CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761406Orig1s000
761406Orig2s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 153118

MEETING MINUTES

Biocon Biologics UK Limited
c/o Biocon Biologics Inc.
Attention: Yoganandareddy Gotluru
General Manager, Global Regulatory Affairs
245 Main St, 2nd Floor
Cambridge MA, 02142

Dear Yoganandareddy Gotluru:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Bmab1200.

We also refer to the meeting/videoconference between representatives of your firm and the FDA on October 26, 2023. The purpose of the meeting was to discuss the content and format of a biologic license application.

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

If you have any questions, contact Sascha Randolph, Regulatory Project Manager/Executive Program and Project Management Staff at (301)796-8546 or Sascha.Randolph@fdah.hhs.gov.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Acting Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
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: October 26, 2023; 10:30 AM. EST.
Meeting Location: Videoconference

Application Number: IND 153118
Product Name: Bmab1200

Indication: Bmab 1200 is being developed for the same indications as those approved for US-licensed Stelara (ustekinumab)

Sponsor Name: Biocon Biologics UK Limited
Regulatory Pathway: 351(k) of the Public Health Service Act

Meeting Chair: Shari Targum, MD
Meeting Recorder: Sascha Randolph, RDH

FDA ATTENDEES

Shari Targum MD., MPH, FACP, FACC, Acting Director, Division of Dermatology and Dentistry (DDD).
Snezana Trajkovic MD, Clinical Team Leader, DDD.
Felisa Lewis MD, Clinical Reviewer, DDD.
Chinmay Shukla Clinical Pharmacology PhD, Scientific Lead, Division of Inflammation, and Immune Pharmacology (DIIP).
Hyewon Kim PhD, Clinical Pharmacology Reviewer, DIIP.
Somesh Chattopadhyay PhD, Biometrics Team Leader, Division of Biometrics VIII (DBVIII).
Frances Andrada MSN, CRNP, FNP-BC, CNRN, Scientific Reviewer, Office of Therapeutic Biologics and Biosimilars (OTBB).
Cristina Ausin Ph.D., Scientific Reviewer, OTBB.
Asha Hewarathna, Product Quality Reviewer, Division of Biotechnology Review and Research III (DBRRIII), Office of Biotechnology Products (OBP).
Sascha Randolph, RDH, BSDH, Regulatory Project Manager, DDD
Susan Rhee, PharmD, Chief of Project Management Staff, Division of Regulatory Operations – Immunology and Inflammation (DRO-II), DDD

SPONSOR ATTENDEES

Raja Sekhar Vanga, MSc, Head, Global Regulatory Affairs
Yoganandareddy, MSc, Therapeutic Area Head, Inflammation
Sneha Padiyar, MSc, Global Regulatory Lead for Bmab1200

Anuj Goel, PhD, Chief Scientific Officer
Anita Krishnan, PhD, Head of Analytical Sciences
Dinesh Baskar, PhD, Global Portfolio Lead
Harish V. Pai, Ph.D, Lead, Analytical Sciences
Sucharitha Jayakar, M.S., Lead, Process Sciences
Sandeep Nilkanth Athalye, M.D., Chief Development Officer
Uwe Gudat, M.D., Chief Medical Officer
Elena Wolff-Holz, M.D., Global Head of Clinical Development, Medical
Subramanian L., M.D., Head Clinical Science, CDMA
Gursharan Singh, MBBS., Ph.D., Medical Lead, CDMA
Sarika Deodhar, M.D., Medical Lead, CDMA
Ashwani Marwah, MSc., Lead, Biostatistics, CDMA
Sivanandam K., Head-Program Management

1.0 BACKGROUND

Purpose of Meeting:
The purpose of the meeting is to discuss the format and content of a complete application for an original biosimilar biological product application under the Program submitted under 351(k) of the PHS Act.

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 Biocon Biologics UK Limited 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).

FDA sent Preliminary Comments to Biocon on October 19, 2023. FDA responses and discussions from the videoconference held on October 26, 2023, are indicated below.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing and Controls (CMC)

Question 1:
At the time of 351(k) BLA submission, Biocon Biologics intends to submit 3 months of available long term (5ºC±3ºC), accelerated (25±2ºC/60±5%RH) and stress stability (40°C±2°C/75%±5%RH) data from Bmab1200 DP process validation (PV) batches. This will be supported by 24 months long term stability data from Bmab1200 SC DP development/clinical batches and 6 months long term and accelerated stability data of Bmab1200 IV DP development batch.

Biocon Biologics proposes to submit additional stability data as a simple stability update within 30 days of submission (in accordance with Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2023 through

2027), and during review cycle (before D120) of the BLA as outlined in the company position below.

Does the Agency agree with Biocon Biologics proposal?

FDA Response to Question 1:
Your plan to submit 3 months of long-term stability data for process validation (PV) batches and 24 months of long-term stability data from Bmab1200 SC DP development/clinical batches and 6 months long term stability data from Bmab1200 IV DP development batch at the time of BLA submission, and submit a simple stability update with 6 months of long term and accelerated data for PV batches of both presentations, followed by 12 month data from 130 mg/26 ml IV vial development batches before day 120 of the BLA review cycle appears reasonable. Note that whether the submitted non-PV batch data can be used to establish shelf life of DP in both PFS and vial presentations will be a review issue based on the totality of information and data provided in the BLA submission (e.g., whether all relevant comparability of DS and DP is successfully established, the container closure system of non-PV batches is representative of commercial DP, etc.).

Also refer to FDA's written response to your BPD Type 2A meeting requested on August 31, 2023, regarding leveraging stability data between the different presentations for shelf-life establishment of the DP.

Meeting Discussion:
None.

Question 2:
Biocon Biologics is conducting shipping validation study for Bmab1200 SC PFS and vial presentations as well as Bmab1200 IV vial presentations. A study protocol is in place for all the SKU's. The study protocol will be submitted as a part of BLA. The shipping validation study will be ongoing in parallel to BLA review. The shipping validation study data will be submitted during BLA review.

FDA Response to Question 2:
It is acceptable to submit the shipping validation protocol and shipping validation data at the initial BLA submission and during BLA review cycle by D120, respectively.

The shipping validation study conditions should be representative of the commercial shipping conditions. Results from these studies (including assessment of product quality attributes, container closure integrity, device functionality, etc) should be provided to the BLA to support that the product quality, device performance and microbial attributes remain intact after exposure to shipping conditions during commercial shipping.

Meeting Discussion:
None.

Question 3:
Biocon Biologics intends to have the same label claim for Bmab1200 130 mg/26 mL IV vial as its reference product Stelara® IV for intravenous route of administration (patient weight-based dose for ustekinumab IV in infusion bag with 0.9% Sodium chloride or alternatively infusion bag with 0.45% sodium chloride). Considering similarity will be established at physio-chemical and biological level, Biocon is of the opinion that no additional compatibility is required to claim intravenous route application through infusion system on the label.

Does the Agency agree with the proposed approach for not conducting any compatibility study with Bmab1200 130 mg/26 mL IV vial for intravenous infusion?

FDA Response to Question 3:
Your approach for not conducting a compatibility study for intravenous infusion of Bmab1200 130 mg/26 mL IV vials may be acceptable in this case if the proposed formulation (qualitative and quantitatively) and labeled in-use conditions of Bmab1200 and the reference product are the same, the data provided support a demonstration that Bmab1200 is highly similar to US-licensed Stelara, and residual risks from differences in quality attributes not covered by comparative analytical assessment, i.e., process/product related impurities, particulate matter (visible and subvisible particles), leachables, excipient grade and source etc., are adequately mitigated to support stability and compatibility of diluted product under the recommended in-use conditions. A final determination will be made based on totality of information/data provided in your BLA submission.
Also note that appropriate microbial challenge studies should be performed to support storage of diluted product.

Meeting Discussion:
None.

2.2. Clinical

Question 4:
Biocon Biologics has conducted a Phase 3 safety and efficacy study in patients with moderate to severe plaque psoriasis for a duration of 28 week with primary efficacy end point at week 12 and re-randomization for patients in Stelara® arm at week 16 (1:1) to receive either Stelara® or Bmab1200 based on recommendations received from the Agency. The study was extended to week 52 to include Japanese Pharmaceuticals and Medical Devices Agency requirements. Biocon plans to submit the Phase 3, week 28 clinical study report for the BLA submission and approval.

Does the Agency agree to Biocon's proposal of submitting the Phase 1 clinical study report and 28-week clinical study report towards BLA submission?

FDA Response to Question 4:
For your initial BLA submission, you propose to submit the full data set for Study BM12H-NHV-01-G-01 (PK similarity study) and the clinical study report (CSR) and the efficacy, safety, immunogenicity, and pharmacokinetics (PK) data for all subjects through Week 28 for Study BM12H-PSO-03-G-02 (comparative clinical study). The full data set and final CSR through Week 52 for Study BM12H-PSO-03-G-02 will be submitted at the 120-day safety update. Your proposal is acceptable.

See Additional comments about content and format of Module 5.

Meeting Discussion:
None.

2.3. Regulatory

Question 5:
The development program of Bmab1200 SC and Bmab1200 IV is common. The Drug substance and manufacturing sites employed for Bmab1200 SC and Bmab1200 IV is same. Common package insert is developed for Bmab1200 SC and Bmab1200 IV in-line with the Reference product, Stelara. Considering the above factors, Biocon is planning to submit single BLA for Bmab1200 SC and Bmab1200 IV. Does the Agency agree with submission of Bmab1200, a proposed biosimilar to Ustekinumab subcutaneous administration and intravenous infusion as a single BLA?

FDA Response to Question 5:
Consistent with the Guidance for Industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees (December 2004), when the products are alike (biological products) in composition, a single original application is appropriate. This approach provides improved ability to manage the lifecycle of the product including subsequent labeling changes and related issues.

If your Bmab1200 SC and IV formulations are alike in composition, then we agree that a single application for both routes of administration (SC and IV) would be appropriate. Alternatively, you can submit information about the SC and IV formulations/compositions prior to submitting the application for our review.

Meeting Discussion:
The Agency explained that the information provided on Biocon's slide numbers 8 and 9 appears acceptable and the Agency does not oppose to Biocon submitting a single BLA.

Additional comments about content and format of Module 5:
Applications are expected to be complete at the time of original submission of the application. For your BLA submission we recommend that you include the following:

a) Submit the datasets for the above studies in CDSIC (both SDTM and ADaM) format. Submit datasets in SAS transport format (.xpt). The analysis datasets should include all variables needed for conducting the analyses included in the study report.

b) Include dataset documentation (define.xml) for tabulation and analysis datasets. The analysis dataset documentation should include sufficient detail, such as definitions or descriptions of each variable in the data set, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables.

c) Include statistical programs for the key primary and secondary analyses, including programs for data imputations.

d) Include all protocols (including protocol amendments) and statistical analysis plans.

e) Include an annotated case report form. If any data is collected via electronic data capture rather than directly on the CRF, include annotated screen shots of the electronic data capture system.

f) Provide the following in your Integrated Summary of Safety (ISS):

1. Analyses of treatment emergent adverse events (TEAEs) to include all TEAEs, treatment-related TEAEs, serious TEAEs, discontinuations due to TEAEs, and Adverse Events of Special Interest (AESIs).

2. Adverse event tables with incidence rate of ≥ 1% regardless of causality.

3. Adverse reaction tables (adverse reactions are defined as those AEs with possible or probable causality) with incidence rate of ≥ 1%. We recommend that you pool related preferred terms in your table (e.g., upper respiratory tract infection, nasopharyngitis, viral upper respiratory tract infection etc.).

4. For the active-controlled period, please include tables of raw incidence rates at ≥1% by treatment group. For the maintenance and extension phases after the single switch, please include a table of raw incidence rates at ≥1%.

5. Conduct an issue-based safety review of your product, provide a list of discussion on key potential safety issues identified during the development of your product. In addition, discuss any factors which impacted the appropriateness of the data and conclusions supported by your safety assessment, e.g., design issues, degree of missing data/handling of dropouts (if there is a targeted safety outcome), frequency/intensity of monitoring, and exposure in at-risk populations.

6. Evaluation of uncommon, rare, or unexpected events that may be possibly related to the study drug.

7. Electronic links to Case report forms (CRFs) and narratives.

8. In the narratives, include the date and study day in the discussion relating to the event(s). E.g., "The event happened on xx/yy/2021 (study day zz)." Also include how the onset of the event relates to exposure (number of doses and date of occurrence relative to most recent dose).

9. Line listings for all abnormal safety findings (e.g., adverse events, vital signs etc.)

10. Shift tables for all laboratory values and vital signs for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.

11. For laboratory data, please "flag" all laboratory values and vital signs that are outside of the reference ranges.

12. A worldwide safety update in addition to safety update report, if the product is approved in any other jurisdiction.

13. Provide safety analyses for the following subgroups:

    i. Race categories include Caucasian, African American, Asian, and Other

    ii. Age groups (18 to <65 and ≥65)

    iii. Ethnicity (Hispanic/Latino or not Hispanic/Latino)

    iv. Sex

    v. Baseline severity

vi. Any prior exposure to biologic products

vii. Provide Case Report Forms (CRF) for all deaths, serious adverse events, hypersensitivity reactions, discontinuations due to adverse events, and severe injection site reactions. Other eCRFs should be readily available upon request. However, if the eCRFs are located in the Clinical Study Report (CSR), then provide links to the eCRFs in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety, and ISS.

viii. Provide narratives for all deaths, serious adverse events (SAEs), subjects who discontinued the study agent due to adverse events (AEs), AEs of special interest, anaphylaxis/hypersensitivity reactions, and pregnancies. Narratives may be included in the CSRs with links to these narratives provided in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety, and ISS.

ix. In the 120-day safety update report (SUR), you should update the BLA application with new safety information learned about the product that may reasonably affect the conclusion of no clinically meaningful difference between your product and the reference product. Provide narratives in the SUR for all subjects who died, experienced SAEs, pregnancies and AESIs.

x. Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. The “coding dictionary” consists of a list of all investigators verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim). The Agency can provide recommendations regarding the pooling of certain preferred terms (e.g., viral upper respiratory tract infection and upper respiratory tract infection) to enhance your safety analysis if you submit your coding dictionary prior to completion of the safety analysis for your BLA.

xi. Include links to the full text version of any referenced articles.

xii. To facilitate review of the data, we recommend that your BLA submission include a summary of the trials in tabular form (See Table 1).

14. Provide a table with the following columns for each of the sites in the comparative clinical study:

i. Site number

ii. Principal investigator

iii. Location: City State, Country

iv. Number of subjects screened

v. Number of subjects randomized

vi. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)

vii. Number of protocol violations (Major, minor, including definition)

15. Marketing applications must include certain information concerning the compensation to, and financial interests of, any clinical investigator conducting clinical studies, including those at foreign sites, covered by the regulation. Refer to the guidance for industry *Financial Disclosure by Clinical Investigators: Guidance for Clinical Investigators, Industry, and FDA Staff*

Table 1.

Type of Study	Study Identifier	Objective(s) of the Study	Study Design and Type of Control	Test Product (s); Dosage Regimen; Route of Administration	Number Subjects Randomized / Analyzed for Safety	Healthy Subjects or Diagnosis of Subjects	Duration of Treatment	Study status; Type of Report/ Location [link to module]
Study Reports of Patient PK and Initial Tolerability Study Reports (Module 5.3.3.2)								
PK similarity								
Study Reports of Controlled Clinical Studies Pertinent to the Claimed Indication (Module 5.3.5.1)								
Clinical similarity								

Meeting Discussion on additional comments on Module 5:
The Sponsor requested clarification whether the Integrated Summary of Safety is requested for safety data of the PK similarity study and comparative clinical study and provided justification for not pooling the data for these two studies. They proposed presenting individual study safety data in the CSR and inclusion of the same in Module 2.7.4.

The Agency stated that the Integrated Summary of Safety (ISS) is a required element for marketing applications. The Sponsor should provide justification in the ISS for not pooling the data of these two studies.

Post Meeting Comment:
We remind you of the Advice/Information Request Letter sent on September 1, 2023 regarding the Agency's updated scientific thinking regarding the necessity of a switching study to support a demonstration of interchangeability for proposed ustekinumab interchangeable biosimilar products. If you intend to seek approval of Bmab1200 as interchangeable with US-licensed Stelara, you must include information in the application to address all statutory requirements, including information you consider relevant to assessing the risk, in terms of safety and diminished efficacy, of alternating or switching between your proposed interchangeable product and US-licensed Stelara, which may include reference to the product-dependent factors discussed in the guidance for industry *Considerations in Demonstrating Interchangeability With a Reference Product*. We also recommend including an assessment of why the comparative analytical and clinical data provided in the application support a low immunogenicity risk if a patient were to be switched between your proposed product and the reference product.

Additionally, please refer to the draft guidance for industry, *Labeling for Biosimilar and Interchangeable Biosimilar Products* (September 2023), and its accompanying Notice of Availability, 88 Fed. Reg. 63957 (September 18, 2023), regarding draft labeling. A final determination on the adequacy of the information submitted to support a demonstration of interchangeability will be determined during the review.

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

The original 351(k) application will be subject to "the Program" under BsUFA III. 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.

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 an initial pediatric study plan (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 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 additional information on

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

how you may fulfill the requirement for pediatric assessments or investigations under PREA, see question and answer I.16 in the guidance for industry, *Questions and Answers on Biosimilar Development and the BPCI Act*.

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.

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). As you develop your proposed PI, we encourage you to review the labeling review resources on the following websites:

- *Biological Products – Specific Labeling Resources*[5] which includes the guidance for industry*: Labeling for Biosimilar Products* (July 2018).
- *Prescribing Information Resources*[6]

For other prescription drug labeling resources such as those for FDA-approved patient labeling, carton and container labeling, labeling databases, and product databases, visit *FDA's Labeling Resources for Human Prescription Drugs* website.[7]

- 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

[2] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
[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] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources
[6] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources
[7] https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

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*.[8]

Prior to submission of your proposed PI, use the Selected Requirements for Prescribing Information (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.

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.

[8] 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.

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 III.

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[9] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[10]. 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*.

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

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.[11]

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.[12]

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

[11] http://www.fda.gov/ectd
[12] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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.

3. 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[13] 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.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

Sponsor inquired about the Agency's feedback related to Human Factors. FDA will provide an update in a separate correspondence.

5.0 ATTACHMENTS AND HANDOUTS

Sponsors slides attached.

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

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/

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