

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761343Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 148203

MEETING MINUTES

Alvotech hf.
c/o PharmaLex USA
Attention: Sheela J. Mitta
US Agent
1700 District Avenue, Suite 100
Burlington, MA 01803

Dear Ms. Mitta:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AVT04.

We also refer to the teleconference between representatives of your firm and the FDA on August 15, 2022. 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 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 Kimberle Searcy, Regulatory Project Manager at 240-402-4454.

Sincerely,

{See appended electronic signature page}

Shari L. Targum, MD, MPH, FACP, FACC
Deputy Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: August 15, 2022, 10:30-11:30 am EST
Meeting Location: Teleconference

Application Number: IND 148203
Product Name: AVT04

Proposed Indication: AVT04 is being developed for the same indications as US-licensed Stelara (ustekinumab)

Sponsor Name: Alvotech hf

Regulatory Pathway: 351(k) of the Public Health Service Act [for biologics]

Meeting Chair: Shari L. Targum, MD
Meeting Recorder: Kimberle Searcy, MPH

FDA ATTENDEES

Shari L. Targum, MD, MPH	Deputy Director, Division of Dermatology and Dentistry (DDD)
Snezana Trajkovic, MD	Clinical Team Leader, DDD
Tong Li-Masters, MD	Clinical Reviewer, DDD
Chinmay Shukla, PhD	Clinical Pharmacology Scientific Lead, Division of Inflammation and Immune Pharmacology (DIIP)
Mohamed Alesh, PhD	Biostatistics Team Leader, Division of Biometrics III (DB III)
Kathleen Fritsch, PhD	Biostatistics Reviewer, DB III
Marlene Schultz-DePalo, MS, MA	Biosimilar Program and Policy Analyst, Office of Biotechnology Products (OBP)
Cristina Ausin, PhD	Scientific Reviewer, Office of Therapeutic Biologics and Biosimilars
Stacey Ricci, MEng, ScD	Director of Scientific Review Staff, Office of Therapeutic Biologics and Biosimilars (OTBB)
Archita Patel, JD	Regulatory Counsel, (OTBB)
Michelle Luo, MD, PhD	Scientific Reviewer, (OTBB)
Ram Sihag, PhD	Team Leader, Division of Biotechnology Review and Research III (DBRR III), OBP,

Frances Andrada, MSN, CRNP, FNP-BC, CNRN	Scientific Reviewer, (OTBB)
Emanuela Lacana, PhD	Deputy Director, (OTBB)
Sarah Brown, Pharm D	Science Policy Analyst, (OTBB)
Christine Corser, PharmD	Analyst, (OTBB)
Shelley Skibinski, PharmD	Program Coordinator, (OTBB)

SPONSOR ATTENDEES

Abid Sattar	Head of Pharmacometry and Clinical Excellence
Bianca Lazea	Clinical Data Management Lead
Brian DiPaolo	Head of Regulatory CMC, Global Regulatory Affairs
Charlene Tedde	Manager, Global Regulatory Affairs
Fausto Berti	Head of Clinical and Medical Affairs
Heimo Stroissnig	Head Clinical Development and Patient Safety
Joanna Sobierska	Medical Lead
Paul Duijzings	Clinical Operations Lead
Nivedita Roy	Head of Regulatory Strategy, Global Regulatory Affairs
Renuka Joshi	Global Regulatory Lead, Global Regulatory Affairs
Sebastien Cougnon	Program Manager, Program Management
Walter Low	Program Head, Program Management
Donald Lewis	Director, Regulatory Affairs Global Biosimilars
Jill Pastore	Manager, Regulatory Affairs Global Biosimilars

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 Alvotech hf 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).

2.0 DISCUSSION

2.1. Regulatory

Question 1:

In accordance with the reference product Stelara, the Sponsor proposes to provide Patient Counselling Information and the Medication Guide for AVT04 without a REMS. Does the FDA concur with this proposal?

FDA Response to Question 1:

Yes.

Meeting Discussion:

None

Question 2:

The reference product Stelara is approved in the US for Plaque Psoriasis (PsO), Psoriatic Arthritis (PsA), Crohn's Disease (CD) and Ulcerative Colitis (UC). In the original BLA, Alvotech plans to seek licensure under section 351(k) of the Public Health Service (PHS) Act, for AVT04 for only two indications – Plaque Psoriasis (PsO) incl. paediatric Plaque Psoriasis in children age 6 years and older (b) (4)

(b) (4) and Psoriatic Arthritis (PsA) (b) (4)

(b) (4) Accordingly, the draft Prescribing Information for AVT04 will be submitted to the original BLA.

Does the FDA have any comments on the proposal of filing fewer indications? Does the FDA have any feedback on the proposed location of AVT04 specific data in the prescribing information and overall concept for the prescribing information?

FDA Response to Question 2:

Your proposal to seek licensure for fewer indications than those for US-Stelara is acceptable. You propose that AVT04 prescribing information (PI) will be drafted in accordance with FDA guidance so that relevant data and information from the US-Stelara PI will be incorporated with appropriate modifications in the AVT04 PI reflecting the safe and effective use of AVT04 for the fewer indications and that AVT04-specific information will be included in the appropriate sections of the full prescribing information.

The overall approach for the prescribing information and the proposed location of AVT04-specific data in the prescribing information appear reasonable. The adequacy of the proposed labeling will be a review issue. US-licensed Stelara is indicated for pediatric patients 6 years and older with moderate to severe plaque psoriasis (PsO) (b) (4)

(b) (4)

(b) (4) Also, US-Stelara PI has recently been revised to include treatment of pediatric psoriatic arthritis (PsA) patients 6 years and older. Update the pediatric assessment for PsA in the pediatric study plan submitted in your BLA.

Meeting Discussion:

(b) (4)

(b) (4)

(b) (4) FDA explained that regarding

any differences in indications from the agreed iPSP, the sponsor must provide an updated pediatric study plan and relevant extrapolation justifications. In addition, any labeling changes regarding the pediatric populations will be a review issue.

2.2. Clinical

Question 3:

Does the Agency concur with the Sponsor's proposal for the clinical documentation of AVT04?

FDA Response to Question 3:

For section 5.3.5.3 of the initial BLA, you propose to only include placeholder documents for the integrated summary of safety (ISS), integrated summary of efficacy (ISE), and integrated analysis of immunogenicity (ISI) including a justification why the actual document is not provided. Section 2.2 will include a "roadmap" of all relevant information to support biosimilarity, a summary of the totality of evidence to support same, and a justification for extrapolation to all indications approved for the reference product Stelara.

Your proposal appears reasonable.

Include the following in your BLA:

- Provide the following in your summary of safety:
 - a. Analyses of treatment emergent adverse events (TEAEs) in the dataset to include all TEAEs, treatment-related TEAEs, serious TEAEs, discontinuations due to TEAEs, and adverse events of special interest (AESIs)
 - b. Adverse event tables with incidence rate of $\geq 1\%$ regardless of causality. For each period of the study, include tables of raw incidence rates at $\geq 1\%$ by treatment group.
 - c. Adverse reaction tables (adverse reactions are defined as those AEs with possible or probable causality) with incidence rate of $\geq 1\%$. Pool related preferred terms in your table (e.g., upper respiratory tract infection, nasopharyngitis, viral upper respiratory tract infection, etc.)
 - d. Conduct an issue-based safety review of your product. Provide a list of discussions on key potential safety issues associated with the class of products or identified during the development of your product. Also, 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].

- e. Electronic links to case report forms (CRFs) and narratives
 - f. Line listings for all abnormal safety findings (e.g., adverse events, vital signs etc.)
 - g. 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.
 - h. An analysis of electrocardiogram (ECG) data
 - i. A worldwide safety update in addition to the safety update report
 - j. Evaluation of uncommon, rare, or unexpected events that may be possibly related to the study drug
- Provide safety analyses for the following subgroups:
 - a. Race categories include Caucasian, African American, Asian, and Other
 - b. Age categories (18 to 45, >45 to 75) and age group (<65 and ≥65)
 - c. Ethnicity (Hispanic/Latino or not Hispanic/Latino)
 - d. Sex
 - e. Baseline severity
 - f. Any prior exposure to ustekinumab products
 - Provide CRFs for all deaths, serious adverse events, hypersensitivity reactions, discontinuations due to adverse events, and moderate/severe injection site reactions. Other eCRFs should be readily available upon request. However, if the eCRFs are located in the clinical study report (CSR), provide links to the eCRFs in the relevant sections of the Overview of Clinical Safety and Summary of Clinical Safety, if applicable.
 - Provide narratives for all deaths, serious adverse events (SAEs), subjects who discontinued the study agent due to adverse events (AEs), AEs of special interest (including tuberculosis infection, malignancies, interstitial pneumonia, eosinophilic pneumonia and cryptogenic organizing pneumonia, and adverse events of posterior reversible encephalopathy syndrome), anaphylaxis/hypersensitivity reactions, and pregnancies. 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/2020 (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). Narratives may be included in the CSRs with links to these narratives provided in

the relevant sections of the Overview of Clinical Safety and Summary of Clinical Safety.

- Provide reference ranges for all laboratory values in the data listings where those laboratory values are presented.
- In the presentation of laboratory data, “flag” all laboratory values and vital signs that are outside of the reference ranges.
- Provide a full-text version of any referenced articles with hyperlinks to each article, as appropriate.
- To facilitate review of the data, we recommend that your BLA submission include a summary of the trials in tabular form such as the following:

Study Identity	Study Objective	Study Design	Study Population	Treatment Groups
PK Similarity Studies				
Comparative Clinical Study				
Other Supportive Studies				

- Provide a table with the following columns for each of the completed comparative clinical studies:
 - a. Site number
 - b. Principle investigator
 - c. Location: City State, Country
 - d. Number of subjects screened
 - e. Number of subjects randomized
 - f. Number of subjects treated who prematurely discontinued (or other characteristic of interest that might be helpful in choosing sites for inspection)
 - g. Number of protocol violations (Major, minor, including definition)
- 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. See Guidance for Clinical Investigators, Industry, and FDA Staff Financial Disclosure by Clinical Investigators.

- In the 120-day safety update report (SUR), per section 505(i) of the act, update the BLA application with new safety information learned about the product that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. Provide narratives in the SUR for all subjects who died, experienced SAEs, pregnancies, and AEs of special interest.
- Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. The “coding dictionary” consists of a list of all investigator 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. If it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim). We 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.

Biostatistics Comments:

- 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. For subjects who had remote assessments or other modifications due to COVID-19 or the situation in Ukraine, include flags in the datasets indicating the modification and clearly document the nature of the deviations.

Clinical Pharmacology Comments:

- a. Submit all electronic datasets pertaining to pharmacokinetic (PK) analysis, including raw data for individual subjects and individual PK parameters (if applicable) as SAS xpt transport files.
- b. For the anti-drug antibodies (ADA) positive subjects observed in your studies, provide a summary table of study number, study subject ID, serum concentrations at each PK time-point, sample ADA status at each immunogenicity assessment time-point, and the primary efficacy outcome (if applicable).

Meeting Discussion Biostatistics for e and f:

The sponsor stated that they have collected some electronic patient-reported outcomes (ePRO) data from subject diaries that has been included in the CRF. The Agency noted that it is important to provide annotated documents that map all of the collected data with the CRFs or comparable documents. The sponsor agreed to provide annotated screenshots of the ePRO data collection system.

The sponsor asked for clarification concerning the requested data flags regarding COVID-19 or Ukraine and noted that the data would be collected in the protocol deviation (DV) domain SDTM datasets. The Agency clarified that the key idea is that the Agency should be able to conduct analyses comparable to any analyses included in the study reports. If subgroup analyses related to COVID-19 or Ukraine were conducted, the ADaM datasets would typically include a variable that would permit such subsetting. If the information from such protocol deviations were used in other ways, it may be reasonable to include information in the Reviewer's Guide to explain how such information was used in analyses.

Clinical Pharmacology for b:

The sponsor's proposal to provide the summary tables for ADA positive subjects in studies AVT04-GL-101 and AVT04-GL-301 appears reasonable.

Question 4:

Does the FDA agree that the proposed content of the 120-day data update is in line with FDA expectation for review and approval of AVT04 per Section 351(k) of the PHS Act?

FDA Response to Question 4:

You plan to include in the initial BLA submission the final clinical study report (CSR) of study AVT04-GL-101 and the primary CSR of study AVT04-GL-301, the latter providing the results for the primary objectives of the study as well as safety and immunogenicity data collected up to Week 28. You do not plan to provide any narratives of deaths, SAEs, AESI, or safety related early discontinuations collected for the period from the cut-off date for the primary CSR to initial BLA submission in section 2.7.4. In the Day

120 safety update of study AVT04-GL-301, you plan to submit narratives of serious adverse events (SAEs), adverse events of special interest (AESI), deaths, and discontinuations for safety reasons, as well as long-term safety, tolerability, immunogenicity, and efficacy data collected from Week 28 till Week 52.

Your proposal appears reasonable.

Also see FDA response to Question 3.

Meeting Discussion:

None

Question 5:

Does FDA agree with the proposed BIMO only for the AVT04-GL-301 Study of the AVT04 BLA?

FDA Response to Question 5:

We do not agree. Submit BIMO data for both Studies AVT04-GL-301 and AVT04-GL-101.

Meeting Discussion:

None

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 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.

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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

¹ <https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm>

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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 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.

APPEARS THIS WAY ON ORIGINAL

² <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended>
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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 201.57⁴ 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 Information⁵ and Pregnancy and Lactation Labeling Final Rule⁶ 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.

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.

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

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<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm>
<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>.

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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 356h⁸ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*⁹. 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*.

⁸ <https://www.fda.gov/media/84223/download>

⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

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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 $\pm$ 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.
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 Document¹⁰ 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.

¹⁰ <https://www.fda.gov/media/131425/download>

Submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

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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/

SHARI L TARGUM
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