CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217150Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 152770

MEETING MINUTES

Sandoz Inc.
Attention: Gregory Seitz
Executive Director, Regulatory Affairs
100 College Road West
Princeton, NJ 08540

Dear Mr. Seitz:

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

We also refer to the teleconference between representatives of your firm and the FDA on April 29, 2022. The purpose of the meeting was to discuss the Sponsor's 505(b)(2) NDA application for Cyclophosphamide injection.

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, please call David Bak, Regulatory Health Project Manager, at 301-796-6299 or email David.Bak@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type:	B
Meeting Category:	Pre-NDA
Meeting Date and Time:	April 29, 2022, at 4:00 PM – 5:00 PM (ET)
Meeting Location:	Teleconference
Application Number:	IND 152770
Product Name:	Cyclophosphamide injection
Indication:	Hodgkin's lymphoma, lymphocytic lymphoma, mixed-cell type lymphoma, histiocytic lymphoma, Burkitt's lymphoma; multiple myeloma, leukemias, mycosis fungoides, neuroblastoma, adenocarcinoma of ovary, retinoblastoma, breast carcinoma, (b) (4)
Sponsor Name:	Sandoz Inc.
Regulatory Pathway:	505(b)(2) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Nicholas Richardson, DO, MPH
Meeting Recorder:	David Bak, PharmD, BCNSP

FDA ATTENDEES

Office of Oncologic Diseases/Division of Hematologic Malignancies II
Nicole Gormley, MD, *Director*
Nicholas Richardson, DO, MPH, *Clinical Team Leader*
Pam Seam, MD, *Clinical Reviewer*

Office of Oncologic Diseases/Division of Hematology Oncology Toxicology
Brenda Gehrke, PhD, *Supervisory Pharmacologist/Toxicologist*
Simon Williams, PhD, *Pharmacologist*

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Nan Zheng, PhD, *Clinical Pharmacology Team Leader*

Office of New Drug Products(ONDP)/Division of New Drug Products I
Sherita McLamore, PhD, *Senior Product Quality Assessor*
Yang Nan, PhD, *Drug Product Assessor*

Office of New Drug Products/Division of Biopharmaceutics
Gerlie Gieser, PhD, *Biopharmaceutics Reviewer*

Office of Oncologic Diseases (OOD)
Jessica Boehmer, MBA, *Regulatory Scientist*

Office of Regulatory Operations for Oncologic Diseases/Division of Regulatory Operations
Theresa Carioti, MPH, *Chief, Project Management Staff*
David Bak, PharmD, BCNSP, *Regulatory Health Project Manager*

SPONSOR ATTENDEES

Sandoz Inc.
Polina Fradkin, Pharm.D., *Director, Regulatory Affairs*
Gregory Seitz, M.S., *Executive Director, Regulatory Affairs*
Lara Hansen, *Associate Director, Regulatory Affairs*
Richard Almond, MBA, *Director, Regulatory Affairs*
Melric Mathias, *Associate Directory Regulatory Affairs*

(b) (4)

1.0 BACKGROUND

Cyclophosphamide products are currently available in several dosage forms including powder lyophilizate for solution reconstitution, and ready-to-dilute solution for intravenous injection or infusion and oral tablets. The Sponsor has developed a ready-to-use liquid formulation for dilution of the reference standard (RS), Cyclophosphamide/Baxter (ANDA 040745), which is a powder. The Sponsor intends to file the application for its Cyclophosphamide injection as a New Drug Application (NDA) via 505(b)(2) route.

The purpose of this meeting is to discuss the Sponsor's 505(b)(2) NDA application for cyclophosphamide injection.

FDA sent Preliminary Comments to Sandoz Inc. on April 26, 2022.

2.0 DISCUSSION

Question 1: *Does the Agency agree with the specification limits for impurities A, C and D which are above ICH recommended levels but are aligned with USP monograph for Cyclophosphamide injection (lyophilized powder formulation)? Does the Agency have any additional comments with respect to Sandoz's proposed specifications?*

FDA Response to Question 1:
The proposed acceptance criteria for impurities A, C and D appear reasonable; however, the final decision will be made at the time of NDA review.

We have the following additional comments:

1. The proposed impurity acceptance criteria for USP compound B, (b) (4) (b) (4) and total impurities are not acceptable at this time. We note that you propose to qualify the acceptance criteria for the aforementioned impurities. The acceptability of the information or data to support the proposed acceptance criteria will be subject to review.

2. The proposed shelf-life limit (NMT (b) (4) %) for any individual unspecified impurity does not seem in line with ICH Q3B (R1). In the NDA submission, include a calculation and a determination of the maximum daily dose for the proposed drug product. Justify the proposed limit for any individual unspecified impurity based on the drug product maximum daily dose or tighten the limit consistent with ICH Q3B(R1).

3. Include a test and an acceptance criterion for the container content in the specifications per USP<697> in the drug product specifications. In addition, set a limit for the minimal fill volume (net container content + USP<1151> recommended excess volume) and an appropriate limit for the maximum fill volume in the drug product specifications.

4. Include a test for container-closure integrity in the drug product specifications per USP<1>.

5. Include a test and acceptance criterion for (b) (4) in the drug product specifications or justify exclusion of the test.

6. Include control of related impurities and degradation products from ethanol and propylene glycol in the drug product specifications as applicable.

Discussion:
Comment #2:
The Agency stated that USP impurities A, C and D are known impurities and that the proposed limits for impurities A, C and D are aligned with the USP monograph, which appears reasonable. The Agency further stated that since the Sponsor's drug product is a new drug product, the limit for any individual unspecified impurity should be set per ICH Q3B(R1) depending on the maximum daily dose (MDD). Accordingly, the Sponsor should calculate the MDD and provide justification for the proposed limit for any individual unspecified impurity.

The Agency stated that ultimately the proposed limit will be a review issue and a final decision will be made during the NDA review.

Comment #3:
The Agency stated that due to the limited information provided in the meeting package, it was unclear that an in-process control was proposed to ensure correct filling volumes and ranges. The Agency noted that in the NDA submission, the Sponsor should include justification for the proposed acceptance criteria for extractable volume including the in-process control of the (b) (4) **The final decision on the adequacy will be made during the NDA review. The Sponsor may refer to CDER's MAPP 5019.1 for additional information.**

Comment #4:
The Agency noted that footnote #5 under Table 5 of the proposed drug product specification in the meeting package indicated the following, "compliance to USP <1> is based on Report on Compliance with US Pharmacopoeia, which is re-assessed on every revision of this general chapter in USP-NF. It is not part of CoA as a test, only as a statement". The Agency stated that it was unclear that the Sponsor's drug product was in full compliance to USP<1>. Container-closure integrity is one of the required universal tests per USP<1>. The Agency recommended that the Sponsor include a test for container-closure integrity in the drug product specifications in the NDA as it is a requirement under USP<1>. The Sponsor stated that they intend to provide evidence in the NDA that the container-closure integrity is in compliance per USP<1>. The Agency stated that the adequacy will be a review issue.

Comment #6:
The Agency stated that according to ICH Q6A (b) (4) (b) (4) (b) (4) **Therefore, the Agency stated that these impurities should be evaluated based on a risk-based approach, as applicable.**

Question 2: *If the Agency does not agree that comparability between RS and Sandoz's product is adequately supported, what additional data/studies are needed to support it?*

FDA Response to Question 2:
In general, the physicochemical comparison between the RS and Sandoz's product provided in Annex B appears reasonable in terms of appearance, pH, viscosity and specific gravity, but not acceptable for osmolality. The final decision about the physicochemical comparison will be made during the NDA review. We have the following additional comments:

1. We could not locate osmolality data of your drug product in your meeting package. Since Sandoz's product contains ethanol and propylene glycol, the osmolality of your product is expected to be high. In the NDA submission, provide osmolality data for the diluted intravenous solutions of the cyclophosphamide injection; the diluents should include each of the applicable diluents listed in the RLD labeling: (b) (4) (b) (4) (b) (4) Justify the solution osmolality levels from the clinical perspective. The decision about whether high osmolality of the diluted solutions of the Sandoz's cyclophosphamide injection is suitable for infusion will be made at the time of NDA review.

2. Perform an assessment of leachables/extractables of the proposed container closure system per USP <1663> and <1664> and submit the data for evaluation.

The adequacy of the comparative *in vitro* protein binding, *in vitro* hemolysis and physico-chemical characterization data, as well as the GLP animal toxicity data to establish the scientific bridge between the proposed concentrate/ready-to-dilute (RTD) injectable solution drug product and the relied upon Listed Drug (LD; powder for injection) product via 21 CFR 320.24(b)(6) will be determined during NDA review when the generated data and the associated study protocols become available for FDA review.

Consider the following comments when designing/conducting the planned comparative *in vitro* and nonclinical studies between the proposed RTD solution drug product and the Reference Standard (RS; powder for injection) drug product, and in the preparation of the scientific bridging justification package to be included in the NDA:

3. For physico-chemical comparisons of all three product presentations of the proposed and RS products, in addition to appearance, pH, viscosity, and specific gravity, measure osmolality, surface tension, and assay, i.e., before dilution (100 mg/mL 'as is' or following powder reconstitution) and after dilution to final drug concentrations of 2 mg/mL and 20 mg/mL with all the LD's label recommended diluents according to labeling instructions. For example, to simulate clinical conditions of use, for the 2 mg/mL final infusion solution, we recommend performing the dilution into the IV diluent bag of appropriate volume instead of in a volumetric flask.

4. In the planned comparative *in vitro* protein binding and *in vitro* hemolysis studies, use final drug concentrations in human plasma/blood that are therapeutically relevant, including but not limited to final drug concentrations as close as feasible to 2 mg/mL and 20 mg/mL.

5. To support comparability between the proposed and relied upon LD products, in the planned GLP toxicity study (intended to qualify the proposed tolerance limits

for certain impurities), add the proposed RTD solution formulation and the RS (prepared according to proposed/approved labeling instructions) as control arms. If feasible, consider determining the comparative plasma cyclophosphamide PK and local safety/tolerability profiles resulting from administration of these control treatments.

6. For the proposed RTD solution drug product, in addition to stability data of the concentrate (100 mg/mL) drug product in its proposed commercial packaging configuration, submit also in-use stability for the diluted products and compatibility data with the recommended diluents in IV bags for up to 24 hours at room temperature and up to 6 days under refrigerated storage, as well as in-use stability data for the partially used vial up to 28 days of refrigerated storage.

Adequate information should be provided in the NDA to justify that any differences between the proposed product and the LD/RS in terms of formulation, dosage form and any other CMC differences, as well as *in vitro*/nonclinical characteristics would not impact clinical PK (disposition) and efficacy/safety/tolerability, as well as ease of preparation (e.g., syringeability) and delivery (e.g., injectability/infusability of the final dilutions) of the proposed drug product. Be aware that if the overall submitted information in the NDA is not deemed adequate to support the scientific bridge between the proposed and the LD product(s), an *in vivo* bioavailability/ bioequivalence (BA/BE) study will be needed to support the approval of your proposed drug product.

Propylene Glycol and Ethanol Excipient Comments

We have the following additional comments regarding the propylene glycol and ethanol excipients:

7. We acknowledge that you have provided a Toxicological Risk Assessment for the levels of ethanol (alcohol) and propylene glycol in your cyclophosphamide product. Submit this risk assessment along with any other information or data supporting the levels of the excipients to the NDA. The decision regarding the safety of the levels of ethanol and propylene glycol in your cyclophosphamide product will be determined during the review of the NDA.

8. Provide data or information to support your claim of minimal drug-drug interaction potential based on the levels of ethanol and propylene glycol in the proposed RTD solution drug product, the proposed dosing regimen, and their impact on major metabolic enzymes.

9. In the NDA, include justification for the levels of ethanol and propylene glycol in the proposed RTD solution drug product from a local tolerability and systemic safety perspective in the context of use by patients, including but not limited to adult and pediatric patients, neonates, and patients with hepatic or renal impairment. Additionally, provide justification from a drug disposition/clinical PK perspective.

Discussion:

Comment #1:

The Agency stated that the Sponsor's approach with respect to osmolality testing of the proposed drug product appears reasonable. The Agency noted that the final decision will be made at the time of NDA review.

Comment #3:

The Agency stated that presentation-specific issues could arise due to unforeseen reasons. The Agency noted that at a minimum, the physico-chemical characterization study should include an evaluation of all proposed commercial presentations of the ready-to-dilute solution drug product versus the relied upon Listed Drug powder product. The Agency recommended allocating the total sample size to all three presentations to provide adequate information to support the Agency's review.

The Agency stated that for all in vitro bridging studies, the Agency expected the testing to include the drug product batches representing the final proposed to-be-marketed product manufactured using the final commercial formulation, process, container-closure system, manufacturing site, etc.

Comment #5:

Scientific bridge:

The Agency stated that it is premature to determine whether the comparative animal PK and local safety/tolerability data are not warranted to support the scientific bridge between the proposed and the LD products. The data and information from comparative physicochemical characterization, in vitro protein binding, in vitro drug-drug interaction, and in vitro hemolysis studies are not available or incomplete. The Agency further noted that if the proposed product is expected to be hypertonic, in vitro hemolysis may not be sufficient to replace local tolerability/safety testing. The Agency stated that if the Sponsor decides not to include the comparative animal PK and safety/tolerability data as part of the scientific bridging package, a robust justification should be included in the NDA.

Planned nonclinical study to qualify impurities:

The Agency stated that the proposed GLP toxicological study is shorter in dosing duration than the typical impurity qualification study, which would include a dosing period of 2 weeks or longer. The adequacy of the study to support the proposed impurity specifications will be subject to review. The Agency also noted that the assessment will include a determination of the adequacy of the toxicological signal in the cyclophosphamide arm that has not been spiked with the candidate impurities.

The Sponsor inquired whether ICHS9 would be taken into consideration given that cyclophosphamide falls under that guidance. The Agency stated that S9

would be taken into consideration; however, the adequacy of the study would be dependent on the toxicological profile of the baseline conditions, in addition to the spiked conditions.

3.0 OTHER IMPORTANT INFORMATION

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

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

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could

result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.

For the latest version of the molecular target list, please refer to FDA.gov.[1]

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.[2]

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

[1] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology
[2] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[3] and Pregnancy and Lactation Labeling Final Rule[4] 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*.

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

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

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.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for

[5] http://www.fda.gov/ectd

sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

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]

[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

(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[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.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[9] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[10]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of

[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] 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.
[10] http://www.regulations.gov

reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling,

we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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*.[11]

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

- RTOR[12]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.
- Assessment Aid[13]

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor provided a response document to the FDA's preliminary comments, and that document is appended at the end of this document

[11] https://www.fda.gov/media/85061/download
[12] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[13] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

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/s/

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