CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761364Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 141843

MEETING PRELIMINARY COMMENTS

Accord BioPharma Inc.
Attention: Sabita Nair, RAC, ASQ-CPGP
VP Regulatory Affairs
1009 Slater Road, Suite 210 B
Durham, NC 27703

Dear Ms. Nair:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for DMB-3115.

We also refer to your March 24, 2023, correspondence, requesting a meeting to obtain agreement on the content of the 351 (k) BLA for DMB-3115.

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 me at 240-402-4454.

Sincerely,

{See appended electronic signature page}

Kimberle Searcy, MPH
Regulatory Health Project Manager
Division of Regulatory Operations for
Dermatology and Dentistry
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:

Preliminary Meeting Comments

APPEARS THIS WAY ON ORIGINAL

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: May 24, 2023, 1:30-2:30 pm EST
Meeting Location: Teleconference

Application Number: IND 141843
Product Name: DMB-3115

Indication: DMB-3115 is being developed for the same indications as those approved for US-licensed Stelara
Sponsor Name: Accord Biopharma Inc.
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 meeting scheduled for May 24, 2023, 1:30-2:30pm EST between Accord Biopharma Inc. 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

Purpose of Meeting:
The purpose of the meeting is to obtain agreement on the 351(k) BLA content for DMB-3115.

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 Accord Biopharma Inc. 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. Chemistry, Manufacturing and Controls

Question 1:

1a. Does the Agency agree with applicant's approach on presentation of DP stability data in the initial BLA? The Applicant intends to supplement the additional stability data during the FDA review period as the data becomes available.

1b. Does the Agency agree with the approach to submit 3-month stability data for the vial with BLA Submission and submit additional stability data during FDA review?

FDA Response to Question 1a:

You describe your approach for submitting stability data for the DMB-3115 drug substance (DS) and drug product (DP) in the original BLA submission and during the BLA review cycle in Tables 2 and 3 of the meeting package. While your approach for submitting the stability data for the DS and DP prefilled syringe (PFS) presentation is reasonable, the Agency does not agree with your approach for the DP vial presentation. As described in ICH Q5C, a minimum of 6 months of stability data should be submitted in cases where storage periods greater than 6 months are requested. Therefore, for the CMC package in the original BLA submission to be considered complete, submit a minimum of 6 months of stability data for the DP vial presentation.

Note that, available real-time stability data from at least 3 DS and DP lots representative of the commercial process, including container closure system and formulation including strength, will be used to determine expiry (shelf-life). The expiry dating period will be determined during the BLA assessment based on totality of the stability data available from all representative DS and DP lots and other supporting studies, such as demonstration of comparability, including comparable stability profiles under accelerated and/or stressed storage conditions.

FDA Response to Question 1b:

As previously communicated, the Agency only accepts simple stability updates during the BLA review cycle. A "simple stability update" should be derived from the analyses performed under the same conditions using the same DS and DP lots in the same container closure systems as described in the stability protocol provided in the original BLA submission. This update will use the same tabular presentation as in the original BLA submission as well as the same mathematical or statistical analysis methods (if any) and will not contain any matrix or bracketing approaches which deviate from the stability protocol in the original BLA submission. Simple stability updates submitted up to month 7 will be assessed and considered in expiry determinations.

Question 2:
The Applicant plans to include the Leachable study plan for the 130 mg vial presentation in the Biologics License Application (BLA). The results will be submitted as an amendment during the review period. Does the Agency agree with this proposal?

FDA Response to Question 2:
In the meeting package, you propose to submit extractable data along with the risk assessment and a leachable study protocol in the original BLA submission and up to 6 months of leachable study data as an amendment during the BLA review cycle for the DP vial presentation (Table 4). Complete E&L data for PFS presentation will be provided in initial BLA. The proposed plan appears reasonable. To ensure timely review of the leachable data of the vial presentation, the amendment should be submitted no later than 3 months after initial filing of the BLA. Note that additional leachable study data may be needed to support the safety of the DP vial presentation at the end of the proposed expiry.

2.2. Clinical

Introduction:

You've conducted a randomized, double-blind, multicenter, parallel-group and active controlled study, Study DMB-3115-2, comparing efficacy, safety, and immunogenicity of subcutaneous injection of DMB-3115 and EU-approved Stelara in subjects with moderate to severe chronic plaque psoriasis.

The primary objective was to evaluate the efficacy of DMB-3115 in comparison with EU-approved Stelara. The secondary objectives were to evaluate to safety, tolerability, PK, and immunogenicity of DMB-3115 compared to EU-approved Stelara.

A total of 605 subjects were randomized in a 1:1 ratio to receive either DMB-3115 or EU-approved Stelara. Randomization were stratified according to patient's body weight at baseline (≤100 kg/45 mg or >100 kg/90 mg), geographic region (EU, US or Rest of the World [ROW]) and the number of previous systemic therapies for psoriasis (<3 or ≥3).

Study DMB-3115-2 included two periods, Period 1 and Period 2.

Period 1:
In Period 1 (from Week 0 to Week 28), subjects received the assigned treatment (DMB-3115 or EU-approved Stelara) at Weeks 0, 4, and 16. Subjects who did not achieve at least Psoriasis Area and Severity Index (PASI) 50 response by Week 12 were discontinued from further treatment with DMB-3115 or EU-approved Stelara.

Period 2:
In Period 2 (from Week 28 to Week 52), subjects randomized to receive DMB-3115 at the beginning of the study continued to receive the same treatment up to Week 40 while subjects randomized to receive EU-approved Stelara at the beginning of the study were re-randomized and re-stratified based on the body weight at Week 28 (≤100 kg/45 mg or >100 kg/90 mg) in a 1:1 ratio to either continue on EU-approved Stelara or transitioned to receive DMB-3115 every 12 weeks up to Week 40 (i.e., 2 doses of investigational product after re-randomization).

Doses at re-randomization (Week 28) for both DMB-3115 and EU-approved Stelara were re-assigned based on the body weight at Week 28 (≤100 kg/45 mg or >100 kg/90 mg). Subjects receiving DMB-3115 continued to receive DMB-3115 up to Week 40 but also followed the re-randomization procedure to maintain blinding.

Only those subjects who achieved at least PASI 75 response at Week 28 were eligible for inclusion into the Period 2 of the study (Transition period: from Week 28 to Week 52).

Question 3:
Does the Agency agree with the Applicant's proposed approach for the presentation of clinical efficacy and safety data in the BLA submission?

FDA Response to Question 3:
Yes, we agree.

We have the following recommendations regarding presentation of efficacy and safety data:

1. Per the Biosimilar User Fee Act (BsUFA) reauthorization for fiscal years (FYs) 2023-2028, (BsUFA III), original 351(k) applications are expected to be complete, at the time of original submission of the application. For approval, you will need to provide adequate clinical data to support a conclusion that there are no clinically meaningful differences between your drug product and the reference product for the proposed indication(s).

2. For your BLA submission we recommend that you include the following for your two studies in your application:
   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 and sensitivity analyses.
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 case report form (CRF), include annotated screen shots of the electronic data capture system.

3. Provide the following in your Summary of Clinical Safety:
   a) Analyses of treatment emergent adverse events (TEAEs) to include all TEAEs, treatment related TEAEs, serious TEAEs, discontinuations due to TEAEs, and AESIs.
   b) Adverse event tables with incidence rate of ≥ 1% regardless of causality.
   c) 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.).
   d) 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%.
   e) 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.
   f) Evaluation of uncommon, rare, or unexpected events that may be possibly related to the study drug.
   g) Electronic links to CRFs and narratives.
   h) 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).
   i) Line listings for all abnormal safety findings (e.g., adverse events, vital signs etc.)
   j) 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.
   k) For laboratory data, please “flag” all laboratory values and vital signs that are outside of the reference ranges.
   l) A worldwide safety update in addition to safety update report, if the product is approved in any other jurisdiction.

4. 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), age group (<65 and ≥65)
   c) Ethnicity (Hispanic/Latino or not Hispanic/Latino)
   d) Sex
   e) Baseline severity
   f) Any prior exposure to biologic products

5. Provide CRFs for all deaths, serious adverse events, hypersensitivity reactions, discontinuations due to adverse events, and moderate/severe injection site reactions. Other electronic CRFs (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 and Summary of Clinical Safety.

6. 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 and Summary of Clinical Safety.

7. 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 AEs of special interest.

8. 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.

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

10. 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:

Trial Identity	Trial Design	Regimen/ schedule/ route	Study Endpoints	Treatment Duration/ Follow Up	No.of subjects enrolled	Study Population	No.of Centers & Countries
Controlled Studies to Support Efficacy and Safety							
Studies to Support Safety							
Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)							

11. Provide a table with the following columns for each of the sites in the comparative clinical study:
    a) Site number
    b) Principal 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)

12. 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.

13. We also recommend that your BLA submission include a summary of a subject's exposure data by phase/stage as formatted in the example below:

USID	Treatment (Drug)	Phase/Stage P: Thr Wk 28 E: Wk 28-	Date of First Exposure	Date of Last Exposure	Total number of doses	Total drug exposure (mg/mL)	Weeks completed	Reason for early discontinuation
001	Ustekinum ab	Primary			4	180mg	28	
001	ABP654	Extension			2	90mg	48	
002	ABP654	Primary			2	90mg	3	AE
etc								

Question 4:

Does the Agency agree that the DMB-3115 clinical development program using PFS for SC administration and scientific justification may be acceptable for extrapolation to the vial presentations and indications (including CD and UC)?

FDA Response to Question 4 :

Yes, we agree that the proposed clinical program using the subcutaneous route of administration may be acceptable for extrapolation to the indications (CD and UC) that require an initial intravenous dose for induction. In general, the SC route of administration is considered more sensitive in detecting clinically meaningful differences in PK and potentially more immunogenic, compared to the IV route of administration.

If DMB-3115 meets the statutory requirements for licensure as a biosimilar product under section 351(k) of the PHS Act, based on among other things, data derived from clinical study(ies) sufficient to demonstrate safety, purity, and potency in an appropriate condition of use, you may seek licensure of DMB-3115 for one or more additional conditions of use for which the reference product is licensed. However, you would need to provide sufficient scientific justification for extrapolating data and information submitted in your application to support licensure of DMB-3115 under section 351(k) as a biosimilar for each condition of use for which licensure is sought.

Such scientific justification for extrapolation of data and information should address, for example, the following issues for the tested and extrapolated conditions of use:

- The mechanism(s) of action in each condition of use for which licensure is sought; this may include:
  - The target/receptor(s) for each relevant activity/function of the product;
  - The binding; dose/response and pattern of molecule signaling upon engagement of target/receptors;
  - The relationships between product structure and target/receptor interactions;
  - The location and expression of the target/receptor(s).
- The pharmacokinetics and biodistribution of the product in different patient populations (relevant PD measures also may provide important information on the mechanism of action);
- The immunogenicity of the product in different patient populations;
- Differences in expected toxicities in each condition of use and patient population (including whether expected toxicities are related to the pharmacological activity of the product or to “off-target” activities); and
- Any other factor that may affect the safety or efficacy of the product in each condition of use and patient population for which licensure is sought.

Differences between conditions of use with respect to the factors described above do not necessarily preclude extrapolation. However, a scientific justification should address these differences in the context of the totality of the evidence supporting a demonstration of biosimilarity. A final decision about the adequacy of any scientific justification will be made by FDA during review of the 351(k) application.

2.1. Administrative/Regulatory

Question 5:

Can the FDA confirm the regulatory steps, if any, would be required to amend the agreed iPSP?

FDA Response to Question 5:
Please refer to the Agreed Initial Pediatric Study Plan – Agreement letter dated April 11, 2022. Since issuance of that letter, US-licensed Stelara was approved for the treatment of pediatric patients 6 years and older with active psoriatic arthritis on July 29, 2022. For any differences in indications from the Agreed iPSP, please provide an updated pediatric study plan and relevant extrapolation justifications in your BLA submission.

Question 6:
Does the Agency agree that since DMB-3115 is a 351K biosimilar to an already approved product, the label and medication guide fulfil risk management requirements and a risk management plan is not necessary to be submitted in the BLA?

FDA Response to Question 6:
We agree.

Question 7:
The Applicant plans to compose an eCTD dossier based on the core structure presented below. Does the Agency agree or have any comments?

FDA Response to Question 7:
The proposed plans to compose an eCTD dossier based on the core structure presented are acceptable.

Additional Product Quality Comments:
To facilitate the Agency's assessment of the BLA submission, provide the information in tables as requested below. The requested tables should summarize information from Module 3 and be submitted in Module 3.2.R. These tables do not replace other sections of Module 3 or impact the nature or amount of information included in those sections of Module 3.

1. Provide the following information in a completed table like the one below for all drug master files (DMFs) referenced in the BLA:

DMF #	DMF type	DMF holder	Item referenced	Link to letter of authorization	Comments (if needed)

2. To facilitate the Agency's assessment of the DS and DP manufacturing process, provide the information for each process parameter and in-process control, as applicable, in the tabular format provided below. Provide a separate table for each unit operation of the DS and DP manufacturing process, as described below.

Title: Unit Operation for DS Manufacturing Process

Process parameter/ In-process control (IPC)[1]	Proposed range for commercial manufacturing process[2]	Criticality classification[3]	Characterized range from process development[2]	Additional data[5], n=?[6]	Process validation range from PPQ runs[2] (min-max[4]), n=?[6]	Justification of the proposed commercial acceptable range[7] (or link to eCTD)

1. Terminology should be adapted to the one used by the manufacturing site(s).
2. As applicable.
3. For example, critical process parameter, key process parameter, non-critical process parameter, IPC, as described in Module 3.
4. Provide mean ± 2 (or 3) SD as optional.
5. For example, historical range (min-max or ± 2 (or 3) SD) from clinical DS lots and/or representative lots.
6. Indicate the total number of lots used for calculating min-max range for each unit operation and list the lot numbers in the footnote, if applicable. If not all lots indicated are included for calculation, provide justification in the footnote or insert a hyperlink to eCTD.
7. This could be a brief verbal description (e.g., "development range", "validation range", or "platform experience").

Title: Unit Operation for DP Manufacturing Process

Process parameter/ In-process control (IPC)[1]	Proposed range for commercial manufacturing process[2]	Criticality classification[3]	Characterized range from process development[2]	Additional data[5], n=?[6]	Process validation range from PPQ runs[2] (min-max[4]), n=?[6]	Justification of the proposed commercial acceptable range[7] (or link to eCTD)

1. Terminology should be adapted to the one used by the manufacturing site(s).
2. As applicable.
3. For example, critical process parameter, key process parameter, non-critical process parameter, IPC, as described in Module 3.
4. Provide mean ± 2 (or 3) SD as optional.
5. For example, historical range (min-max or ± 2 (or 3) SD) from clinical DP lots and/or representative lots.
6. Indicate the total number of lots used for calculating min-max range for each unit operation and list the lot numbers in the footnote, if applicable. If not all lots indicated are included for calculation, provide justification in the footnote or insert a hyperlink to eCTD.

7. This could be a brief verbal description (e.g., “development range”, “validation range”, or “platform experience”).

3. To facilitate the Agency’s assessment of the control strategy for the product, provide information for quality attributes and process and product related impurities for DS and DP in the following tabular format. Provide a separate table for the DS and DP.

Quality Attributes (including process and product related impurities for DS and DP)	Criticality classification[1]	Impact[2]	Source[3]	Analytical method[4]	Proposed control strategy[5]	Justification of the proposed control strategy[6]

1. Indicate if it is a CQA or not.
2. What is the impact of the attribute (e.g., contributes to potency, immunogenicity, safety, efficacy, etc.)?
3. What is the source of the attribute or impurity (e.g., intrinsic to the molecule, fermentation, purification column, etc.)?
4. List all methods used to test an attribute in-process, at release, and/or on stability. For example, if two methods are used to test identity, list both methods for that attribute.
5. List all strategies by which the attribute is controlled (e.g., in-process testing, validated removal, release testing, stability testing, etc.).
6. This could be a brief verbal description or links to the appropriate section of the eCTD.

4. To facilitate the Agency’s assessment of the adequacy of the proposed commercial DS and DP release specifications, provide information for each release specification in the tabular format provided below. Please provide a separate table for DS and DP, as described below. Use footnotes for each column of grouped results to indicate the lots used for each calculation of the minimum-maximum range, and provide the number of lots (n=?) in the table.

Release Specification for DS							
Attribute	Analytical method	Proposed commercial release acceptance criteria	Release results from developmental and nonclinical DS lots (n=?) (min-max)	Release results from clinical DS lots (n=?) (min-max)	Release results from DS PPQ lots (n=?) (min-max)	Release results from all DS lots[a] manufactured using the commercial process (n=?) (min-max)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)
a. Include all lots with available release data that were manufactured following the proposed commercial process, including those prior to PPQ campaign. Provide a list of lots included in the analysis as a footnote in the table.							

Release Specification for DP							
Attribute	Analytical method	Proposed commercial release acceptance criteria	Release results from developmental and nonclinical DP lots (n=?) (min-max)	Release results from clinical DP lots[a] (n=?) (min-max)	Release results from DP PPQ lots (n=?) (min-max)	Release results from all DP lots[b] manufactured using the commercial process (n=?) (min-max)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

a. Include all lots used in any clinical testing, regardless of scale, process, or manufacturing location, etc. List all lots as a footnote in the table.
b. Include all lots with available release data that were manufactured following the proposed commercial process. Provide a list of lots included in analysis as a footnote in the table.

5. To facilitate the Agency's assessment of the adequacy of the stability specifications of DS and DP, provide stability information for storage at recommended condition for each stability specification in the tabular format provided below. Please provide a separate table for DS and DP, as described below. If any stability acceptance criteria are different from the corresponding release acceptance criteria for which the same analytical method is used, provide justification as to why different acceptance criteria are proposed for release and stability. Include footnotes in the tables to list all lots that were used in each assessment. The assessment should consider data from all stability time points, not limited to the release and end of proposed shelf-life time points. If a lot has not completed stability testing to the end of proposed shelf-life, include data from all time points that are currently available.

Stability Specification for DS				
Attribute	Analytical method	Stability acceptance criteria	Stability results for lots stored at recommended long-term storage condition (n=?) Min – Max (Range for all data from time 0 to proposed end of shelf life or currently available time points)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

Stability Specification for DP				
Attribute	Analytical method	Stability acceptance criteria	Stability results for lots stored at recommended long-term storage condition (n=?) Min – Max (Range for all data from time 0 to the proposed end of shelf life or currently available time points)	Justification of specification (e.g., clinical experience, manufacturing capability, etc.)

6. To facilitate the Agency's assessment of the suitability of the analytical methods for DS and DP release and stability testing and for in-process test methods, provide summarized results of method validation in the tabular format provided below. Provide a separate table for each analytical method. Each parameter (e.g., specificity, precision, accuracy, etc.) should be described in a separate row. Add additional rows for additional parameters as needed. Study design should include a brief description of the testing material (such as lot information), the number of tests (e.g., the number of replicates, runs, plates, analysts, etc., if applicable), design of the experiment, approach of data reporting, and other important overview information regarding the validation of that parameter, as needed. Indicate in the table title the name of the method and all applicable programs where it is used (e.g., DS release/stability, DP release/stability, and in-process testing).

Summary of Validation Results for XXX (Method) (Used for DS/DP release/stability, in-process testing, etc.)			
Location of testing site:		**Location where method was validated:**	
System Suitability Acceptance Criteria:			
Parameter	Study design	Acceptance criteria	Validation results

7. Regarding the immunogenicity testing in the BLA submission, we recommend you provide an Integrated Summary of Immunogenicity (ISI) in section 2.7.2.4 Special Studies or section 5.3.5.3 Reports of Analysis of Data from More than One Study. This ISI should include: (1) Immunogenicity Risk Assessment, (2) Tiered Bioanalytical Strategy and Assay Validation Summaries, (3) Clinical Study Design and Detailed Immunogenicity Sampling Plans, and (4) Clinical Immunogenicity Data Analysis. For more information, refer FDA guidance for industry *Immunogenicity Testing of Therapeutic Protein Products —Developing and Validating Assays for Anti-Drug Antibody Detection*.

8. FDA Manual of Policies and Procedures MAPP 5019.1 Rev 1: "Allowable Excess Volume/Content in Injectable Drug and Biological Products" has recently become effective as of January 28, 2022. Accordingly, in addition to current DP specifications for the vial presentation, the new DP specification of "gross content of drug product (mL per vial)" is expected for the marketing application. Refer to MAPP 5019.1 for additional information.

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.

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

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.

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

[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

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 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]

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[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

[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.

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.

MANUFACTURING FACILITIES

All facilities should be registered with FDA at the time of the 351(k) sBLA 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 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

RECOMMENDATIONS FOR FORMATTING OF CLINICAL PHARMACOLOGY SUBMISSIONS FOR APPLICATIONS

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

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:
    a. Include the rationale for the selected dose used in the PK (and PD similarity, when applicable) study(ies) in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    b. Include a summary evaluation of the impact of immunogenicity on the activity (e.g., efficacy/PD), safety, and pharmacokinetics, as is applicable, for the studies included in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
    c. Present the PK (and PD, when applicable) parameter data as geometric mean with coefficient of variation, mean ± standard deviation, and median with range in the study reports and throughout the BLA.
    d. Provide analysis data sets for all concentration-time and derived PK (and PD, when applicable) parameter datasets as SAS transport files (*.xpt). A description of each data item should be provided in a define.pdf file. Any concentrations or subjects that have been excluded from the analysis should be flagged and maintained in the datasets.
2. Include the following information in a tabular format in the 351(k) BLA for each of the completed clinical studies:
    a. Site number
    b. Principal investigator
    c. Site Location: Address (e.g., Street, City, State, Country) and contact information (i.e., phone, fax, email)
    d. Location of Principal Investigator: Address (e.g., Street, City, State, and Country) and contact information (i.e., phone, fax, email). If the Applicant is aware of changes to a clinical investigator's site address or contact information since the time of the clinical investigator's participation in the study, we request that this updated information also be provided.
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[11] 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.

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

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

APPEARS THIS WAY ON ORIGINAL

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/

GORDANA DIGLISIC
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