CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761165Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

PIND 125841

MEETING MINUTES

Bioeq GmbH
Attention: Michael Trieb, Ph.D., MBA
Head of Regulatory Affairs
Bergfeldstraße 9
83607 Holzkirchen, Germany

Dear Dr. Trieb:

Please refer to your Pre-Investigational New Drug Application (PIND) file for FYB201. We also refer to the Biosimilar Biological Product Development (BPD) Type 4 Meeting between representatives of your firm and the FDA on December 14, 2018.

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

If you have any questions, call Michael Puglisi, Regulatory Project Manager, at (301) 796-0791.

Sincerely,

{See appended electronic signature page}

Wiley A. Chambers, M.D.
Deputy Director
Division of Transplant and Ophthalmology Products
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:
Meeting Minutes

FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type/ Category:	Biosimilar / Biosimilar Biological Product Development (BPD) Type 4 Meeting
Meeting Date and Time:	December 14, 2018, 10:00 am (EST)
Meeting Location:	Teleconference
Application Number:	PIND 125841
Product Name:	FYB201
Indication:	FYB201 is being developed for the same indications as approved for US-licensed Lucentis.
Sponsor/Applicant Name:	Bioeq GmbH
Meeting Chair:	Wiley Chambers
Meeting Recorder:	Michael Puglisi

FDA PARTICIPANTS:
Wiley Chambers/ Deputy Division Director
William Boyd/ Clinical Team Leader
Maria Rivera/ Nonclinical Reviewer
Lori Kotch/ Nonclinical Supervisor
Amit Somani/ Clinical Pharmacology Reviewer
Philip Colangelo/ Clinical Pharmacology Team Leader
Yunfan Deng/ Statistics Reviewer
Jens Fricke/ Product Quality Reviewer
Willie Wilson/ Product Quality Team Leader
Yu-Ting Weng/ Quality Statistics Reviewer
Tianhua Wang/ Quality Statistics Team Leader
Emanuela Lacana/ Associate Director, Biosimilar Policy, OBP
Michael Puglisi/ Regulatory Project Manager
Sue Lim/ Director of the Scientific Review Staff, OND Therapeutic Biologics and Biosimilars Team
Stacey Ricci/ OND Therapeutic Biologics and Biosimilars Team
Leila Hann/ OND Therapeutic Biologics and Biosimilars Team
Eva Temkin/ OND Therapeutic Biologics and Biosimilars Team

EASTERN RESEARCH GROUP ATTENDEE:
Hannah Busey/ Eastern Research Group, Inc., Independent Assessor

SPONSOR ATTENDEES:
Yuan Chen/ Regulatory Affairs Manager, Bioeq GmbH
Jens Gross/ Global Program Manager, Bioeq GmbH
Michael Trieb/ Head of Regulatory Affairs, Bioeq GmbH
Florian Strohmaier/ Director, Drug Regulatory Affairs and Quality Management, Formycon AG

MEETING OBJECTIVE:
To discuss structure, format, and content of the planned BLA application for FYB201 as a proposed biosimilar to US-licensed Lucentis (ranibizumab) for the same indications as approved for US-licensed Lucentis.

SUMMARY OF DISCUSSION:
Agency responses to the questions outlined in the October 4, 2018, background package (see bolded text below) were provided to the Sponsor in an email dated December 10, 2018, (see text in italics below). This meeting served to clarify those responses. The discussion during the meeting is reflected in normal font.

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 Bioeq GmbH 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).

DISCUSSION:

Questions for the Agency:

1. **Does FDA agree** (b) (4)

   Agency Response: You have not provided sufficient information about your proposed plan for FDA to comment at this time. (b) (4)

   (b) (4)

   Meeting Discussion: The Sponsor provided a slide presentation (attached) that was followed during the meeting. (b) (4)

2. **Since no respective guidance documents are available to support sponsors in detailed planning for the preparation of the briefing materials, could the Agency provide further details regarding the anticipated need for and/or the expected date for an advisory committee meeting including an outline on expected materials?**

   Agency Response: A decision regarding the need for an Advisory Committee meeting would be made after submission of the BLA(s). General information, including examples of briefing materials for other applications, is available at: https://www.fda.gov/AdvisoryCommittees/.

   Meeting Comment: There was no discussion of this matter during the meeting.

3. **A table of contents of module 1 including a brief description of all documents is provided in Table 1 of the Briefing Book. Those sections in bold are planned to be included in the BLA. Does FDA agree that the proposed documents and their location as described are considered adequate and sufficient? The applicant kindly asks for the Agency's advice in case there are additional documents required.**

   Agency Response: The outline of planned to-be-submitted Module 1 documents is acceptable; however, the Agency may request additional materials and documents during the review process if necessary.

   Meeting Comment: There was no discussion of this matter during the meeting.

4. **Does FDA agree that an amendment of the agreed iPSP before submission of the BLA due to the changed indications of the reference product is not required?**

   Agency Response: Agree.

   Module 1.9 would be expected to contain the agreed-upon pediatric study plan (containing your proposed sought indications of Neovascular age-related macular degeneration (nAMD), Retinal vein occlusion (RVO), Diabetic macular edema (DME), Diabetic retinopathy in patients with DME indications) where you would request a drug-specific waiver for each of these indications for the biosimilar for all pediatric age groups.

Module 1.9 would also be expected to contain your request for drug-specific waivers for all pediatric age groups for the diabetic retinopathy and myopic choroidal neovascularization indications along with justification and a sentence which clearly states that these indications were not previously included in the agreed iPSP.

Meeting Comment: There was no discussion of this matter during the meeting.

5. **Does FDA agree that it is justified according to the FDA guidance "Environmental Assessment of Human Drug and Biologics Applications" to claim a categorical exclusion under 21 CFR 25.31(c) from the need to prepare an EA for FYB201?**

Agency Response: *Agree.*

Meeting Comment: There was no discussion of this matter during the meeting.

6. **Does FDA agree that SPL documents are not needed for initial filing and can be provided later during the BLA review phase?**

Agency Response: *Disagree. Labeling in SPL format should be submitted with the initial application. For more information, see FDA guidance for industry, Providing Regulatory Submissions in Electronic Format—Content of Labeling (https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM072331.pdf). Additional information can about SPL be found here: https://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm.*

Meeting Comment: There was no discussion of this matter during the meeting.

7. **Does FDA agree that** (b) (4) **in the labeling as proposed is acceptable?**

Agency Response: *We defer comment on labeling until a thorough review of the BLA application(s) has been conducted.*

Meeting Comment: There was no discussion of this matter during the meeting.

8. **Does FDA agree that patient labeling is not required for FYB201?**

Agency Response: *Patient labeling is not required for submission of the BLA(s). Determination of whether the application would require patient labeling is made during review of the application.*

Meeting Comment: There was no discussion of this matter during the meeting.

9. **Does FDA agree that the NDC is not essentially needed at the time of the BLA filing and the drug product manufacturer has to apply for the NDC of our biosimilar product only prior commercialization?**

   Agency Response: Actual NDC codes on the draft labeling are not required for submission of the BLA(s) but draft labeling will need to identify placeholders where the NDC will be located. Drug listing submissions (including labeler code requests and NDC reservations, if appropriate) may be sent to FDA at any time prior to approval, but no later than the time of marketing and commercial distribution.

   Meeting Comment: There was no discussion of this matter during the meeting.

10. **Does the FDA agree that neither a RiskMAP nor a REMS is required for FYB201?**

    Agency Response: Neither a RiskMAP nor a REMS is required to be submitted with the original BLA(s) filing for this product. A determination of the requirement for a RiskMAP or REMS is made during review of the BLA(s).

    Meeting Comment: There was no discussion of this matter during the meeting.

11. **Does FDA agree that a name review request can also be submitted before the planned BLA without having an active IND?**

    Agency Response: Agree. Name reviews are performed by the Division of Medication Error Prevention and Analysis, Office of Medication Error Prevention and Risk Management, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research and can be submitted prior to BLA submission, but the final review of the proposed name will be performed during the BLA review.

    If you intend to have a proprietary name for this product, we recommend you submit a request for a proposed proprietary name review as soon as possible. If you require information on submitting a request for proprietary name review or BsUFA performance goals associated with proprietary name reviews, we refer you to the following:

    - *Guidance for Industry Contents of a Complete Submission for the Evaluation of Proprietary Names (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM075068.pdf)*

    - Biosimilar Biological Product Reauthorization Performance Goals and Procedures Fiscal Years 2018 through 2022, *https://www.fda.gov/downloads/ForIndustry/UserFees/BiosimilarUserFeeActBsUFA/UCM521121.pdf*

    Meeting Comment: There was no discussion of this matter during the meeting.

12. A table of contents of module 2 including a brief description of all documents is provided in Table 2 of the Briefing Book. Those sections in bold are planned to be included in the BLA.

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

Agency Response: The outline of planned to-be-submitted Module 2 documents is acceptable; however, the Agency may request additional materials and documents during the review process if necessary.

Meeting Comment: There was no discussion of this matter during the meeting.

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

Agency Response: Your proposal to place this justification of extrapolation of indications in Modules 2.5.1 and 2.5.3 is acceptable.

Meeting Comment: There was no discussion of this matter during the meeting.

14. In line with FDA's recommendations received in two Type 2 meetings, one clinical trial (COLUMBUS-AMD) has been conducted to demonstrate that there are no clinically meaningful differences between the biosimilar product and the reference product in terms of safety, purity, and potency. As patient benefit per se has already been shown for the reference product, the applicant is of the opinion that a repetition of published information concerning the safety and efficacy of ranibizumab is not necessary in the CTD clinical summaries of the biosimilar. Clinical summary sections would only be sensible if own study data of several clinical trials were available.

For that reason, the applicant is of the opinion that it is sufficient to submit the complete clinical overview (2.5), the COLUMBUS-AMD clinical study report (5.3.5.1), the Integrated Summary of Immunogenicity (ISI) (2.5.3 and 5.3.5.3) and the Summary of Biopharmaceutics and Associated Analytical Methods (2.7.1). These sections will contain all the information about the clinical development of the biosimilar product. Sections 2.7.2, 2.7.3 and 2.7.4 will be defined as "not applicable" in order to have a complete dossier in CTD. Consequently the ISI which should have been presented in section 2.7.2.4 will be included in section 2.5.3. The corresponding tables, figures and dataset are provided in section 5.3.5.3 in any case.

Is this approach of presenting the clinical information in module 2 acceptable for the FDA?

Agency Response: Rather than defining the Module sections as "not applicable," we recommend that you cite the Module location where the information is located.

We also recommend that you provide a summary of the PK substudy under Section 2.7.2 (Summary of Clinical Pharmacology Studies). Alternately, you can choose to include this summary under Section 2.5 (Clinical Overview).

Meeting Discussion: In Slides 7 -13, the Sponsor addresses the Agency's recommendation to provide a summary of the PK sub-study under Section 2.7.2 and to provide a clinical study report for this PK sub-study in Section 5. The Agency agreed with the proposed organization of data as proposed in Slide 9 and stated it prefers the Sponsor follow Option B as described on Slide 12, which calls for preparation of a separate clinical study summary for the PK subgroup and inclusion of this summary in the respective sections (2.7.2 and 5). The proposed table of contents for the report as proposed in Slide 13, was acceptable to the Agency.

15. **In accordance with the suggested approach for the clinical summary, the applicant also proposes for the nonclinical summary not to repeat published information on the reference product. Only own data of the conducted rabbit study will be summarized in section 2.6.4 together with the descriptions of the methods used during this study. The other sections of the nonclinical summary (2.6.1-2.6.3 and 2.6.5-2.6.7) will also be submitted in order to have a complete dossier in CTD but defined as "not applicable". In addition, a complete nonclinical overview (section 2.4) and the full rabbit study report (section 4.2.2.2) will be provided.**

    Is this approach of presenting the nonclinical information in module 2 acceptable for the FDA?

    Agency Response: In addition to Section 2.6.4 Pharmacokinetic Written Summary, Section 2.6.5 Pharmacokinetics Tabulated Summary should also be included for the rabbit PK/tolerability study.

    Meeting Comment: There was no discussion of this matter during the meeting.

16. **a) Does the proposed location of information in Module 3 adequately address the Agency's expectations on the location of the respective information in the CTD or would the Agency propose different locations for data?**

    Agency Response: The Agency agrees with the proposed location of information within Module 3.

    Meeting Comment: There was no discussion of this matter during the meeting.

    b) All relevant data on QC method validation is planned to be presented in 3.2.S.4.2 for Drug Substance and in 3.2.P.5.3 for Drug Product (standard ICH M3 approach)

and not in the regional US part of the CTD as proposed in the above quoted Guidance for Industry "M4Q: The CTD – Quality". The advantage of this format for the reviewer is that the data on method validation will be located directly following the modules on analytical procedures. Is this approach acceptable to the Agency?

Agency Response: *The Agency agrees with the proposed approach of presenting all relevant data on QC method validation for drug product in Module 3.2.P.5.3. You state that all relevant QC method validation data for drug substance will be presented in Module 3.2.S.4.2, however, Table 3 in the briefing document indicates that this data will be presented in Module 3.2.S.4.3. It is the Agency's expectation that QC method validation for drug substance not be presented in Module 3.2.S.4.2. Refer to the Additional Agency Comments section below for additional feedback regarding the Agency's expectation on QC method validation.*

Additional Comments:
[CMC]Table 3 in the briefing document states that "relevant" method validation information will be located in Sections 3.2.S.4.3 and 3.2.P.5.3. Details were not provided regarding the type and amount of method validation information Bioeq plans to submit to demonstrate the suitability of methods for their intended use. It is the Agency's expectation that Sections 3.2.S.4.3 and 3.2.P.5.3 include method validation/verification reports for all non-compendial and compendial methods intended to support the lot release and stability testing for commercial drug substance and drug product. The method validation reports should support the suitability of the methods at all intended commercial testing sites.

Meeting Discussion: In regard to the recommended type and amount of method validation information, the Sponsor proposed to not include the original reports, but to provide edited versions of the reports as described in Slide 4. The Agency agreed with the Sponsor's general proposal, however, the original validation reports should also be submitted to the BLA. In regard to the proposal for addressing method transfer as described in Slide 4, the Agency stated that the submission of the initial full validation for the originating laboratory alone is not sufficient to support method transfer, and that method transfer data should be submitted to the BLA. The Agency agreed that the Sponsor's proposal for addressing method revalidation as described in Slide 4 is reasonable. In general, the suitability of the method validation reports will be a review issue and additional information and data may be requested upon review.

17. Is the approach to present the manufacturing and testing sites which were only used for development in different sections acceptable to the Agency?

Agency Response: *The Agency agrees with the proposal to present the manufacturing and testing sites used during the developmental phase of FYB201in the corresponding drug substance (Section 3.2.S.2.6 and Section 3.2.S.7) and drug product (Section 3.2.P.2.3 and Section 3.2.P.8) sections.*

Meeting Comment: There was no discussion of this matter during the meeting.

18. **Recently published draft guidance documents encourage the definition of explicit established conditions in regulatory submissions including ICH Q12 and FDA Guidance for Industry "Established Conditions: Reportable CMC Changes for Approved Drug and Biologic Products". The applicant is considering to identify explicit established conditions and provide a list including their location within the CTD in Module 2, section 2.3 Introduction to the Quality Overall Summary.**

    Does the Agency support this approach of defining explicit established conditions based on the draft guidance documents cited above?

    Agency Response: *Agree.*

    Meeting Comment: There was no discussion of this matter during the meeting.

19. **A table of contents of module 4 including a brief description of all documents and references is provided in Table 4 of the Briefing Book. Those sections in bold are planned to be included in the BLA.**

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

    Agency Response: *See response to Question 20.*

    Meeting Comment: See Meeting Discussion for Question 20.

20. **Does FDA agree with the proposed location of the rabbit study report in module 4?**

    Agency Response: *We prefer you include the tissue ocular distribution data in Section 4.2.2.2 Absorption and the ocular and systemic toxicity data in Section 4.2.3.1. Single-Dose Toxicity Study.*

    Meeting Discussion: The Sponsor proposed to provide the rabbit study report in section 4.2.2.2 and to provide a detailed Reviewer's Guide in section 4.2.3.1 with references to the relevant subsections of the combined PK/Toxicity report in section 4.2.2.2 (see Slides 5 and 6). The Agency agreed this is an acceptable approach.

21. **A table of contents of module 5 including a brief description of all documents and references is provided in Table 5 of the Briefing Book. Those sections in bold are planned to be included in the BLA.**

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

Agency Response: *The outline of planned to-be-submitted Module 5 documents is acceptable; however, the Agency may request additional materials and documents during the review process if necessary.*

Meeting Comment: There was no discussion of this matter during the meeting.

22. Does FDA agree that the described format of the CSR and study data are acceptable?

Agency Response: *Acceptable. In addition, please submit all the SAS program codes used to produce the efficacy and safety analysis results presented in the study reports of the comparative clinical study. Please also provide define documents to explain the purpose of the submitted SAS codes.*

Meeting Comment: There was no discussion of this matter during the meeting.

23. In total 477 patients were randomized into the confirmatory safety and efficacy trial. In compliance with ICH E3, we intend to submit only those Case Report Forms (CRFs) which are connected to deaths, other serious adverse events, and withdrawals for adverse events which would be about 76 CRFs in total.

Does FDA agree that other CRFs are not required in the BLA?

Agency Response: *No. In addition to the CRFs proposed, we request that CRFs for all discontinued patients (regardless of the reason for discontinuation) be submitted for each clinical study.*

Meeting Comment: There was no discussion of this matter during the meeting.

24. As a result of the first BPD Type 2 meeting on May 12, 2015, our confirmatory safety and efficacy trial does also include a PK subgroup of 60 patients in which systemic ranibizumab concentration close to Cmax after first and sixth IVT injections, and ADA formation at one day and one week after first IVT injection have been assessed. These results will be incorporated in the main CSR as safety aspects.

Does FDA agree that no separate report is necessary for the PK subgroup?

Agency Response: *No, we do not agree. We recommend that you provide a clinical study report for this PK sub-study under the relevant subsection in Section 5. We also recommend that you include the results of the immunogenicity evaluation within the same study report.*

Meeting Comment: See Meeting Discussion for Question 14.

Additional Agency Comments:

CMC MICROBIOLOGY
The FDA is providing additional product quality microbiology comments for you to consider during development of your commercial manufacturing process and preparation of your 351(k) BLA submission.

All facilities should be registered with the 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). Include in the BLA submission a complete list of the manufacturing and testing sites with their corresponding FEI numbers. A preliminary manufacturing schedule for the drug substance and drug product should be provided in the BLA submission to facilitate the planning of pre-license inspections during the review cycle. Manufacturing facilities should be in operation and manufacturing the product under review during the inspection.

The CMC Drug Substance section of the 351(k) BLA (Section 3.2.S) should contain information and data summaries for microbial and endotoxin control of the drug substance. The information should include, but not be limited to the following:

- *Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).*
- *Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).*
- *Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).*
- *Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).*
- *Information and summary results from the shipping validation studies (3.2.S.2.5).*
- *Drug substance bioburden and endotoxin release specifications (3.2.S.4).*
- *Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).*

The CMC Drug Product section of the 351(k) BLA (Section 3.2.P) should contain validation data summaries to support the aseptic processing operations. For guidance on the type of data and information that should be submitted, refer to the 1994 FDA Guidance for Industry "Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products" at http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf.

The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

- *Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.*
- *Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.*
- *Parameters for filling and capping for the vials.*
- *A list of all equipment and components that contact the sterile drug product (i.e. the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.*
- *Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.*
- *Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.*

The following study protocols and validation data summaries should be included in Section 3.2.P.3.5, as appropriate:

- *Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.*
- *Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.*
- *In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.*
- *Isolator decontamination summary data and information, if applicable.*

- *Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.*
- *Information and summary results from shipping validation studies*
- *[Validation of capping parameters, using a container closure integrity test.]*

The following product testing and method validation information should be provided in the appropriate sections of Module 3.2.P:

- *Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed in lieu of sterility testing for stability samples every 12 months (annually) until expiry.*
- *Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.*
- *Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> Bacterial Endotoxin Test (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time. Low endotoxin recovery studies may not be necessary for products that do not contain polysorbate.*

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

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

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with

FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

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

Finally, in accordance with the BsUFA II agreement, FDA has contracted with an independent contractor, Eastern Research Group, Inc. (ERG), to conduct an assessment of the Program. ERG will be in attendance at this meeting as silent observers to evaluate the meeting and will not participate in the discussion. Please note that ERG has signed a non-disclosure agreement. Information on the Program is available at https://www.fda.gov/forindustry/userfees/biosimilaruserfeeactbsufa/default.htm

PREA REQUIREMENTS

Under the Pediatric Research Equity Act [section 505B of the Federal Food, Drug and Cosmetic Act (FD&C Act) (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 or deferred.

You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive initial PSP that addresses each indication. For indications for which the labeling for the reference product contains adequate pediatric information, you may be able to fulfill PREA requirements by satisfying the statutory requirements for biosimilarity and providing an adequate scientific justification for extrapolating the pediatric information from the reference product to your proposed product (see question and answer I.11 in FDA's guidance for industry on Biosimilars: Questions and Answers Regarding Implementation of the Biologics Price Competition and Innovation Act of 2009). For conditions of use for which the reference product does not have adequate pediatric information in its labeling, a waiver (full or partial), or a deferral, may be appropriate if certain criteria are met.

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) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review

resources on the PLR Requirements for Prescribing Information and Pregnancy and Lactation Labeling Final Rule 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 (http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf).

In addition, you should review the draft FDA Guidance for Industry, "Labeling for Biosimilar Products," March 2016 at https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM493439.pdf

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 entitled Nonproprietary Naming of Biological Products, available at: https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm459987.pdf, 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.

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: http://www.fda.gov/ectd.

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 http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway.

MANUFACTURING FACILITIES
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.				

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:

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332466.pdf

https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/UCM332468.pdf.

Meeting Comment: There was no discussion of the Additional Agency Comments during the meeting.

ACTION ITEM:
The Agency agreed to provide minutes of the meeting within 30 days.

ATTACHMENT:
A copy of the Sponsor's slide presentation is attached.

8 Pages have been Withheld in Full as b4 (CCI/TS) immediately following this page

---

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/

WILEY A CHAMBERS
01/10/2019 04:40:22 AM