# CENTER FOR DRUG EVALUATION AND RESEARCH

***APPLICATION NUMBER:***

# 761231Orig1s000

# ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 135128

**MEETING MINUTES**

mAbxience, S.L.
Attention: Ravi S. Harapanhalli, PhD
Senior Vice President, Global Regulatory Affairs
Amneal Pharmaceuticals
21 Colonial Drive
Piscataway, NJ 08854

Dear Dr. Harapanhalli:

Please refer to your Pre-Investigational New Drug Application (PIND) file for MB02.

We also refer to the teleconference between representatives of your firm and the FDA on February 1, 2021. The purpose of the meeting was to discuss the content and format of the proposed Biologics License Application (BLA).

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, call me at (301) 796-0704.

Sincerely,

*{See appended electronic signature page}*

Gina M. Davis, M.T.
Senior Regulatory Health Project Manager
Division of Regulatory Operations - Oncologic Diseases for DO3
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

# MEMORANDUM OF MEETING MINUTES

| | |
|---|---|
| **Meeting Type:** | Biosimilar |
| **Meeting Category:** | BPD Type 4 |
| **Meeting Date and Time:** | February 1, 2021 from 3:00 PM – 4:00 PM |
| **Application Number:** | 135128 |
| **Product Name:** | MB02 |
| **Indication:** | MB02 is being developed for the same indications as approved for US-licensed Avastin |
| **Sponsor/Applicant Name:** | mAbxience, S.L. |
| **Regulatory Pathway:** | 351(k) of the Public Health Service Act |

**Office of Oncologic Diseases**
Division of Oncology 3 (DO 3)
Lola Fashoyin-Aje, M.D., MPH, Deputy Director, DO3
Sandra Casak, M.D., Medical Team Lead, DO3
Margaret Thompson, M.D., Medical Officer, DO3

Division of Hematology Oncology Toxicology (DHOT)
Matthew Thompson, Ph.D., MPH, Nonclinical Team Lead (acting), DHOT
Dubravka Kufrin, Ph.D., Nonclinical Reviewer, DHOT

**Office Clinical Pharmacology**
Division of Cancer Pharmacology I (DCP I)
Salaheldin Hamed, Ph.D., Clinical Pharmacology Reviewer, DCPI

Division of Cancer Pharmacology II (DCP II)
Edwin Chow, Ph.D, Clinical Pharmacology Reviewer DCPII

**Office of Biostatistics**
Division of Biostatistics V (DB V)
Joyce Cheng, PhD, Team Lead, DBV
Abhishek Bhattacharjee, Ph.D., Statistics Reviewer, DB V

**Office of Biotechnology Products (OBP)**
OBP Immediate Office
Marlene Schultz-DePalo, M.S., M.A., RAC

Division of Biotechnology Review and Research-I (DBRRI)
Rachel Novak, Ph.D., Review Chief and Product Quality Team Lead, DBRRI
Lymarie Maldonado-Báez, Ph.D., Product Quality Reviewer, DBRRI

**Office of Therapeutic Biologics and Biosimilars**
Immediate Office
Emanuela Lacana, Ph.D, Deputy Director

Scientific Review Staff (SRS)
Stacey Ricci, Sc.D., Director, SRS
Cristina Ausin, Ph.D., Scientific Reviewer, SRS
Michelle Luo, M.D., Ph.D, Scientific Reviewer , SRS
Sarah Brown, Policy Analyst, SRS
Tyree Newman, Senior Regulatory Health Project Manager, SRS

**Office of Regulatory Operations**
Division of Regulatory Operations, (DOR)
Gina Davis, M.T., Senior Regulatory Health Project Manager, DOR

**SPONSOR ATTENDEES**

**mAbxience, S.L.**

Ayman Ibrahim, Global Head, Regulatory Affairs
Bastian Baeumer, Senior Manager, Regulatory CMC
Laxmi Adhikary, Chief, Scientific Officer
Susanna Millan, Medical Director
Felicitas Bullo, Medical Advisor
Marie Elise Beydon, Team Leader, R&D

(b) (4)

**Amneal Consulting**
Ravi S. Harapanhalli, PhD Senior Vice President, Global Regulatory Affairs
Srinivas Kone PhD, Senior Vice President, Head of Scientific Affairs, Global R&D, Generic Division
(b) (4) Consultant
(b) (4) onsultant
, Consultant

**BACKGROUND**

On October 29, 2020, mAbxience submitted a biosimilar product development (BPD) Type 4 meeting request to discuss the content and format of a proposed 351(k) Biologics License Application (BLA) for MB02, a proposed biosimilar to US-licensed Avastin (bevacizumab).

According to the Sponsor, MB02 is a humanized IgG1κ monoclonal antibody that binds selectively to the human vascular endothelial growth factor (VEGF). MB02 is being developed to have the same dosage form and strengths (Injection: 100 mg/4mL (25 mg/mL) and 400 mg/16 mL (25 mg/mL) in a single-dose vial) as US-licensed Avastin. mAbxience plans to seek marketing approval of MB02 for the same indications for which US-licensed Avastin (bevacizumab) is approved.

**Regulatory History**

On June 30, 2017, mAbxience and FDA held a BPD Type 2 meeting to discuss the proposed development program for MB02. Specific topics under discussion included the adequacy of the proposed 3-way comparative analytical assessment between MB02, US-licensed Avastin, and EU-approved Avastin in support of a proposed 351(k) BLA; the adequacy of the nonclinical program to support the proposed BLA; and the adequacy of the proposed comparative clinical study (CCS) in patients with non-small cell lung cancer (NSCLC) to support the proposed BLA.

On December 17, 2017, FDA issued an advice and information letter regarding the similarity margin proposed for the CCS, Study MB02-C-02-1.

On October 4, 2018, a BPD Type 2 meeting was held to discuss Chemistry, Manufacturing and Controls (CMC) issues raised during the meeting held on June 30, 2017, the investigations performed, the proposed actions implemented, and the newly generated comparative analytical data as well as the final protocols of the clinical studies.

On September 30, 2019, FDA issued written responses in response to the July 1, 2019 meeting request to questions related to differences in impurities (%HHL) observed between MB02 and US-licensed Avastin. FDA encouraged mAbxience to implement any process changes deemed necessary to ensure the manufacture of a product that is highly similar to US-licensed Avastin prior to submission of a 351(k) BLA.

On October 14, 2020, a BPD Type 2 meeting was held to discuss the adequacy of the CMC and clinical development program for MB02. FDA reiterated that demonstration that MB02 is highly similar to US-licensed Avastin, and the establishment of the analytical component of the scientific bridge between MB02 , US-licensed Avastin, and EU-approved Avastin is based on review of the totality of data and information submitted to the 351(k) BLA. FDA stated that mAbxience's proposed approach with respect to pursing a marketing application appeared reasonable; however, ultimately, whether additional clinical studies would be needed would be a review issue.

On October 1, 2021, mAbxience submitted an initial pediatric study plan (iPSP) request, currently under review.

## Clinical

A brief summary of the MB02 clinical studies intended to support the demonstration that there are no clinically meaningful differences between MB02 and US-licensed Avastin is below:

• Study MB02-A-05-18 "A Randomised, Double-Blind, Three-Arm, Single Dose, Parallel Study To Compare the Pharmacokinetics, Safety and Immunogenicity of MB02 (Bevacizumab Biosimilar Drug), US-licensed Avastin® and EU-approved Avastin® in Healthy Male Volunteers". In this study, healthy male volunteers were randomized 1:1:1 (randomization stratified by weight, stratum 1 60- <77.5 kg and stratum 2 ≥ 77.5- ≤ 95 kg) to receive a single 3 mg/kg dose of MB02, EU-Avastin or US-Avastin. The primary endpoints were the 3-way comparison of the area under the serum concentration-time curve (AUC) from time 0 to infinity (AUC[0-∞]) and the maximum observed serum concentration (Cmax). Thirty-eight subjects were enrolled in each arm. mAbxience states that the pairwise comparisons of MB02 versus EU Avastin, MB02 versus US-Avastin, and EU-Avastin versus US-Avastin were similar for the primary endpoints, as the 90% CI for the geometric LS means ratios were fully contained within the predefined limits of 0.80 to 1.25.

• Study MB02-C-02-17, "STELLA - A Randomized, Multicenter, Multinational, Double-Blind Study to Assess the Efficacy and Safety of MB02 (Bevacizumab Biosimilar Drug) Versus Avastin® in Combination with Carboplatin and Paclitaxel for the Treatment of Subjects with Stage IIIB/IV Non-squamous Non-Small Cell Lung Cancer (NSCLC)". Patients were randomized 1:1 to receive chemotherapy (carboplatin AUC 6 and paclitaxel 200 mg/m$^2$ ) plus MB02 or EU-Avastin 15 mg/kg every 3 weeks up to 6 cycles. After 6 cycles patients could have continued to receive MB02/EU-Avastin monotherapy treatment every 3 weeks until evidence of disease progression or until unacceptable toxicity. The primary endpoint was objective response rate (ORR) by RECIST 1.1 at Week 18 as assessed by an independent radiological review committee (IRC). A total of 627 patients were randomized to the MB02 arm (315 patients) or EU-Avastin (312 patients) and included in the ITT population; a total of 621 patients received treatment. The IRC assessment of ORR in the ITT population was 40.3% (95% CI: 34.9 to 46.0) in the MB02 arm and 44.6% (95% CI: 39.0 to 50.3) in the EU-Avastin arm, with a RR of 0.910 (90% CI: 0.780 to 1.060), within the boundaries of the similarity margin predefined by the FDA (0.73, 1.36).

mAbxience states that in line with the structure outlined in ICH M4 "Common Technical Document" and CDER's standards, the BLA will be submitted as Electronic Common Technical Document (eCTD) format and the data will be submitted in the standardized SDTM/ADaM format.

According to the meeting package, mAbxience regards the PREA requirements covered with the iPSP submission (dated October 1, 2020) and that "due the established approach for a bevacizumab biosimilar product the pending approval of the iPSP is considered a formality and does not preclude the application to be filed". mAbxience expects to submit the agreed iPSP during the review of the proposed BLA.

FDA sent Preliminary Comments to mAbxience on January 27, 2021.

**FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by mAbxience and as the Agency's thinking evolves on certain statutory provisions regarding applications submitted under section 351(k) of the Public Health Service Act (PHS Act).**

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## SPONSOR SUBMITTED QUESTIONS AND FDA RESPONSES

1. With regard to the content and format of the final BLA submitted under 351 (k) of the PHS act does the Agency agree with mAbxience' position that:

   a. The structure fulfils FDA's requirements for a complete application?

      **FDA Response:** Based upon the proposal included in the briefing document the proposed content appears to support a complete application; however, a final determination will be made during the filing review.

      mAbxience's preliminary response: mAbxience thanks FDA for the response and acknowledges that the final determination of the content will be made during filing review.

      **Discussion during the teleconference:** FDA acknowledged mAbxience's response and no further discussion occurred.

   b. The analytical characterization data and reports are located in the eCTD structure according to FDA's expectations?

      **FDA Response:** The proposed content and format for the analytical characterization data and reports, including their proposed location in the eCTD structure appears acceptable. However, the final determination on the adequacy of the comparative analytical data submitted to support a demonstration that MB02 is highly similar to US-licensed Avastin will be made from an assessment of the totality of the data and information included in a 351(k) BLA.

      mAbxience's preliminary response: mAbxience thanks FDA for the response and acknowledges that the final determination of the content will be made during filing review.

      **Discussion during the teleconference:** FDA acknowledged mAbxience's response and no further discussion occurred.

c. The clinical files and data format fulfil FDA's requirements for the BLA assessment?

**FDA Response:** Based upon the summary provided in Annex 1 of the meeting package, the proposed content of the planned BLA appears acceptable; however, a final determination will be made during the filing review.

FDA agrees with mAbxience's plan to provide the study data in the standardized SDTM/ADaM format.

However, FDA was unable to locate the sample data that is referenced by mAbxience to have been submitted in parallel with this meeting request; FDA cannot therefore comment on this data's conformance to standards, structure, and format.

mAbxience's preliminary response: In line with FDA's recommendation sample data was sent for review December 11th, 2020 to ensure conformance to standards, structure, and format before submission of the final application.

mAbxience would appreciate FDA's feedback on the review status and foreseen confirmation of conformance.

Sample data was sent for FDA's conformance check December 11th, 2020 via text environment and received the following acknowledgement of receipt.

Center for Drug Evaluation and Research (CDER)
U.S.Food and Drug Administration

SUBJECT:ACKNOWLEDGEMENT OF SUBMISSION RECEIPT
SENT FROM:FDA ELECTRONIC SUBMISSIONS GATEWAY (ESG)
PREPROD

Account Name:Amneal Pharmaceuticals PA
Message (b) (4)
CoreId:

File Count: 107
Directory Count: 19

DateTime Receipt Generated: 12-11-2020, 21:15:58
Time Zone: Eastern

**Discussion during the teleconference:** FDA stated that the submission was not received and requested that mAbxience re-submit this information. mAbxience asked whether it would be acceptable to submit the BLA without

FDA review of the submission. FDA stated that it is mAbxience's risk to submit without FDA agreement.

In addition, FDA has the following requests:

i. Submit a stand-alone document in Module 2 that provides the justification for extrapolation to other indications.

mAbxience's preliminary response: mAbxience acknowledges FDA's comment and proposes to present the justification for extrapolation as dedicated attachment to Module 2.5. Does the FDA agree?

**Discussion during the teleconference:** FDA agreed that this proposal was acceptable.

ii. The ADAM datasets ADAE, ADLB and ADVS must include a flag identifying events occurring during the combination chemotherapy/MB02-EU-Avastin period.

mAbxience's preliminary response: mAbxience acknowledges FDA's comment and would like to ask whether the following specification with variables currently included could be applicable for identifying monotherapy:

(b) (4)

Does the FDA agree?

**Discussion during the teleconference:** mAbxience acknowledged that the proposed variables would not adequately identify adverse events or laboratory data in patients who received less than 6 cycles of combination therapy before switching to the monotherapy portion. FDA and mAbxience agreed that the datasets should contain a flag identifying events occurring during the combination chemotherapy/MB02-EU-Avastin period. mAbxience agreed to provide the information in BLA submission.

iii. Include an .xpt or .xlxs file with the financial disclosure information.

mAbxience's preliminary response: mAbxience acknowledges FDA's comment and confirms that the financial disclosure information will be provided. Does FDA agree that pdf format is acceptable?

**Discussion during the teleconference:** FDA explained that PDF format is acceptable and clarified that in addition to the PDF, mAbxience should

submit the data in an excel format. mAbxience will consider the request from FDA.

iv. Provide SAS programs used to create the derived datasets for the efficacy endpoints and the SAS programs used for efficacy data analysis. If the SAS programs use any SAS macro, provide all necessary macro programs.

mAbxience's preliminary response: mAbxience acknowledges FDA's comment and confirms that the recommendation will be considered.

**Discussion during the teleconference**: FDA acknowledged mAbxience's response and no further discussion occurred.

2. With regard to the final BLA submitted under 351 (k) of the PHS act does the Agency agree with mAbxience' position that the studies to support a demonstration of biosimilarity are clearly identified?

**FDA Response:** FDA agrees to mAbxience's proposal to submit studies MB02-A-05-18 MB02-C-02-17, "STELLA" to support the comparative clinical and PK assessment in the proposed BLA.

Regarding the proposed comparative analytical assessment studies, the overall testing strategy depicted in Figure 1 in the briefing package, and the general comparability approach of the selected product quality attributes, appears appropriate. However, the adequacy of data to support the comparative analytical assessment, including data to support comparability between the MB02-SP and MB02-DM lots and the establishment of the three-way analytical component of the scientific bridge between MB02, US-licensed Avastin and EU-approved Avastin, will be a review issue and will be determined based on the totality of the information submitted in a 351(k) BLA.

FDA also refers to the preliminary comments dated July 24, 2017, (e.g., regarding the data needed to support the scientific bridge), October 19, 2018 and October 20, 2020 (e.g., regarding observed differences between MB02 and US-licensed Avastin, including but not limited to differences in HHL impurities) for additional recommendations.

mAbxience's preliminary response: mAbxience would like to give FDA confirmation that in case supportive data on residual uncertainty is deemed necessary mAbxience will be happy to provide additional evidence during the review cycle. Does the FDA concur?

**Discussion during the teleconference:** FDA stated that clarifying information would be requested as needed during the review of the BLA. FDA emphasized

that the BLA should be complete upon submission, meaning that all studies, and all reports should be complete with no pending results.

3. With regard to the PREA requirements for a bevacizumab biosimilar product does the Agency agree that:

   a. the 351 (k) BLA can be submitted and filed with the iPSP approval process still ongoing?

      **FDA Response:** FDA reiterates previous advice that mAbxience should not submit a marketing application before the FDA has confirmed agreement on the iPSP. Note that this advice has been previously conveyed to mAbxience in the October 14, 2020 meeting minutes as a post-meeting addendum.

      mAbxience's preliminary response: FDA's response is acknowledged and mAbxience confirms that the BLA will be submitted only after agreement on the iPSP is reached.

   b. the endorsed iPSP can be amended to the application during the review process?

      **FDA Response:** Refer to FDA response above.

      mAbxience's preliminary response: mAbxience would appreciate FDA's feedback on the review status and foreseen timing final endorsement.

      **Discussion during the teleconference:** FDA clarified that a letter of agreement/no agreement will be issued 120-days after submission of the original iPSP.

## ADDITIONAL QUESTION

mAbxience

4. Considering that positive opinion was received from CHMP (EU) recently, does FDA see additional value for the review process if the CHMP assessment report is attached to Module 1 of the final 351(k) BLA?

   **Discussion during the teleconference:** FDA stated that while it would be mAbxience's decision to submit the CHMP assessment report, FDA's review of the marketing application is unlikely to be influenced by the decisions of other regulatory authorities.

## OTHER TOPICS

| Topic | Approach |
|---|---|
| **Labeling** | The applicant will follow list of indications from other approved biosimilars such as MVASI™ and Zirabev™<br><br>**Discussion during the teleconference:** FDA clarified that labeling should be based on the US-licensed Avastin label and not the biosimilar labels. FDA requested a clean and track-ed version label based on current US-licensed Avastin label. Labeling should reflect the indications for which the applicant is seeking licensure. Refer to FDA guidance for Industry *Labeling for Biosimilar Product* (July 2018). FDA noted that FDA will not be able to license a biosimilar for an indication protected by orphan exclusivity until the expiration of that exclusivity. The Agency referred the applicant to FDA draft guidance for industry, *Biosimilars and Interchangeable Biosimilars: Licensure for Few Than All Conditions of Use for Which the Reference Product Has Been Licensed* for information about timing considerations for submission of a 351(k) BLA and unexpired exclusivity. |
| **Nonproprietary Name** | The applicant will provide up to 10 proposed non-meaningful suffixes for FDA's evaluation<br><br>**Discussion during the teleconference:** mAbxience said they would follow FDA guidance. FDA agreed with mAbxience's proposal to follow the guidance. |
| **Tradename** | The applicant will propose the global tradename ALYMSYS for FDA's evaluation<br><br>**Discussion during the teleconference:** FDA acknowledged sponsor's position and had no input to provide at this time. |
| **Manufacturing Schedule** | The applicant will include an estimated manufacturing schedule of MB02-DM at the DS and DP manufacturing site for potential pre-approval inspection dates<br><br>The tentative dates will be starting from June 2021 onwards.<br><br>Can FDA give an estimate if on-site pre-approval inspections will be feasible or if FDA plans to conduct remote inspections? |

| | |
|---|---|
| | **Discussion during the teleconference:** FDA explained that the expectation is for mAbxience to submit a manufacturing schedule as part of the BLA submission and to be in production and ready for an on-site inspection during review of the BLA. Upon submission of the BLA, FDA will be in communication with mAbxience concerning the planning and scheduling of the inspectional activities, as appropriate. Additionally, the manufacturing schedule provided should include details of the timing of specific unit operations. |
| **Applicant** | Amneal will be the applicant in the BLA although mAbxience is the pre-IND holder.<br><br>mAbxience will provide an authorization letter (licensor-licensee agreement) for Amneal to be attached to Module 1. Does the FDA agree?<br><br>**Post-meeting comment:**. FDA agrees that Amneal may submit a letter of authorization to cross-reference the mAbxience IND under module 1.<br><br>Amneal as applicant will be responsible to cover the BLA maintenance fee. Is it still appropriate that mAbxience covers the submission fee as pre-IND holder?<br><br>**Post Meeting Comment:** FDA recommends that mAbxience contact the BsUFA user fee staff at CDERCollections@fda.hhs.gov for a response to the question related to BsUFA Fees. |

## DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to "the Program" under BsUFA II. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions regarding the approach to developing the content for risk evaluation and mitigation strategies (REMS), where applicable, patient labeling (e.g., Medication Guide and Instructions For Use) and, where applicable, the development of a Formal Communication Plan. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components

of the application are expected to be included in the original application and are not subject to agreement for late submission.

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

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

Finally, in accordance with the BsUFA II agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement.

Information on the Program is available at FDA.gov.[1]

## PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (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 a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(l) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit a iPSP as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages

[1] https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm

the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.16 in the draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act*. For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[2]. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended

**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)[3] and 201.57[4] including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[5] and Pregnancy and Lactation Labeling Final Rule[6] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.[7]

In addition, you should review the FDA guidance for industry *Labeling for Biosimilar Products* (July 2018).

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

**NONPROPRIETARY NAME**

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

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

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

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[3] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1

[5] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm 084159.htm

[6] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

[7] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

## 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.[8]

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 *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[9]

## 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).

[8] http://www.fda.gov/ectd
[9] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

## MANUFACTURING FACILITIES

All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Manufacturing and testing facilities will be subject to the CGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection, 2-7 months after the submission of the BLA. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the BLA to facilitate planning of pre-license inspections during the review cycle. For a BLA submission, when providing the preliminary manufacturing schedule, we encourage you to bear in mind the anticipated time frame for the late-cycle meeting for applications subject to "the Program" under BSUFA II.

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, BLA 012345, Establishment Information for Form 356h."

| Site Name | Site Address | Federal Establishment Indicator (FEI) or Registration Number (CFN) | Drug Master File Number (if applicable) | Manufacturing Step(s) or Type of Testing [Establishment function] |
|---|---|---|---|---|
| (1) | | | | |
| (2) | | | | |

Corresponding names and titles of onsite contact:

| Site Name | Site Address | Onsite Contact (Person, Title) | Phone and Fax number | Email address |
|---|---|---|---|---|
| (1) | | | | |
| (2) | | | | |

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[10] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[11]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

**OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS**

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated 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*.

[10] https://www fda.gov/media/84223/download

[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

**RECOMMENDATIONS FOR FORMATTING OF CLINICAL PHARMACOLOGY SUBMISSIONS FOR APPLICATIONS**

If you are planning to include a clinical pharmacology study as part of your 351(k) BLA marketing application, we have the following general best practice recommendations for you to keep in mind as you prepare your submission, including guides for formatting your submission.

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:

    a. Include the rationale for the selected dose used in the PK (and PD similarity, when applicable) study(ies) in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).

    b. Include a summary evaluation of the impact of immunogenicity on the activity (e.g., efficacy/PD), safety, and pharmacokinetics, as is applicable, for the studies included in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).

    c. Present the PK (and PD, when applicable) parameter data as geometric mean with coefficient of variation, mean ± standard deviation, and median with range in the study reports and throughout the BLA.

    d. Provide analysis data sets for all concentration-time and derived PK (and PD, when applicable) parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.

2. Include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:

    a. Site number

    b. Principal investigator

    c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)

    d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.

Submit all PK (and PD, when applicable) bioanalytical method validation reports and bioanalytical study reports.

In addition, complete the summary tables using the templates available in the 'Bioanalytical Methods Templates' Technical Specifications Document[12] to provide the information regarding the bioanalytical methods for pharmacokinetic and/or biomarker assessments used in clinical pharmacology studies and their life-cycle information pertaining to the studies. Submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1

[12] https://www.fda.gov/media/131425/download

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

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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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/s/

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GINA M DAVIS
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