CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

215331Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 141660

MEETING MINUTES

MAIA Pharmaceuticals, Inc.
Attention: Srikanth Sundaram, PhD
Chief Scientific Officer
707 State Road, Suite 104
Princeton Gateway Building
Princeton, NJ 08540

Dear Dr. Sundaram:

Please refer to your Pre-Investigational New Drug Application (PIND) file for bortezomib.

We also refer to the teleconference between representatives of your firm and the FDA on July 29, 2021. The purpose of the meeting was to discuss the adequacy of the nonclinical, clinical, and CMC data in support of the proposed NDA.

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

Sincerely,

{See appended electronic signature page}

Bindu Kanapuru, MD
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:	Type B
Meeting Category:	Pre-NDA
Meeting Date and Time:	Thursday, July 29, 2021, 10:00 AM – 11:00 AM (ET)
Meeting Location:	Teleconference
Application Number:	IND 141660
Product Name:	Bortezomib
Indication:	Treatment of adult patients with multiple myeloma or mantle cell lymphoma
Sponsor Name:	MAIA Pharmaceuticals, Inc.
Regulatory Pathway:	505(b)(2) of the Federal Food, Drug, and Cosmetic Act
Meeting Chair:	Bindu Kanapuru, MD
Meeting Recorder:	David Bak, PharmD, BCNSP

FDA ATTENDEES

OOD/Division of Hematologic Malignancies II
Nicole Gormley, MD, *Director*
Bindu Kanapuru, MD, *Clinical Team Leader*
Alexandria Schwarsin, MD, *Clinical Reviewer*

OOD/Division of Hematology Oncology Toxicology
Brenda Gehrke, PhD, *Supervisory Pharmacologist/Toxicologist*
Shwu-Luan Lee, PhD, *Pharmacologist*

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

ONDP/Division of New Drug API
Paresma Patel, PhD, *Branch Chief, Drug Substance*
Haripada Sarker, PhD, *Drug Substance Assessor*

ONDP/Division of Biopharmaceutics
Om Anand, PhD, *Biopharmaceutics Lead*
Anitha Govada, PhD, *Biopharmaceutics Reviewer*

Office of Clinical Pharmacology/Division of Cancer Pharmacology I
Huiming Xia, PhD, *Clinical Pharmacology Team Leader (Acting)*
Miao Zhao, PhD, *Clinical Pharmacology Reviewer*

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

MAIA
Srikanth Sundaram, PhD, *Chief Scientific Officer*
Bikram Malik, *Project Management*
Daniel Stewart, *Product Development*
Sasank Kunadharaju, PhD, *Product Development*
John Alessandro, *Technical Operations*

Consultant to MAIA
(b) (4)

1.0 BACKGROUND

MAIA Pharmaceuticals, Inc. (MAIA) is proposing to submit a 505(b)(2) new drug application (NDA) for a ready-to-use (RTU) formulation of bortezomib injection. MAIA is relying upon the listed drug (LD), VELCADE (bortezomib) Injection (NDA 21602, Millennium Pharmaceuticals, Inc.), for approval.

VELCADE (bortezomib) for Injection, is marketed in a single product presentation (3.5 mg of bortezomib as a sterile lyophilized white to off-white powder in a single-use vial) indicated for treatment of adult patients with multiple myeloma and mantle cell lymphoma. VELCADE is reconstituted with either 1.4 mL of 0.9% sodium chloride injection for a nominal concentration of 3.5 mg/1.4 mL (2.5 mg/mL) for administration via the subcutaneous route or 3.5 mL of 0.9% sodium chloride injection for a nominal concentration of 3.5 mg/3.5 mL (1 mg/mL) for administration via the intravenous route. MAIA is proposing to market their bortezomib for the same indications as Velcade, but in two presentations – 3.5 mg/1.4 mL (2.5 mg/mL) and 3.5 mg/3.5 mL (1 mg/mL) – in ready-to-use single-dose vials.

The purpose of this meeting is to discuss the adequacy of the nonclinical, clinical, and CMC data in support of the proposed NDA. MAIA plans to submit an NDA for both presentations – 3.5 mg/1.4 mL and 3.5 mg/3.5 mL for the intravenous route of administration only. [redacted] (b) (4)

FDA sent Preliminary Comments to MAIA Pharmaceuticals, Inc. on July 23, 2021.

2.0 DISCUSSION

Question 1: *Given the differences in formulation between MAIA's product, the Listed Drug, and other approved 505(b)(2) NDA bortezomib products cited above, does the Agency agree that the proposed application still meets the requirements for a 505(b)(2) NDA?*

FDA Response to Question 1:
As FDA previously stated in Pre-IND/Pre-NDA Meeting Minutes dated February 13, 2020, a 505(b)(2) application appears to be an acceptable approach, based on the information provided. Also, please refer to the additional information below under the heading "505(b)(2) Regulatory Pathway".

DISCUSSION: ***There was no discussion.***

Question 2: *Does the Agency concur with MAIA's proposed approach for the Prescribing Information to be included in the NDA?*

FDA Response to Question 2:
Your proposed approach seems reasonable. However, the specific details to be included in the USPI will be a review issue.

DISCUSSION: ***There was no discussion.***

Question 3: *Does the Agency agree that drug substance information to be included in the NDA is adequate to support the filing?*

FDA Response to Question 3:
The proposed drug substance information to be included in the NDA submission appears reasonable. The proposal to submit the drug substance quality information by cross reference to Type II DMF [redacted] (b) (4) appears reasonable, provided the DMF is current.

DISCUSSION: ***There was no discussion.***

Question 4: *Does the Agency agree that the proposed drug substance specification is adequate to support the NDA filing?*

FDA Response to Question 4:
The proposed drug substance specification appears acceptable, and the final determination will be made at the time of NDA review.

DISCUSSION: ***There was no discussion.***

Question 5: *Does the Agency agree that the proposed drug product specification is adequate to support the NDA filing?*

FDA Response to Question 5:
The proposed drug product specifications are adequate to file an NDA. The final determination on the adequacy of the proposed specifications will be made during the NDA review.

DISCUSSION: ***There was no discussion.***

Question 6: *Does the Agency concur with MAIA's proposal for the stability data to be included in the NDA at the time of filing?*

FDA Response to Question 6:
The stability data proposed to be included in the planned NDA is acceptable. The shelf-life of the drug product will be determined during the NDA review based on the totality of the data submitted in the application.

DISCUSSION: ***There was no discussion.***

Question 7: *Because there have been no changes to the formulations, MAIA believes that no studies are needed to support the level of inactive ingredients present in MAIA's proposed products for the NDA. Does the Agency concur?*

FDA Response to Question 7:
Based on the meeting package, there have been no changes to the formulations since the pre-IND meeting; therefore, as mentioned in the Agency's response in the pre-IND meeting minutes, no additional studies appear to be needed to support the levels of the inactive ingredients present in MAIA's proposed products for the NDA. The acceptability of the levels of the inactive ingredients will be determined during the review of the NDA submission.

DISCUSSION: ***There was no discussion.***

Question 8: *Does the Agency concur that the in vitro hemolysis study is adequate to provide the needed evidence that MAIA's products have a comparable tolerability to the Listed Drug when administered intravenously at either 1 mg/mL or 2.5 mg/mL?*

FDA Response to Question 8:
Based on the results of the in vitro hemolysis study included in the meeting package, the in vitro study appears to support the notion that both MAIA products (1 mg/mL and 2.5 mg/mL vials) are negative for hemolysis and have comparable tolerability to the Listed Drug when administered intravenously. The acceptability and adequacy of the study will be determined upon the review of the NDA submission.

DISCUSSION: There was no discussion.

Question 9: *Does the Agency agree that no toxicology studies are required in the NDA filing to demonstrate that MAIA's product has a comparable safety profile to the Listed Drug as the impurity specifications are within the ICH Q3B thresholds?*

FDA Response to Question 9:
The impurity specifications of MAIA's bortezomib product appear to be in line with the ICH Q3B guidance and comparable with the LD impurity profile according to the information provided in the meeting package. Therefore, no toxicology studies appear to be warranted for the filing of the NDA. The acceptability of the proposed impurity specifications will be determined during the review of the NDA submission.

DISCUSSION: There was no discussion.

Question 10: *Does the Agency concur that the in vitro pharmacodynamic study to compare the proteasome inhibition activity of MAIA's product and the Listed Drug is adequate to serve as the appropriate bridging study for the NDA filing?*

FDA Response to Question 10:
Your proposed in vitro pharmacodynamic study to compare proteasome inhibition appears appropriate as supporting in vitro experimental data for the 1 mg/mL presentation of the proposed product. However, the adequacy of the in vitro pharmacodynamic bridging will be evaluated during the NDA review based on the totality of the data submitted in the application.

DISCUSSION: There was no discussion.

Question 11: *Does the Agency agree that justification for the Biowaiver to be included in the Meeting Package is adequate to support filing of the NDA for the intravenous route?*

FDA Response to Question 11:
A biowaiver is not feasible for the proposed product because of the differences in inactive ingredients. However, the "bridge" between the proposed drug product and LD can be established for the intravenous route of administration using in vitro comparative physiochemical data, data from in vitro experiments, and published literature data as supporting data to demonstrate that the difference in the excipients do not affect the disposition kinetics of bortezomib in human subjects. Note that the adequacy of the

overall information/data supporting the bridge between the proposed drug product and the LD will be evaluated during the NDA review based on the totality of the data submitted in the application.

DISCUSSION:

Follow-up questions:
2.a Should MAIA not include a request for a waiver of in vivo bioavailability or bioequivalence in the NDA?

Discussion for Follow Up Question 11.2a: **FDA reiterated that a biowaiver under the CFR-Title 21 Part 320.22(1) regulation is not feasible because the proposed drug product is not qualitatively and quantitatively (Q1/Q2) the same as that of the listed drug product. FDA confirmed that the request for a waiver of the submission of in vivo bioavailability or bioequivalence evidence does not need to be included in the NDA**.

2.b If a biowaiver request does not need to be included in the NDA, the Sponsor intends to provide the requested information for the establishment of the scientific bridge (namely Attachment V of the meeting package) either in/or as an attachment to the cover letter. The proteasome inhibition study report(s) will be included in Module 5, as indicated in the NDA TOC submitted in the meeting package. Does the Agency concur?

Discussion for Follow Up Question 11.2b: **FDA stated that the Sponsor should submit the bridging report with the supporting information and data in Section 2.7.1 and cross reference relevant sections by providing a link to the files of supporting studies including the in vitro proteasome inhibition study report as described. The Agency recommended that Sponsor refer to Section 2.7.1 in Section 1.12.15.**

Question 12: *Does the Agency agree that no bioequivalence (pharmacokinetic) study is required to support filing of the NDA for the intravenous route?*

FDA Response to Question 12:
The information provided in the meeting package, for a scientific bridge between the proposed and listed products for intravenous route of administration, appears reasonable for the filing of the NDA. However, the in vitro comparative physiochemical data, in vitro experimental data and published literature should be provided comparing all presentations of the (1 mg/mL and 2.5 mg/mL) proposed product with the LD after reconstitution. The need for additional clinical studies will be a review issue. In addition, see the responses to Questions 11 and 12.

DISCUSSION:

Follow-up questions:
1.a. In light of the agreement reached with the Agency at the Pre-IND meeting to perform the in vitro proteasome inhibition bridging study using only the 1 mg/mL presentation as it is the worst-case, what is the Agency's rationale for now requiring a comparative study with the 2.5 mg/mL presentation also?

Discussion for Follow Up Question 12.1a:
FDA clarified that the Sponsor's proposal to conduct the in vitro proteosome inhibition study on the 1 mg/mL presentation appears reasonable for the initial NDA submission based on the supportive information provided in the meeting package. The adequacy of the assay will be determined during the NDA review.

1.b. Does the Agency concur that the totality of the data presented in Attachment 5 of the meeting package establishes an adequate scientific bridge for both presentations of MAIA's product to the Listed Drug?

Discussion for Follow Up Question 12.1b:
FDA stated that the Sponsor's proposed approach for bridging appears reasonable. The final determination regarding the acceptability of the data supporting the bridge will be a review issue under the future NDA. To support bridging of the additional strength 2.5 mg/mL for intravenous administration, the Sponsor should submit an adequate justification with supporting data, including side by side comparison of formulations (1mg/mL and 2.5 mg/mL of the proposed product and the LD) and physicochemical characterization [pH, tonicity, osmolality, drug concentration and administered volume] demonstrating that differences between the proposed injectable solution and listed drug product, do not have any impact on the disposition, efficacy and safety of the proposed drug product.

The adequacy and acceptability of the overall information/data provided to address the differences and fully support the scientific bridge between MAIA Pharmaceuticals proposed product (both 1mg/mL and 2.5 mg/mL presentations) and the LD product will be a review issue under the NDA.

Question 13: *Does the Agency agree that no additional studies are necessary to demonstrate that MAIA's product has the same clinical safety and efficacy as the Listed Drug VELCADE for the intravenous route?*

FDA Response to Question 13:
The Agency cannot confirm if clinical studies will not be necessary to support the intended 505(b)(2) approval at this time. The need for additional clinical studies will be a review issue.

DISCUSSION: ***There was no discussion.***

Question 14: *Based on the NDA Table of Contents to be included in the Meeting Package, are there any other items that the Agency requires for filing and approval of the NDA?*

FDA Response to Question 14:
Your proposal for the content of your application appears appropriate; however, final determination for acceptance of filing or approval will be made following receipt and review of your complete NDA application.

DISCUSSION: ***There was no discussion.***

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

[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

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[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.

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

[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

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 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 *for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

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

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

(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 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

[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

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.

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

Advancing Oncology Decentralized Trials

FDA Oncology requests that applicants submitting data to support NDA/BLA applications to 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 in the COVID-19 pandemic that permitted some aspects of

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

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 use of “decentralize” aspects of clinical trials prospectively in the post-COVID era.

For details please refer to: https://www.fda.gov/about-fda/oncology-center-excellence/advancing-oncology-decentralized-trials.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

No additional items for discussion.

5.0 ACTION ITEMS

No other 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.

8 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

BINDU N KANAPURU
07/29/2021 02:27:06 PM

PIND 141660

MEETING MINUTES

MAIA Pharmaceuticals, Inc.
Attention: Srikanth Sundaram, PhD
Chief Scientific Officer
707 State Road, Suite 104
Princeton Gateway Building
Princeton, NJ 08540

Dear Dr. Sundaram:[1]

Please refer to your pre-investigational new drug application (PIND) file for Bortezomib.

We also refer to the teleconference between representatives of your firm and the FDA on January 23, 2020. The purpose of the meeting was to discuss the proposed type of NDA filing and the adequacy of the proposed NDA for the final formulation selected.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Patricia Garvey, Lead Regulatory Project Manager, at (301) 796-8493.

Sincerely,

{See appended electronic signature page}

Bindu Kanapuru, MD
Clinical Team Leader (Acting)
Division of Hematologic Malignancies II
Office of Oncologic Diseases
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

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

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-IND/Pre-NDA

Meeting Date and Time: March 23, 2020 at 10:00 AM – 11:00 AM (ET)
Meeting Location: Teleconference

Application Number: PIND 141660
Product Name: Bortezomib
Indication: (1) treatment of adult patients with multiple myeloma
(2) treatment of adult patients with mantle cell lymphoma
Sponsor/Applicant Name: MAIA Pharmaceuticals, Inc.

Meeting Chair: Bindu Kanapuru, MD
Meeting Recorder: Patricia Garvey, RPh

FDA ATTENDEES

Office of Oncologic Diseases (OOD)/Division of Hematologic Malignancies II
Nicole Gormley, MD, Director (Acting)
Bindu Kanapuru, MD, Clinical Team Leader (Acting)
Alexandria Schwarsin, MD, Clinical Reviewer

OOD/Division of Hematology, Oncology, Toxicology
Brenda Gehrke, PhD, Supervisory Pharmacologist (Acting)
Ramadevi Gudi, PhD, Pharmacology/Toxicology Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases
Patricia Garvey, RPh, Lead Regulatory Project Manager

Office of New Drug Products (ONDP)/Division of New Drug Products I Branch 2
Anamitro Banerjee, PhD, Branch Chief (Acting)
Sherita McLamore, PhD, Quality Assessment Lead (Acting)
Amit Mitra, PhD, Reviewer

ONDP/Division of New Drug API
Ali Al Hakim, PhD, Director

ONDP/Division of Biopharmaceutics Branch 1
Angelica Dorantes, PhD, Biopharmaceutics Branch Chief
Om Anand, PhD, Team Leader (Acting)
Qi Zhang, PhD, Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Olanrewaju Okusanya, PharmD, MS, Clinical Pharmacology Team Leader
Amal Ayyoub, PhD, Clinical Pharmacology Reviewer

SPONSOR ATTENDEES

MAIA Pharmaceuticals, Inc.
Srikanth Sundaram, PhD, Chief Scientific Officer
Bikram Malik, Project Management
Daniel Stewart, Product Development
John Alessandro, Technical Operations
Noushin Rahimi, Quality

Consultant to MAIA
(b) (4)

1.0 BACKGROUND

MAIA Pharmaceuticals, Inc. (MAIA) is proposing to submit a 505(b)(2) new drug application for a ready-to-use formulation of bortezomib injection. MAIA is relying upon the listed drug (LD), VELCADE (bortezomib) Injection (NDA 021602, Millennium Pharmaceuticals, Inc.), for approval.

VELCADE (bortezomib) for Injection is marketed in a single product presentation (3.5 mg as a sterile lyophilized powder in a clear single-use vial) indicated for treatment of adult patients with multiple myeloma or with mantle cell lymphoma. VELCADE is reconstituted with either 1.4 mL of 0.9% sodium chloride injection for a nominal concentration of 3.5 mg/1.4 mL (2.5 mg/mL) for administration via the subcutaneous route or 3.5 mL of 0.9% sodium chloride injection for a nominal concentration of 3.5 mg/3.5 mL (1 mg/mL) for administration via the intravenous route. The 1 mg/mL concentration may also be used for subcutaneous administration "if local injection site reactions occur following VELCADE administration subcutaneously" at the higher 2.5 mg/mL concentration (see Section 2.9 of the VELCADE US prescribing information).

MAIA is proposing to market their bortezomib for the same indications as Velcade, but in two presentations – 3.5 mg/1.4 mL (2.5 mg/mL) and 3.5 mg/3.5 mL (1 mg/mL) – in ready-to-use single-dose vials. The MAIA's products are supplied ready to use at the same concentrations that the listed drug is used for administration but without the need to reconstitute. (b) (4)

The purpose of this meeting is to obtain agreement with the Agency on the proposed type of NDA filing and the adequacy of the proposed NDA for the final formulation selected for the registration batches and corresponding target package insert:

- Confirmation of type of filing - 505(b)(2) NDA is proposed
- Confirmation that the inactive ingredients are not novel and do not require any special studies to qualify them
- Agreement that the studies (CMC, Nonclinical and Clinical) are comprehensive and appropriate for the proposed NDA
- Agreement that no bioequivalence (pharmacokinetic) study is required to support the NDA

FDA sent Preliminary Comments to MAIA Pharmaceuticals, Inc. on January 21, 2020.

2.0 DISCUSSION

2.1. Administrative

Question 1: *Given the differences in formulation between MAIA's product, the listed drug, and other approved 505(b)(2) bortezomib products cited in Section 4.1, does the Agency agree that the proposed application meets the requirements for a 505(b)(2) NDA?*

FDA Response to Question 1: A 505(b)(2) application appears to be an acceptable approach at this time based on the information provided. Please also refer to the information below under the heading "505(b)(2) Regulatory Pathway".

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

2.2. Chemistry, Manufacturing and Controls

Question 2: *Does the Agency agree with the proposed specifications for the drug substance?*

FDA Response to Question 2:
Your proposed specification for Bortezomib drug substance appears reasonable. Final determination will be made at the time of NDA review.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 3: *Does the Agency concur with the ICH Q3B defined Identification and Qualification Thresholds of NMT 0.5% and NMT 1.0%, respectively?*

FDA Response to Question 3:
Yes, provided the degradation products are not genotoxic.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 4: *Does the Agency concur with the proposed specifications for the drug product?*

FDA Response to Question 4:
Yes, the approach for setting the drug product specification appears reasonable. However, final decision on the adequacy of the tests, acceptance criteria and analytical methods will be made during the proposed NDA review. Also, see additional CMC comments for the proposed NDA.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

2.3 Nonclinical

Question 5: *Does the Agency agree that there are no novel inactive ingredients in MAIA's formulations and that no additional studies are needed to support the levels of the inactive ingredients used in MAIA's formulations?*

FDA Response to Question 5:
Based on the information provided in the briefing package, the Agency agrees that no additional studies are needed to support the levels of the inactive ingredients present in MAIA's formulations at this time. This issue will need to be revisited if any changes to the formulations are made. The acceptability of the levels of the inactive ingredients will be determined during the review of the IND.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 6a: *Does the Agency concur that the in vitro hemolysis study is adequate to provide the needed evidence that MAIA's product has a comparable tolerability to the listed drug when administered intravenously?*

FDA Response to Question 6a:
Yes, your in vitro hemolysis study appears sufficient to evaluate the comparable tolerability of your bortezomib product to the listed drug for intravenous administration; the adequacy of the study will be determined following the review of the data.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 6b: *Does the Agency concur no local tolerance studies are required to support the clinical development of this product?*

FDA Response to Question 6b:
Yes, based on the information provided in the briefing package indicating that the levels of excipients and solvents are below those in approved IV (b) (4) products, your approach for not conducting a local tolerance study appears reasonable. The final determination will be made at the time of the IND review.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 7: *Does the Agency agree that no toxicology studies are required to demonstrate that MAIA's product has a comparable safety profile to the listed drug if the impurity specifications are within the ICH Q3B qualification threshold?*

FDA Response to Question 7:
Based on the information provided in the meeting package, your approach to not conduct a toxicology study unless the impurities exceed the limits in the ICH guidances is reasonable. Justification for the level of impurities may be also based on the levels in the listed drug, in a side-by-side comparative study. Final determination on the acceptability of the proposed specifications and the qualification of all impurities will be made at the time of the NDA review.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 8: *Does the Agency agree that the proposed repeat dose toxicology study is appropriate to qualify any impurities that may be present above the ICH Q3B qualification threshold (1.0%) in MAIA's product?*

FDA Response to Question 8:
Yes. Your proposed repeat dose study appears sufficient for impurity qualification; however, the adequacy of the study and the qualification of the impurities will be determined at the time of the NDA review. Also see the response to Question 7.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

2. 4 Clinical

Question 9: *Does the Agency concur that the proposed in vitro pharmacodynamic study to compare the proteasome inhibition activity of MAIA's product and the listed drug is adequate to serve as the appropriate bridging study and provide scientific data in support of the biowaiver request?*

FDA Response to Question 9:
Your proposed comparative in vitro pharmacodynamic study to compare proteasome inhibition appears appropriate as a bridging study. Also see the response to Question 10 regarding the biowaiver request.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Question 10: *Does the Agency agree that no bioequivalence (pharmacokinetic) study is required to support the NDA?*

FDA Response to Question 10:
We consider that for the IV route, it could be feasible to establish the "bridge" between the proposed drug product and the LD using in vitro comparative physiochemical data, data from in vitro experiments, and published literature results regarding the effects of the difference in the excipients on the disposition kinetics of bortezomib in human subjects. Noted that the adequacy of the overall information/data supporting the bridge between the proposed drug product and the LD will be made at the time of NDA review. In addition, be aware that if the submitted information is not deemed adequate, data from a bioequivalence study evaluating the proposed drug product and the LD will be required to support the approval of the proposed drug product following the IV route of administration.

(b) (4)

Question 11: *Does the Agency agree that no additional studies are necessary to demonstrate that MAIA's product has the same clinical safety and efficacy as the listed drug VELCADE?*

FDA Response to Question 11:
The Agency cannot confirm if additional clinical studies will be needed to support the intended 505(b)(2) submission and approval at this time. The need for additional clinical studies will be a review issue. Also see the response to Question 10.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

2.5 General

Question 12: *Based on the NDA Table of Contents included in Attachment 2, are there any other items that the Agency requires for filing and approval of the NDA?*

FDA Response to Question 12:
The proposed product would likely trigger PREA. Submit the waiver request in an initial pediatric study plan (iPSP) 210 days prior to NDA submission, refer to the PREA Requirements subsection below.

See also the response to Question 10.

Discussion:
The Sponsor accepted FDA's response, no discussion occurred.

Additional CMC Comments for the proposed NDA:

1) Stability studies of drug product: Submit stability data from 3 distinct batches of each strength using different drug substance lots under upright and inverted orientations. Matrixing and bracketing are allowed. For details of stability recommendation follow ICH Q1A(R2) and related ICH stability guidance.

   Discussion:
   The Sponsor accepted FDA's response, no discussion occurred.

2) In vitro studies: Include comparative physico-chemical properties of proposed and listed drug product after dilution prior to administration. The monitored properties may include: pH, osmolality, physico-chemical and microbiological stability. The physical stability may be determined by comparison of the assay values of un-filtered and filtered [redacted (b) (4)] samples.

   Discussion:
   [redacted (b) (4)]

   FDA clarified that the comment 2 is applicable if dilution of the drug product is necessary prior to administration.

3) Extractable/leachable: Submit the leachable and extractable information for the container/closure system and all product contact parts of manufacturing equipment [redacted (b) (4)]

   Discussion:
   The Sponsor accepted FDA's response, no discussion occurred.

3.0 OTHER IMPORTANT MEETING 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.[2]

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

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 FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[3] 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]

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.

[3] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[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 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.

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions "shall be submitted in such electronic format as specified by [FDA]." FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.[7]

[7] http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format--- Standardized Study Data.* This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, Study Data Technical Conformance Guide,[8] as well as email access to the eData Team (cder-edata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page[9] that provides specifications for Sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND Sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND Sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov.[10] For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA

[8] https://www.fda.gov/media/88173/download
[9] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[10] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber

supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the phase 3 trials. The FDA Study Data Technical Conformance Guide[11] (Section 7.2 eCTD Sample Submission pg. 30) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site.[12] When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.[13]

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND Sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources[14] and the CDER/CBER Position on Use of SI Units for Lab Tests website.[15]

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

[11] https://www.fda.gov/media/88173/download
[12] https://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[13] https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber
[14] http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm
[15] https://www.fda.gov/media/109533/download

Guidance will be subject to rejection. For more information please visit FDA.gov.[16]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for 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 *for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[17]

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.”

[16] http://www.fda.gov/ectd
[17] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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)				

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).[18] 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.[19]

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 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.

[18] 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.
[19] http://www.regulations.gov

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.

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's response to the Agency's Meeting Preliminary Comments is appended to these minutes.

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This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

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