CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761379Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 141478

MEETING PRELIMINARY COMMENTS

Formycon AG
C/o: Granzer Regulatory Consulting & Services
Attention: Scott Oglesby, PhD
Regulatory Consultant
6518 Green Rise Road
Hillsborough, NC 27278

Dear Dr. Oglesby:[1]

Please refer to your pre-investigational new drug application (PIND) file for FYB202.

We also refer to your May 17, 2023, correspondence, received May 17, 2023, requesting a meeting to discuss the content and format of your proposed biosimilar BLA submission.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

If you have any questions, call Dawn Williams, Safety Regulatory Project Manager, at (301)796-5376.

Sincerely,

{See appended electronic signature page}

Dawn Williams, BSN
Safety Regulatory Project Manager
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs

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

Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: Type 4

Meeting Date and Time: July 19, 2023
Meeting Format: Teleconference

Application Number: PIND 141478
Product Name: FYB 202
Proposed Indications: For the treatment of:

Adult patients with:

- Moderate to severe plaque psoriasis (Ps) who are candidates for phototherapy or systemic therapy
- Active psoriatic arthritis (PsA), (b) (4) (b) (4)
- Moderately to severely active Crohn's disease (CD)
- Moderately to severely active ulcerative colitis (UC)

Pediatric patients 6 years and older weighing 60kg or more with:

- Moderate to severe plaque psoriasis (Ps), who are candidates for phototherapy or systemic therapy
- Active psoriatic arthritis (PsA)

Sponsor Name: Formycon AG
Regulatory Pathway: 351(k) of the Public Health Service Act

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the teleconference on July 19, 2023, at 11:00am-12:00pm between Formycon AG and the Division of Dermatology and Dentistry. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda. Contact the Regulatory Project Manager (RPM) if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

1.0 BACKGROUND

We have had the following meetings with you:

- March 18, 2022, Guidance (Human Factors)
- November 22, 2021, BPD Type 3
- February 13, 2019, BPD Type 2

We have sent the following correspondences to you:

- September 16, 2021, Pediatric Study Plan- Written Response
- June 14, 2019, Special Protocol- No Agreement

FDA may provide further clarifications of, or refinements and/or changes to these preliminary responses and the advice provided at the meeting based on further information provided by Formycon AG 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. Multi-Disciplinary Questions

FYB202 is an ustekinumab (IL-12/23 blocker) biosimilar, with the proposed treatment of the following populations:

- Adults and pediatric patients 6 years and older and weighing 60kg or more with:
  - Moderate to severe plaque psoriasis (PsO) who are candidates for phototherapy or systemic therapy
  - Active psoriatic arthritis (PsA) (b) (4) (b) (4)
- Adults with:
  - Moderately to severely active Crohn's disease (CD)
  - Moderately to severely active ulcerative colitis (UC)

The Sponsor proposes to develop the following presentations:

- 45mg/0.5mL PFS for SC injection
- 90mg/1mL PFS for SC injection
- 5 mg/mL concentrate for solution for infusion in a single-dose vial containing 130 mg ustekinumab in 26 mL for use as intravenous induction dose in the treatment of CD and UC

The 45 mg vial presentation will not be included in the initial BLA submission but will be submitted as a post-authorization supplement.

The Sponsor plans to submit 3 clinical studies in their BLA:

- FYB202-01-01 (315 subjects) and FYB202-01-02 (491 subjects) – Both of these are 3-arm, randomized, single-dose, bridging studies in healthy volunteers to demonstrate PK equivalence between FYB202, US-licensed Stelara, and EU-approved Stelara. In FYB202-01-01, the results showed variability in the UV spectroscopy method that only affected the protein content estimation for

FYB202 arm and not the EU-Stelara and US-Stelara arms. At the recommendation of the FDA, the Sponsor conducted a second bridging study. The pooling of data for these studies will be limited to safety and immunogenicity data.

- FYB202-03-01 (392 subjects) – Comparative clinical study in subjects with moderate-to-severe plaque psoriasis. The primary efficacy endpoint was assessed at Week 12 with a single switch at Week 28 and an extension period from Weeks 28 to 56.

Question 1:

Does the FDA agree that the proposed documents and their location in module 1 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required.

FDA Response to Question 1:

The proposed documents for clinical review (financial disclosure, investigational brochure, labeling, and pending iPSP) are acceptable. Include a Reviewers Guide in Module 1.2, current labeling test for the reference drug in Module 1.14.3.3, and the requests for the proprietary and non-proprietary names in Module 1.18.

Question 2:

Regarding the iPSP the sponsor has submitted an agreed iPSP (v2.0) on December 14, 2021. To date no agreement letter has been received. If correspondence confirming FDA agreement to our agreed iPSP needs to be part of the FYB202 record for us to file our 351(k) application can FDA issue such a correspondence?

FDA Response to Question 2:

Currently under review by the sponsor.

Question 3:

Does the FDA agree that the proposed documents and their location in module 2 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required.

FDA Response to Question 3:

The proposed documents for module 2 are acceptable.

Question 4:

Does the FDA agree with the proposed location for the justification of extrapolation of indications?

FDA Response to Question 4:

Your proposal to include the justification for extrapolation across the reference product's approved indications in section module 2, section 2.5.3 of the clinical overview is acceptable.

Question 5:
Does the Agency agree that the proposed contents of module 2.7.1. as provided in Table 4 in section 20.2 is adequate?

FDA Response to Question 5:
The overall plan for Section 2.7.1 appears reasonable.

Question 6:
Does the Agency accept the applicant's proposal to provide a comprehensive safety analysis in the Summary of Clinical Safety in module 2.7.4 with supportive documentation and additional integrated analyses in the Integrated Summary of Safety, module 5.3.5.3 as proposed in section 20.2 and section 20.5?

FDA Response to Question 6:
You propose to include the Integrated Summary of Safety (ISS) under Module 2.7.4, Summary of Clinical Safety. There may be situations in which sections 2.7.3, Summary of Clinical Efficacy, and 2.7.4, Summary of Clinical Safety, would be sufficiently detailed to serve as the narrative portion of the Integrated Summary of Efficacy (ISE) and ISS, respectively, while still concise enough to meet the suggested size limitations for Module 2. In such situations, the ISE and ISS can be split across Module 2 and Module 5, with the narrative portion located in section 2.7.3 or 2.7.4 and the appendices of tables, figures, and datasets located in section 5.3.5.3. If the ISE or ISS is split across modules in this way, it is critical to include a clear explanation of where the parts are located. This explanation should be placed both in Module 2 (section 2.7.3 or 2.7.4) and in Module 5 (section 5.3.5.3). You are referred to the Guidance for Industry, *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document*.

In the ISS under Module 2.7.4, Summary of Clinical Safety, you propose to pool the safety and immunogenicity data of healthy volunteers in PK studies FYB202-01-01 and FYB202-01-02. This proposal is acceptable.

You propose that the comprehensive assessment of safety in patients with psoriasis from the comparative clinical study (FYB202-03-01) be included in the ISS under Module 2.7.4 and supportive documentation and additional integrated analyses included in module 5.3.5.3. This proposal is acceptable.

Question 7:
Does the FDA agree that the proposed documents and their location in module 3 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required?

FDA Response to Question 7:
The overall submission plan for module 3 appears reasonable.

Question 8:

Does the FDA agree that the proposed documents and their location in module 4 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required.

FDA Response to Question 8:

We agree that the proposed documents and their location in module 4 are considered adequate and sufficient.

Question 9:

Does the Agency agree that the proposed documents and their location in module 5 are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required.

FDA Response to Question 9:

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 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 (AE) 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 including Caucasian, African American, Asian, and Other
    ii. Age categories (18 to 45, >45 to 75), age group (<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 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), 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 AEs, AESIs, 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 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; 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 such as the following:

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								

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)

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*.

Question 10:
Does the Agency agree that the submission of site level bioresearch monitoring (BIMO) datasets are not required for the Phase I studies (FYB202-01-01) and FYB202-01-02)?

FDA Response to Question 10:
Your proposal appears reasonable.

Question 11:
Does the FDA agree that an obligation to submit study results information in CilnicalTrials.gov does not apply to study FYB202-03-01?

FDA Response to Question 11:
We will provide the response to this question post meeting in final meeting minutes.

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.[2]

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

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

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*[3]. 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)[4] and 201.57[5] 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*[6] which includes the guidance for industry: *Labeling for Biosimilar Products* (July 2018).
- *Prescribing Information Resources*[7]

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

[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.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

[6] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources

[7] https://www.fda.gov/drugs/fdas-labeling-resources-human-prescription-drugs/biological-products-specific-labeling-resources

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.[8]

- 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*.[9]

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.

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[8] https://www.fda.gov/drugs/laws-acts-and-rules/fdas-labeling-resources-human-prescription-drugs

[9] 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.

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.

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.[10]

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.[11]

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.

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

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[12] and the guidance for industry, *Identification of Manufacturing Establishments in*

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

Applications Submitted to CBER and CDER Questions and Answers[13]. 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*.

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

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

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.
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[14] 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.

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

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/s/

DAWN WILLIAMS
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