Nonclinical Reviewer, DHOT
Anjali Shukla, PhD	Product Quality Team Lead
Phillip Angart, PhD	Product Quality Reviewer
Hong Zhao	Clinical Pharmacology Team Lead
Yibo Wang	Clinical Pharmacology Reviewer
Joyce Cheng	Biostatistics Team Lead, Division of Biostatistics 5 (DBV)
Sirisha Mushti	Biostatistics Reviewer, DBV
Christina Leach, PharmD	Regulatory Project Manager, DO3

SPONSOR ATTENDEES (tentative)

Jonathan Cheng, MD - SVP, Oncology Global Development
Paul Basciano, MD - Global Development Project Lead
Shivani Srivastava, MD - Clinical Development Team Lead
Mena Abaskharoun, PharmD - Study Director CA224047
Yuliya Skorina, MD - Medical Safety Assessment Lead
Katy Simonsen, PhD - Senior Director Biostatistics
Anne Marie Sobiesk, PhD - Protocol CA224047 Statistician

Amit Roy, PhD - Head, Pharmacometrics
Satyendra Suryawanshi, PhD, MPharm - Clinical Pharmacology Lead
Christopher Harbison, PhD - Precision Medicine Lead
Marie-Laure Papi, PharmD - Deputy TA head, Global Regulatory Oncology
Andro Shenouda, PharmD - Relatlimab, Global Regulatory Team Lead
Cynthia Wojtaszek, MSN - Relatlimab, US Regulatory Lead

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 1pm, EST, May 11, 2021, between Bristol-Myers Squibb Company 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

Regulatory

BMS-986213 is a fixed dose combination (FDC) of relatlimab and nivolumab. On March 24, 2021, FDA received a Type B Meeting Request from Bristol-Myers Squibb Company (hereafter referred to as BMS) to discuss the adequacy of the topline results of Study CA224047 to support review of a marketing authorization and reach agreement on the content of a complete application. FDA granted this request as teleconference on April 7, 2021. The proposed indication is:

> for the treatment of metastatic or unresectable melanoma in adult and pediatric patients age 12 years and older.

Requests to participate in Project Orbis, Real-time Oncology Review (RTOR, and the Assessment Aid were included. FDA has agreed to the submission of an Assessment Aid. BMS submitted a formal request to participate in RTOR on April 19, 2021 and Project Orbis on April 20, 2021. Approval to participate in RTOR was granted on April 30, 2021.

On December 22, 2017, an original IND 136382 was submitted for protocol CA224047

entitled, “A Randomized, Double-Blind Phase 2/3 Study of Relatlimab Combined with Nivolumab vs Nivolumab in subjects with Previously Untreated Metastatic or Unresectable Melanoma.” The Study May Proceed letter was issued on January 19, 2018.

On September 13, 2019, a telephone conference (TC) was held between BMS and FDA. BMS informed FDA about follow-up communications, initiated by the Chair of the Data monitoring Committee (DMC), in which the DMC Chair informed BMS that the trial met the pre-specified criteria to proceed to the “Phase 3” portion of the trial and that, based on the effect size observed, BMS plans to add a second interim analysis for efficacy.

FDA granted Fast Track Designation to relatlimab/nivolumab on November 20, 2019, for the treatment of patients with metastatic or unresectable melanoma.

FDA granted the Conditionally Accepted Proprietary Name OPDUALAG on September 2, 2020.

A Type F meeting was held on March 24, 2020 to discuss the proposed initial pediatric study plan (iPSP). FDA agreed to BMS’s iPSP on September 15, 2020.

On November 9, 2020, FDA received a Type C Meeting Request from BMS to gain feedback and align with FDA on the content and technical format of a planned BLA and to reach agreement on the modules to be submitted for early review. FDA granted this request as Written Responses Only on November 10, 2020 and meeting minutes were issued on January 19, 2021.

On February 5, 2021, FDA received a Type B Meeting Request from BMS to gain feedback on the planned approach to cross-reference BLA 125554 for OPDIVO, working cell bank qualification protocol, and timing of pre-license inspection. FDA granted this request as Written Responses Only on February 23, 2021 and meeting minutes were issued on April 2, 2021.

This combination received orphan designation on August 18, 2017, for the treatment of Stage IIB to Stage IV melanoma.

Chemistry, Manufacturing, and Controls

BMS-986213 is a fixed dose combination product containing relatlimab (BMS-986016) and nivolumab (BMS-936558), at a protein mass ratio of (b) (4) respectively, provided as a sterile solution in a single vial for intravenous administration. The drug product contains 4 mg/mL (80 mg/vial) of relatlimab and 12 mg/mL (240 mg/vial) of nivolumab (b) (4) (b) (4) sucrose, (b) (4) polysorbate 80, and (b) (4) pentetic acid at pH 5.8. BMS-986213 consists of relatlimab and nivolumab (b) (4) drug

substances produced from recombinant Chinese hamster ovary cell culture processes. Relatlimab and Nivolumab are human monoclonal antibodies of the IgG4 class.

Clinical

Pivotal Study CA224047
Study CA224047 is an ongoing, randomized (1:1), double-blind, two-part study evaluating BMS-986213, a fixed-dose combination (FDC) of relatlimab and nivolumab, versus nivolumab alone in patients ≥12 years of age with previously untreated, unresectable or metastatic melanoma. In Part 2 of the study, the primary endpoint is progression-free survival (PFS) assessed by blinded independent central review (BICR) using RECIST v1.1. Overall survival (OS) and overall response rate (ORR) are the key secondary endpoints. Effects in predefined biomarker-defined subgroups (LAG-3 and PD-L1) will be assessed as exploratory endpoints.

Patients are treated with BMS-986213 (relatlimab 160 mg + nivolumab 480 mg and adolescents <40 kg dosing is relatlimab 2 mg/kg + nivolumab 6 mg/kg) or nivolumab 480mg (adolescent subjects <40 kg dosing is 6 mg/kg) once every 4 weeks (Q4W). Randomization is stratified by PD-L1 status (≥1% vs <1%), LAG-3 status (≥1% vs <1%), BRAF status (V600 mutation-positive vs. wild-type), and AJCC 8th edition for staging (M0/M1any[0] vs M1any[1]).

Treatment will continue until disease progression or treatment discontinuation, whichever occurred later. Treatment beyond initial investigator-assessed RECIST v1.1-defined progression is permitted. Tumor assessments are performed at 12 weeks from randomization, every 8 weeks until week 52, and every 12 weeks thereafter. No cross-over as allowed.

An adaptive two-part study design is being used. On August 26, 2019, Part 2 was initiated based on the interim PFS results which indicated that the hazard ratio (HR) was ≤0.8. The final PFS analysis will be performed when 365 PFS events have occurred to ensure 85% power to detect a HR of 0.73 (PFS of 6.9 months for nivolumab and 11.8 months for BMS-986213) at a two-sided alpha of 0.049. OS is the key secondary endpoint in the hierarchical testing. Two interim analyses are planned for efficacy on OS after 210 (70%) deaths and 270 (90%) deaths. Final OS analysis would be performed after 300 events occurred. The statistical assumptions were median OS of 49.2 months in the BMS-986213 arm versus 36.9 months in the nivolumab arm. ORR would not be tested unless OS was statistically significant.

Efficacy Results
As of the data-lock date of March 9, 2021, a total of 714 patients were randomized (355 in the BMS-986213 arm and 359 in the nivolumab arm). Baseline demographics and disease characteristics were similar across treatment arms. Patients in the BMS-986213 arm had a higher percentage of stage M1c (43% vs. 25%), a poor prognostic factor relative to lower stage disease. The study population included a substantial proportion

of patients aged 75 years or above (19.4% overall). Of note, although the study permitted patients aged 12 and above to enter, no adolescents between ages 12 to 17 were enrolled.

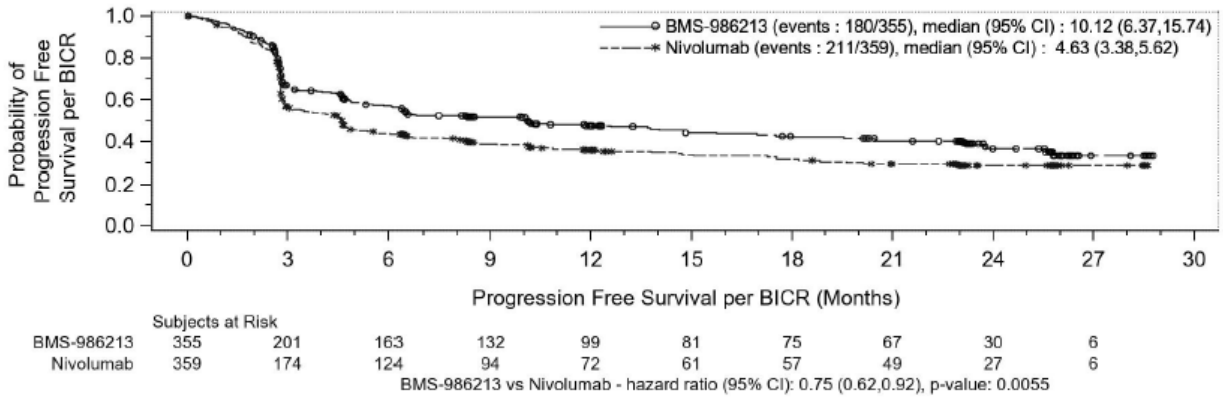
The primary endpoint of PFS was statistically significant with a HR=0.75 (95% confidence interval [CI] 0.62, 0.92).

Table 1. Results of PFS per BICR - Study CA224047

	FDC N=355	Nivolumab N=359
PFS		
Number of Events (n, %)	180 (51)	211 (59)
Median PFS (95% CI) (mo)[a]	10.1 (6.37, 15.74)	4.6 (3.38, 5.62)
HR (95% CI)[b]	0.75 (0.62, 0.92)	
p-value	0.0055	

Source: Meeting package
Statistically significant at alpha = 0.049
[a]Based on Kaplan-Meier estimates.
[b]Stratified Cox proportional hazards model.

Figure 1. KMS Curve of PFS per BICR-Study CA224047



Source: copied from the meeting package
Statistical model for hazard ratio and p-value: Stratified Cox proportional hazard model and stratified log-rank test.
Stratified by LAG3 (>=1% vs <1%), BRAF (Mutation Positive vs Mutation Wild-type), AJCC M Stage (M0/M1any[0] vs M1any[1]).
PD-L1 was removed from stratification because it led to subgroups with fewer than 10 subjects.

Efficacy favored the BMS-986213 arm across subgroups as defined by stratification factors including AJCC 8th edition M-stage (by LDH at baseline), LAG-3 expression, PDL1 expression, and BRAF status but these were not formally tested. Patients with LAG-3 expression ≥5% had a median PFS of 20 (10, NA) months vs. 10 (5.4, 19.6) months. At the time of the data lock, OS at the first planned interim analysis was not statistically significant.

Safety Results

A total of 714 patients received at least one dose of study drug and were assessible for safety. Most patients experienced at least on treatment-emergent adverse event (TEAEs) (97% in the BMS-986213 arm and 94% in the nivolumab arm). The most common TEAES (occurring in ≥20%) in the BMS-986213 arm and nivolumab arm were fatigue (29% vs. 20%), pruritis (25% vs. 17%), arthralgia (24% vs. 15%), diarrhea (23% vs 17%). Grade 3-4 AEs occurred in 40% in the BMS-986213 arm and 33% in the nivolumab arm. Serious AEs (SEAs) occurred in 34% of patients in the BMS-986213 arm and 29% in the nivolumab arm. AEs leading to discontinuation were generally higher in the BMS-986213 arm. There were 3 (0.8%) deaths due to AEs in the BMS-986213 arm (hemophagocytic lymphohistiocytosis, acute edema of lung, and pneumonitis) and 2 (0.6%) in the nivolumab arm (sepsis and myocarditis, and pneumonia). Discontinuations due to an AE occurred in 19% in the BMS-986213 arm versus 11% in the nivolumab arm. The most common immune-mediated AEs in the BMS-986213 arm compared to the nivolumab arm were hypothyroidism (18% vs. 14%), colitis (7% vs. 3.1%), rash (7% vs. 6%), hyperthyroidism (6% vs. 7%), hepatitis (4.5% vs. 2.2%), adrenal insufficiency (4.2% vs. 0.8%) and pneumonitis (3.7% vs. 1.7%). AEs of special interest occurred infrequently in both treatment arms.

Supportive Study CA224020
Study CA224020 is an ongoing, open-label, dose escalation and cohort expansion study of relatlimab as a single-agent and in combination with nivolumab in patients ≥18 years (Parts A, B, C, D, E) or ≥12 years of age (Parts C [melanoma only], D, and E) with advanced solid tumors. Varying doses, regimens, schedules, and formulations were evaluated.

Supportive efficacy data will be limited to patients with previously untreated, unresectable or advanced melanoma in Part C (n=66) and Part E (n=38). In Part C, patients received sequential dosing of relatlimab 80 mg + nivolumab 240 mg once every 2 weeks (Q2W). In Part C, the ORR was 47% (95% CI: 34.6, 59.7) with a complete response (CR) in 11 (17%) and a partial response (PR) in 20 (30.3%) patients. The median duration of response was not reached and ranged from 1.9+ to 43.1+ months. In Part E, patients were treated with co-administration of relatlimab 160 mg + nivolumab 480 mg Q4W. With a median follow-up of 9.4 months, the BICR confirmed ORR was 32% (95% CI: 17, 51), with a CR achieved in 3 (49%) patients and a PR in 8 (24%) patients. As Part E is still enrolling, the data cutoff date for interim analysis of CA224020 does not provide sufficient follow-up time for calculation of a mature response.

Supportive safety data from Part A and B, and safety data from Part C from patients with advanced or metastatic melanoma who progressed while on anti-PD(L)-1 therapy, patients with previously untreated melanoma, and all patients treated with relatlimab 80 mg + nivolumab 240 mg Q2W will be provided as supportive data in the proposed BLA. In addition, safety data from Part D1 treated with relatlimab 80 mg + nivolumab 240 mg Q2W coadministration, relatlimab 160 mg + nivolumab 480 mg Q4W coadministration, and relatlimab 160 mg + nivolumab 480 mg Q4W FDC) will be provided as supportive data for the proposed BLA.

As of the data-lock of February 25, 2021, 412 patients with received at least one dose of relatlimab 160 mg + nivolumab 480 mg Q4W. There were 38 patients who received the proposed dose in patients with previously untreated melanoma (Part E) and 82 patients with previously treated melanoma who received the FDC product from Part D1.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the FDA agree that results from Study CA224047, supported by CA224020, provides an acceptable basis for the evaluation of the benefit-risk balance of rela+nivo FDC and may support regular approval of patients with unresectable or metastatic melanoma based on the final assessment of benefit-risk?

   FDA Response: FDA agrees that the previously discussed content and format and proposed clinical package would support filing of a Biologics License Application (BLA) for regular approval. Note that to support the benefit:risk assessment, evidence that treatment with rela+nivo FDC does not worsen OS compared to nivolumab alone, is needed. Therefore, FDA requests that DMC minutes related to the IA1 OS analysis be directly released to FDA to preserve study blind. Additionally, provide the timeline for when the IA2 OS analysis results may be available for submission to the FDA.

2. Does the FDA agree that the detailed information included in the Dec-2020 administrative pre-BLA background package (refer to BMS pre-BLA Type C Meeting background document, DCN 930162743, Seq. 135) and the data planned for inclusion in this pre-BLA background document, constitutes a complete application in support of a BLA submission?

   FDA Response: FDA agrees, however refer also to FDA Response to Question#1 for additional requests regarding IA1 OS. Additional information may also be requested during review of the submission.

3. If BMS is accepted into RTOR, does the FDA agree that a formal request for Priority Review does not need to be included in the Complete Application?

   FDA Response: Although FDA has accepted this application for RTOR, this acceptance does not guarantee or influence the review timeline of the application or approvability. A formal request for Priority Review must be included in the original BLA submission. BMS may expressly request priority review as described in the Guidance for Industry Expedited Programs for Serious Conditions – Drugs and Biologics. FDA informs the applicant of a Priority Review designation within 60 days of the receipt of the original BLA.

ADDITIONAL COMMENTS

Clinical Pharmacology

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". 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:

4. What is the basis for selecting the doses and dosing regimen used in the registration trials to support the BLA? 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 recommended dosage and administration.

5. What are the exposure-response relationships for efficacy, safety and biomarkers?

6. How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of relatlimab? What dose modifications are recommended?

7. 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:

8. Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

9. 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 range as appropriate.

10. Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The patients' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

    a. 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 patients that have been excluded from the analysis should be flagged and maintained in the datasets.

b. Identify individual patients with dosage modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dosage modifications in the datasets.

11. Submit the following for the population pharmacokinetic analysis reports:

a. Standard model diagnostic plots

b. Individual plots for a representative number of patients. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.

c. Model parameter names and units in tables.

d. Summary of the report describing the clinical application of modeling results.

Refer to the pharmacometric data and models submission guidelines.

12. Submit the following information and data to support the population pharmacokinetic analysis:

a. SAS transport files (*.xpt) for all datasets used for model development and validation

b. A description of each data item provided in a Define.pdf file. Any concentrations or patients that have been excluded from the analysis should be flagged and maintained in the datasets

c. 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)

13. 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, exposure-response relationships, and pharmacometric data and models submission guidelines.

Proprietary Name Review

14. A request for proprietary name review for Opdualag should be submitted once the marketing application is submitted. BMS may include the conditionally

acceptable suffix name in all labels and labeling as per the conditionally acceptable letter for the non-proprietary name.

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

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 7, 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.[1]

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

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

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

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

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

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[3]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for 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.

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[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

- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

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 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*

[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

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]

NONPROPRIETARY NAME

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

ADVANCING ONCOLOGY DECENTRALIZED TRIALS

[8] https://www.fda.gov/media/85061/download

FDA Oncology requests that applicants submitting data to support NDA/BLA applications voluntarily add flags to datasets in order to discriminate between REMOTE assessments and TRIAL SITE assessments. The intent is to allow FDA to learn from trials conducted during 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 in order to foster appropriate prospective use of “decentralized” aspects of clinical trials in the post-COVID era.
For details please refer to: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials.”

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/

CHRISTINA L LEACH
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