CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761299Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PIND 136459

MEETING MINUTES

Alvotech Swiss AG
c/o Development Consulting Services, PharmaLex US
1700 District Avenue, Suite #100
Burlington, MA 01803

Attention: Anna Perelka
Senior Manager, Regulatory Affairs

Dear Ms. Perelka:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for AVT02.

We also refer to the telecon between representatives of your firm and the FDA on October 6, 2021. The purpose of the meeting was to discuss and obtain concurrence on the content and format of a proposed supplemental BLA for interchangeability to support the filing of the 351(k) supplemental BLA.

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

If you have any questions, call me at 301-796-2777.

Sincerely,

{See appended electronic signature page}

Sadaf Nabavian, PharmD
CDR, US Public Health Service
Rheumatology and Transplant Medicine
Division of Regulatory Operations -
Immunology and Inflammation
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

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

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: October 6, 2021; 8:00-9:00 a.m. EST
Meeting Location: Teleconference

Application Number: PIND 136459
Product Name: AVT02

Indication: AVT02 is being developed for the same indications as those approved for US-licensed Humira

Sponsor: Alvotech Swiss AG (PharmaLex US)

Regulatory Pathway: 351(k) of the Public Health Service Act

Meeting Chair: Nikolay P. Nikolov, MD
Meeting Recorder: Sadaf Nabavian, PharmD

FDA ATTENDEES

Nikolay Nikolov, MD, Director, Division of Rheumatology and Transplant Medicine (DRTM), Office of Immunology and Inflammation (OII), Office of New Drugs (OND)

Anil Rajpal, MD, MPH, Clinical Team Leader, DRTM, OII, OND

Nadia Habal, MD, Clinical Reviewer, DRTM, OII, OND

Shari Targum, MD, Deputy Director, Division of Dermatology and Dentistry (DDD), OII, OND

Felicia Lewis, MD, Clinical Reviewer, DDD, OII, OND

Dawn Williams, BSN, Safety Regulatory Project Manager, DDD

Sandhya Apparaju, PharmD, Clinical Analyst, Division of Gastroenterology (DG), OII, OND

Ping Ji, PhD, Clinical Pharmacology Team Leader, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)

Shalini Wickramaratne Senarath Yapa, PhD, Clinical Pharmacology Reviewer, DIIP, OCP, OTS

Xianghong (Emily) Jing, PhD, Review Chief, Division of Biotechnology Review and Research II (DBRRII), Office of Biotechnology Products (OBP), Office of Pharmaceuticals Quality (OPQ)

Brian Roelofs, PhD, Product Quality Team Leader, DBRRII, OBP, OPQ

Ian McWilliams, PhD, Product Quality Reviewer, DBRRII, OBP, OPQ

Madushini Dharmasena, PhD, Microbiologist Reviewer, Biotechnology Manufacturing Branch 2 (BMB2), Division of Biotechnology Manufacturing (DBM), Office of Pharmaceutical Manufacturing Assessment (OPMA)

Stacey Ricci, MEng, ScD, Director, Scientific Review Staff (SRS, Office of Therapeutic Biologics and Biosimilars (OTBB), OND

Cristina Ausin, PhD, Reviewer, SRS, OTBB, OND

Sarah Schrieber, PharmD, Reviewer, SRS, OTBB, OND

Sarah Brown, PharmD, Science Policy Analyst, SRS, OTBBS, OND

Thomas Herndon, MD, SRS, OTBB, OND

Archita Patel, Regulatory Counsel, Policy Staff (PS), OTBB, OND

Christine Corser, Analyst, PS, OTBB, OND

Mohamed Alosh, Statistical Team Leader, Division of Biometrics III (DB3), Office of Biostatistics (OB), OTS

Kathleen Fritsch, PhD, Mathematical Statistical Reviewer, DB3, OB, OTS

Yongman Kim, PhD, Statistical Team Leader, DB4, OB, OTS

Carol Galvis, PhD, Nonclinical Team Leader, Division of Pharmacology Toxicology for Immunology and Inflammation (DPTII), OII, OND

Jason Flint, MBA, PMP, Associate Director for Human Factors, Division of Medication Error Prevention and Analysis I, Office of Surveillance and Epidemiology, Center for Drug Evaluation and Research

Sadaf Nabavian, PharmD, Sr. Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation (DROII), Office of Regulatory Operations (ORO), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)

SPONSOR ATTENDEES

ALVOTECH

Kimber Poffenberger, SVP, Head Global Regulatory Affairs
Norris Pyle, Director, Global Regulatory Affairs
Nivedita Roy, VP, Head Global Regulatory Strategy
Lisa Clausen, Senior Manager, Global Regulatory Affairs
Joseph McClellan, Chief Scientific Officer
Fausto Berti, SVP, Head Clinical and Medical Affairs
Sesselja Omarsdottir, SVP, Head Pharmaceutical Sciences
Elin Edwald, Director, Head Combination Products and Devices
Kathiravan Narayanan, VP, Head manufacturing
Cecilia Michel, Senior Director, Head Pharmaceutical Sciences Strategy
Heimo Stroissnig, VP, Head Clinical Development and Clinical Safety
Karpagavalli Damodharan, Manager, Global Regulatory Affairs

TEVA

Cory Wohlbach, VP, Regulatory Affairs Global Biosimilars
Donald Lewis, Director, Regulatory Affairs Global Biosimilars
Maria Burkholder, Director, Regulatory Affairs Global Biosimilars
Jill Pastore Manager, Regulatory Affairs Global Biosimilars

1.0 BACKGROUND

The purpose of the meeting is to discuss the content and format of a complete supplemental application for a future 351(k) sBLA submission demonstrating interchangeability of AVT02 with US-licensed Humira. Alvotech Swiss AG/PharmaLex US submitted a request for a meeting on July 9, 2021, and the briefing package was also received on July 9, 2021. DRTM granted the meeting on August 14, 2021, as a teleconference meeting between Alvotech Swiss AG/PharmaLex US and DRTM. The meeting was scheduled for October 6, 2021.

The Sponsor's questions are noted in *italic* font below, followed by FDA's responses are in bold font and any Discussion between the Sponsor and FDA are in normal font. For the meeting the Sponsor requested to discuss Questions 2, 3, 4b, and 5b.

FDA sent Preliminary Comments to the Sponsor on October 5, 2021.

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 the Sponsor 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

FDA INTRODUCTORY COMMENTS:

Your original BLA (761205) for AVT02 (40 mg/0.4 mL autoinjector) as biosimilar to U.S.-licensed Humira (40 mg/0.4 mL autoinjector) is currently under review. Therefore, the comments below are only relevant if an approval decision is made for BLA 761205 and only with respect to the 40 mg/0.4 mL autoinjector.

Question 1:

Does the FDA agree that the proposed content of the planned supplement meets the statutory requirements of Section 351(k)(4) for licensure of AVT02 as an interchangeable product with US-licensed Humira?

FDA Response to Question 1:

To support a demonstration of interchangeability, section 351(k)(4) of the Public Health Service Act provides, among other things, that information submitted in the application (or supplement) must be sufficient to show that the proposed interchangeable product "is biosimilar to the reference product" and that the proposed interchangeable product "can be expected to produce the same clinical result as the reference product in any given patient." FDA expects that sponsors will submit data and information to support a showing that the proposed interchangeable product can be expected to produce the same clinical result as the reference product in all of the reference product's licensed conditions of use.

A sponsor must also demonstrate that "for a biological product that is administered more than once to an individual, the risk in terms of safety or diminished efficacy of alternating or switching between use of the biological product and the reference product is not greater than the risk of using the reference product without such alternation or switch." See guidance for industry Considerations in Demonstrating Interchangeability With a Reference Product (May 2019), available at https://www.fda.gov/media/124907/download.

Based on the information provided in the meeting package for your proposed interchangeable product, AVT02, the proposed content of your planned supplement seems reasonable. The adequacy of the data and information in the submission to support a demonstration of interchangeability will be a review issue.

Discussion:

No further discussion was needed.

Question 2:

a. ***Does FDA agree with the proposed format and content of the AVT02 sBLA for interchangeability?***
b. ***Alvotech proposes to submit additional new Module 1.2, 2.2, 2.5 and 2.7 documents, which will specifically include the information relevant for the interchangeability claim, instead of adding information to the existing BLA module versions. Does FDA agree with this approach?***
c. ***Does the FDA have comments on the proposed approach for presentation of data and analyses for Study AVT-02-GL-302 in the clinical study report and Module 2.5 Clinical Overview and Module 2.7 Clinical Summaries sections?***

FDA Response to Question 2a:

Overall, we agree with the proposed format and content of the AVT02 sBLA for interchangeability. We have the following additional comments:

1. *Module 5 should contain the PK and ADA bioanalytical methods for the switching study (study AVT02-GL-302)*
2. *Module 5 should contain an 'integrated summary of immunogenicity' document which should include, but not limited to, the assessment for the impact of ADA and nAb on the PK, efficacy, and relevant safety endpoints for the switching study (study AVT02-GL-302).*

The Clinical Study Reports section should include the study report, all versions of the protocol, the statistical analysis plan, and an annotated case report form. Submit tabulation datasets (SDTM format) and analysis datasets (ADaM format preferred) in SAS transport format (.xpt). The analysis datasets should include all variables (including derived variables) needed for conducting the primary, secondary, and sensitivity analyses included in the study report. 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 dataset, algorithms for derived variables (including source variables used), and descriptions for the codes used in factor variables. Submit statistical programs for all complex or non-standard analyses.

Discussion:

The FDA provided clarification that immunogenicity data from the switching study only needed to be included in the 'integrated summary of immunogenicity' document. The FDA added that information on the ADA and nAb assays, PK assay, in addition to the immunogenicity results from the switching study should be included in this summary document. The information should be included in Module 5.

The Sponsor sought clarification on the selected method to follow for developing validating assays for ADA detection and to confirm if it is expected to follow the FDA guidance on the immunogenicity testing of therapeutic protein products and if the method would be acceptable to the FDA. The FDA accepted the Sponsor's proposal.

FDA Response to Question 2b:

Your proposal appears reasonable.

Discussion:

No further discussion took place.

FDA Response to Question 2c:

Overall, the proposed approach for presentation of data and analyses for Study AVT02-GL-302 in the clinical study report (CSR), Module 2.5, and Module 2.7 appears to be reasonable, however the proposed modification to the statistical analysis plan for the primary PK endpoints will be a review issue. Because making an unplanned change to the analysis is a significant issue that can impact the ability to interpret the results of the study, include in your submission a comprehensive discussion of the decision-making process that led to your proposed modification. Also discuss any other potential options that you considered and your rationale for selecting your final proposal.

You should include the results of the statistical analysis using geometric mean ratios (original analysis) in an appendix to the CSR.

Please provide the following in your study safety report:

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

b. *Adverse reaction tables (adverse reactions are defined as those AEs with possible or probable causality) with incidence rate of ≥ 1%.*

c. *In addition to providing overall incidence rates of adverse reactions, conduct an analysis of the safety data from the switching study (study AVT02-GL-302) by treatment period to evaluate whether the switch between AVT02 and EU-Humira were associated with increased or decreased risk of adverse reactions.*

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

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

f. *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.*

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

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

i. *Provide narratives for all deaths, serious adverse events (SAEs), subjects who discontinued the study drug due to adverse events (AEs), and 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.*

j. *In the 120-day safety update report (SUR), you should update the sBLA application with new safety information learned about the product that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. Provide narratives in the SUR for all subjects who died, experienced SAEs, pregnancies, and AEs of special interest.*

k. *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). We can provide recommendations regarding the pooling of certain preferred terms (e.g., viral upper respiratory tract infection and upper respiratory tract infection) to enhance your safety analysis if you submit your coding dictionary prior to completion of the safety analysis for your sBLA.

l. Include the full text version of any referenced articles.

Discussion:

No further discussion was needed.

Question 3:

With the planned sBLA, an interchangeability designation is sought for AVT02 based on the data package including the 40 mg/0.4 mL autoinjector presentation. Alvotech proposes (b) (4) ***Does FDA agree that the interchangeability designation initially granted for 40 mg/0.4 mL AVT02-AI would also apply to the additional strengths and presentations registered via CMC supplement?***

FDA Response to Question 3:

See FDA Introductory Comments.

After FDA approves your pending BLA 761205 for your proposed biosimilar, AVT02 for the 40 mg/0.4 mL autoinjector, you may submit a supplement seeking interchangeability with US-licensed Humira for the 40 mg/0.4 mL autoinjector. (b) (4)

Discussion:

The Sponsor sought clarification on (b) (4)

approval of BLA 761205 seeking biosimilarity to US-Humira for AVT02 40 mg/0.4 mL AI. The Sponsor informed the FDA that data for interchangeability will be ready for submission in the next few months (Q4 of 2021 or Q1 of 2022). The FDA stated that if the Sponsor plans to submit the supplement for interchangeability with clinical data, it will be under a 10-month review clock. Further, BLA 761205 would need to be approved before the Sponsor could submit a supplemental BLA for interchangeability.

The Sponsor asked that if an interchangeability determination is made with respect to the 40 mg/0.4 mL AI (b) (4)

The Sponsor asked if the clinical data that support the 40 mg/0.4 mL AI as interchangeable (b) (4) (b) (4) The FDA stated that (b) (4) (b) (4) sufficient data should be submitted to verify the performance of the device and also sufficient data and justification (b) (4) The FDA clarified that it does not necessarily mean that new clinical data are needed to support a demonstration of interchangeability (b) (4) The Sponsor stated that they have also been in contact with DMEPA to obtain guidance (b) (4) on the safety device for the AI.

The FDA suggested that the Sponsor submit a meeting request to discuss the content (b) (4) in the context of interchangeability. The Sponsor noted that they had additional questions that have been submitted to BLA 761205.

Post-meeting Comment:

FDA acknowledges the additional questions Alvotech has submitted in an amendment dated September 24, 2021 to BLA 761205. FDA will provide responses to these questions in a separate communication under the BLA.

Question 4:

a. ***Alvotech plans to submit the Week-28 CSR for study AVT02-GL-302 as part of the sBLA package. A safety update report with results from the optional extension phase until week-52 is proposed to be submitted during the ongoing sBLA review in month 4 of the 10-month review clock. Does the FDA agree?***

b. ***In case FDA determines that a comparative use human factor study is required for interchangeability of the AI presentation, Alvotech proposes to submit the study report during the ongoing sBLA review no later than month 4 of the 10 months sBLA review clock. Does FDA agree?***

FDA Response to Question 4a:

Your proposal appears reasonable. See Response to Question 2c regarding the content of the safety summary.

Discussion:

No further discussion was needed.

FDA Response to Question 4b:

If we determine that a comparative use human factors study is required to support interchangeability of the AI presentation, we recommend that you submit the study report with the initial sBLA submission.

Discussion:

The Sponsor sought clarification on the comparative use human factor (HF) study and stated that they submitted the protocol for feedback in May/July and communicated in July on the initiation of the comparative HF study based on the protocol submitted prior to DMEPA being able to provide feedback. The Sponsor informed the FDA that the study is now completed, and the Sponsor will include the final study report as part of Module 5.3.5.4 as part of the interchangeability supplement if it is acceptable to the FDA.

The FDA stated that from the DMEPA's perspective they will be prepared to review the results when submitted and were agreeable that the report be included in Module 5. The Sponsor also plans to include the threshold analysis and include the results in Module 5.3.5.4 and the summary of the overall results will be included in the clinical overview and as well in Module 2.7.3. The FDA accepted the proposal to include the results in Module 5.

Question 5:

a. ***Does the FDA agree with the proposed labeling changes to the Prescribing Information for the sBLA for interchangeability?***

b. ***The interchangeability statement in the prescribing information as per FDA guidance does not specify the concentration of the reference product the biosimilar is interchangeable to. However, Alvotech expects that AVT02 will be approved as an interchangeable biosimilar (b) (4) (b) (4) with a product concentration of 100 mg/mL. Does the Agency agree?***

c. ***Alvotech plans to submit further supplements for AVT02 in parallel to the review of the sBLA for interchangeability, which include changes to the labeling of AVT02. Does FDA agree that (b) (4) (b) (4) updated labeling documents will be submitted during the ongoing review of the sBLA for interchangeability?***

FDA Response to Question 5a:
We cannot agree at this time with the proposed labeling changes to the Prescribing Information for your planned sBLA for interchangeability; this will be a review issue.

Discussion:

No further discussion was needed.

FDA Response to Question 5b:
See FDA Introductory Comments and FDA Response to Question 3.

Your proposed sBLA for interchangeability only includes the 40 mg/0.4 mL autoinjector. Therefore, approval of your sBLA for interchangeability to US-licensed Humira would be specific to the 40 mg/0.4 mL autoinjector. (b) (4)

Discussion:

The Sponsor sought clarification on how the interchangeability statement should be presented in labeling and if the approval will be specific to the product at a

concentration of 100 mg/mL. The FDA referred the Sponsor to the preliminary responses and added that the current pending BLA is for the 40 mg/0.4 mL AI and is the same strength and presentation for the proposed interchangeability supplement.

FDA Response to Question 5c:
See FDA Introductory Comments and the FDA Response to Question 3 and 5b.

Proposed labeling will be reviewed during review of the supplement(s).

Discussion:

No further discussion was needed.

Question 6:

Does FDA agree that in case of an interchangeability designation, AVT02 will be exempt from PREA requirements and that no further updates of the iPSP will be required?

FDA Response to Question 6:
FDA is still considering the response to your question. We will provide feedback in a follow-up communication.

Discussion:

No further discussion was needed.

Post-meeting Comment to Question 6:

On September 4, 2020, you submitted BLA 761205 for AVT02 as biosimilar to US-Humira. The BLA does not seek an interchangeability determination and would not be approved as interchangeable with the reference product. Accordingly, we understand your question to be regarding a scenario in which BLA 761205 is approved and AVT02 is licensed as biosimilar to US-Humira and—pursuant to a subsequent supplement to the BLA—AVT02 is later determined to meet the standards for interchangeability.

Section 505B(*l*)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) states that a biosimilar product that FDA "has not determined to meet the standards…for interchangeability…shall be considered to have a new active ingredient" under PREA. Accordingly, if BLA 761205 is approved and AVT02 is licensed as biosimilar to US-Humira, AVT02 would be considered to have a new active ingredient for purposes of PREA and the BLA would trigger pediatric study requirements under PREA (see section 505B(a)(1)(A) of the FD&C Act).

Section 505B(*l*)(2) of the FD&C Act states that "[a] biological product that is interchangeable with a reference product…shall not be considered to have a new active ingredient" under PREA. Accordingly, if AVT02 is subsequently (i.e., after initial licensure as a biosimilar product) determined to meet the standards for interchangeability, AVT02 would no longer be considered to have a new active ingredient for purposes of PREA. As a result, the supplement seeking such interchangeability determination would not trigger pediatric study requirements under PREA on the basis of a new active ingredient.

We note, however, that section 505B(*l*)(2) of the FD&C Act does not apply retroactively to eliminate PREA PMRs previously imposed once an interchangeability determination is made. Rather, applicability of PREA is determined only once in the context of each application or supplement. Accordingly, if your application for your proposed biosimilar product is approved and the product is subsequently determined to meet the standards for interchangeability, any previously imposed PREA requirements that have not been fulfilled at the time of such interchangeability determination would remain in place.

3.0 ADDITIONAL INFORMATION

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 FDA.gov.[2]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(l) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For 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.16 in the draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act*. 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.

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

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[3]. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d)[4] and 201.57[5] including the Pregnancy and Lactation Labeling Rule (PLLR) (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[6] and Pregnancy and Lactation Labeling Final Rule[7] 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

[3] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
[4] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1
[5] http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=201.56&utm_campaign=Google2&utm_source=fdaSearch&utm_medium=website&utm_term=21%20CFR%20201.56&utm_content=1
[6] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[7] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

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]

In addition, you should review the FDA guidance for industry *Labeling for Biosimilar Products* (July 2018).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

On January 13, 2017, FDA issued a final guidance for industry *Nonproprietary Naming of Biological Products*, stating that, for certain biological products, the Agency intends to designate a proper name that includes a four-letter distinguishing suffix that is devoid of meaning.

Please note that certain provisions of this guidance describe a collection of information and are under review by the Office of Management and Budget under the Paperwork Reduction Act of 1995 (PRA). These provisions of the guidance describe the submission of proposed suffixes to the FDA, and a sponsor's related analysis of proposed suffixes, which are considered a "collection of information" under the PRA. FDA is not currently implementing provisions of the guidance that describe this collection of information.

However, provisions of the final guidance that do not describe the collection of information should be considered final and represent FDA's current thinking on the nonproprietary naming of biological products. These include, generally, the description of the naming convention (including its format for originator, related, and biosimilar biological products) and the considerations that support the convention.

Your proposed 351(k) BLA would be within the scope of this guidance. As such, FDA intends to assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

[8] When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MANUFACTURING FACILITIES

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

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*.

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 supplement, 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).

[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

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

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

None

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SADAF NABAVIAN
11/22/2021 07:01:49 PM

PIND 136459

MEETING MINUTES

Alvotech Swiss AG
c/o Development Consulting Services, PharmaLex US
1700 District Avenue, Suite #100
Burlington, MA 01803

Attention: Bill Miller, PhD
Senior Director, Development Consulting & Scientific Affairs

Dear Dr. Miller:[1]

Please refer to your Pre-Investigational New Drug Application (PIND) file for AVT02.

We also refer to the telecon between representatives of your firm and the FDA on July 16, 2020. The purpose of the meeting was to provide feedback on the format and content of a complete application for a future 351(k) BLA submission as an original biosimilar biological product.

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

If you have any questions, call Sadaf Nabavian, Senior Regulatory Project Manager, at 301-796-2777.

Sincerely,

{See appended electronic signature page}

`

Sadaf Nabavian, PharmD
CDR, US Public Health Service
Sr. Regulatory Project Manager
Rheumatology and Transplant Medicine
Division of Regulatory Operations for Immunology and Inflammation
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

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

Enclosure:

- Meeting Minutes

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Biosimilar
Meeting Category: BPD Type 4

Meeting Date and Time: July 16, 2020; 8:00-9:00 a.m. EST
Meeting Location: Teleconference

Application Number: PIND 136459
Product Name: AVT02

Indication: AVT02 is being developed for the same indications as those approved for U.S.-licensed Humira
Sponsor: Alvotech Swiss AG (PharmaLex US)

Regulatory Pathway: 351(k) of the Public Health Service Act

Meeting Chair: Nikolay Nikolov, MD
Meeting Recorder: Sadaf Nabavian, PharmD

FDA ATTENDEES

Nikolay Nikolov, MD, Director (Acting), Division of Rheumatology and Transplant Medicine (DRTM), Office of Immunology and Inflammation (OII), Office of New Drugs (OND)
Rachel Glaser, MD, Clinical Team Leader, DRTM, OII, OND
Nadia Habal, MD, Clinical Reviewer, DRTM, OII, OND
Sabiha Khan, MD, Clinical Reviewer, DRTM, OII, OND
Ping Ji, PhD, Clinical Pharmacology Team Leader, Division of Inflammation and Immune Pharmacology (DIIP), Office of Clinical Pharmacology (OCP), Office of Translational Sciences (OTS)
Renu Singh, PhD, Clinical Pharmacology Reviewer, DIIP, OCP, OTS
Patrick Lynch, PhD, Product Quality Team Leader, Division of Biotechnology Review and Research II (DBRRII), Office of Biotechnology Products (OBP), Office of Pharmaceuticals Quality (OPQ)
Lei Zhang, PhD, Product Quality Reviewer, DBRRII, OBP, OPQ
Madushini Dharmasena, PhD, Microbiologist Reviewer, Division of Biotechnology Manufacturing Branch 2 (DBM2), Office of Pharmaceutical Manufacturing Assessment (OPMA)
Marlene Schultz-Depalo, MS, MA, RAC, OBP-IO Biosimilar Program and Policy Analyst, OBP, OPQ
Hannah Busey, Office of Strategic Programs
Candace Gomez-Broughton, PhD, Microbiologist Team Leader, DBM1, OPMA

Cristina Ausin, PhD, Reviewer, Office of New Drugs (OND), Therapeutic Biologics and Biosimilars Staff (OTBB), Scientific Review Staff (SRS)
Stacey Ricci, MEng, ScD, Director (Acting), OND, OTBB, SRS
Sarah Schrieber, PharmD, Reviewer, OND, OTBB, SRS
Tyree Newman, Sr. Regulatory Project Manager, OND, OTBB, SRS
Leila Hann, Policy Analyst, OND, OTBB, SRS
Ginto Pottackal, PhD, Statistical Reviewer, Division of Biometrics III (DBIII), Office of Biostatistics (OB), Office of Translational Sciences (OTS)
Yongman Kim, Statistical Team Leader, DBIII, OB, OTS
Mohamed Alosh, Statistical Team Leader, Division of Biometrics III
Anup Srivastava, PhD, Nonclinical Reviewer, Division of Pharmacology Toxicology for Immunology and Inflammation (DPTII), Office of Immunology and Inflammation (OII), Office of New Drugs (OND)
Carol Galvis, PhD, Nonclinical Team Leader, DPTII, OII, OND
Sadaf Nabavian, PharmD, Sr. Regulatory Project Manager, Division of Regulatory Operations for Immunology and Inflammation (DROII), Office of Regulatory Operations (ORO), Office of New Drugs (OND), Center for Drug Evaluation and Research (CDER)
Millie Shah, Lead General Health Scientist, Division of Medication Error and Prevention and Analysis (DMEPA)
Avani Bhalodia, RPH, DMEPA
Suzanne Hudak, MS, Device Reviewer, Center for Devices and Radiological Health (CDRH)
Kathleen Fritsch, PhD, Mathematical Statistical Reviewer, Division of Biometrics III
Sandhya Apparaju, PharmD, Clinical Analyst, Division of Gastroenterology (DG)
Nichelle Rashid, Safety Project Manager Team Leader, DMEPA
Snezana Trajkovic, MD, Team Leader, Division of Dermatology and Dentistry (DDD)
Rumi Young, PhD, Biomedical Engineer, Division of Health Technology Iii C
Maryjoy Mejia, MD, Medical Reviewer, DDD

SPONSOR ATTENDEES

Cecilia Michel, Director, Analytical Strategy and Comparability
Charlotte Kornbo, Senior Vice President, Quality
Elin Edwald, Director, Device Development
Fausto Berti, Senior Vice President, Clinical and Medical Affairs
Heimo Stroissnig, Vice President, Clinical and Medical Affairs,
Inga Lily Gunnarsdottir, Associate Director, Portfolio and Alliance Management
Sean Lloyd, Director, DP Manufacturing and MSAT
Joseph McClellan, Chief Scientific Officer
Junaid Muneer, Director, USP Manufacturing Operations
Kathiravan Narayanan, Vice President, DS Manufacturing and MSAT
Kimber Poffenberger, Senior Vice President, Global Regulatory Affairs
Nivedita Roy, Senior Director, Global Regulatory Affairs
Thomas Lengsfeld, Senior Director, Global Regulatory Affairs
Tine Kold Oleson, Vice President Program Leadership

Sesselja Omardottir, Senior Vice President, Analytical Research and Development
Sean Lloyd, Director, DP Manufacturing and MSAT

1.0 BACKGROUND

Alvotech/Pharmalex submitted a BPD Type 4 meeting request on May 11, 2020, to discuss the format and content of a complete application to support a future 351(k) BLA submission for AVT02, as a biosimilar to US-licensed Humira.

The FDA's preliminary comments were sent to Alvotech/Pharmalex on July 14, 2020. On July 16, 2020, Alvotech/Pharmalex provided the discussion points to FDA's preliminary comments and requested to discuss Question 1, 4, 6, 7, and General Comments regarding CCI testing for AVT02-AI and rabbit pyrogen testing on AVT02-DP batch.

Alvotech/Pharmalex's questions are in ***bold italics***; FDA's preliminary response is in *Italics,* Sponsor's pre-meeting response is in bold font and any discussion points captured during the meeting are in normal font under the Discussion Section. Any slides, attachments and handouts will be included in Section 6.

FDA may provide further clarifications of, or refinements and/or changes to the responses and the advice provided at the meeting based on further information provided by Alvotech 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

During the introductory comment Alvotech stated that they're planning to develop their proposed biosimilar to US-Humira for AVT02 and focusing on the 40 mg/0.4 ml as prefilled pen presentation (AVT02-AI) and developing per the guidance provided from the EMA and FDA and in accordance with the guidance from Japan.

Alvotech also informed the FDA that they plan to submit the original 351(k) BLA on August 31, 2020, and informed the FDA (b) (4) Alvotech acknowledged all comments in the response to Question 1 and will work with the FDA based on the recommendations set forth. Alvotech sought further clarification on points 4 and 6 (see Discussion section under both points 4 and 6).

Question 1:
Does the FDA agree that the proposed approach follows the 351(k) statutory requirements and supports review of the AVT02 BLA? Does FDA have any feedback on the overall content and organization of the AVT02 BLA?

FDA Response to Question 1:
For your 351(k) application, if you consider animal data are not required to support a demonstration of biosimilarity, submit a justification for why animal studies are unnecessary in your application under section 351(k)(2)(A)(i)(I)(bb).

We note that you plan to submit the summary of the PK results from studies AVT02-GL-101, (b) (4) *AVT02-GL-301,* (b) (4) *in Module 2.7.1. We recommend that you submit the summary of results of study AVT02-GL-102 in Module 2.7.1 and submit the summary of results of the remaining PK studies and special studies including summary of immunogenicity results in Module 2.7.2.*

Your proposals to cross reference AVT02 characterization information in Section 3.2.S.3 to relevant content in Module 3.2.R.3, and include separate leaves in Module 3 for the drug product (AVT02-DP PFS), the drug product assembled with the autoinjector (AVT02-AI) (b) (4) (b) (4) *appear reasonable. Section 3.2.S.3 should include any additional analytical characterization results and information for quality attributes that are not part of the comparative analytical assessment. We have the following general recommendations on data and information that should be included in section 3.2.R to support your comparative analytical assessment. Your section 3.2.R should include:*

a) *Table(s) with the expiration dates and date of testing of U.S.-licensed Humira and E.U.-approved Humira lots;*
b) *The risk assessment of quality attributes included in the comparative analytical assessment;*
c) *Rationale(s) for selecting particular AVT02, U.S.-licensed Humira, and E.U.-approved Humira lots from all available lots for each quality attribute tested.*
d) *Table(s) or listing of all sites where the comparative analytical assessment was conducted and identify the testing site(s) for each method.*

Include the following in Module 5 of your future BLA submission:

1. *Subject narratives for all deaths, all serious adverse events (AEs), and AEs resulting in discontinuation. In the narratives, include the date and study day in the discussion relating to the event(s) e.g. "The event happened on xx/yy/2020 (study day zz). Also include how the onset of the event relates to exposure (number of doses and date of occurrence relative to most recent dose).*

2. *Reference ranges for all laboratory values in the data listings where those laboratory values are presented.*

3. *In the presentation of laboratory data, "flag" all laboratory values and vital signs that are outside of the reference ranges*

4. *Include tables of raw incidence rates of adverse events at ≥1% by treatment group as well as the exposure-adjusted rates (in patient-years) by treatment group.*

Sponsor's Pre-Meeting Response to no. 4:
Alvotech will generate tables as per FDA recommendation and include these tables as Appendix to the Module 2.7.4. Does the FDA agree with this approach?

Discussion:

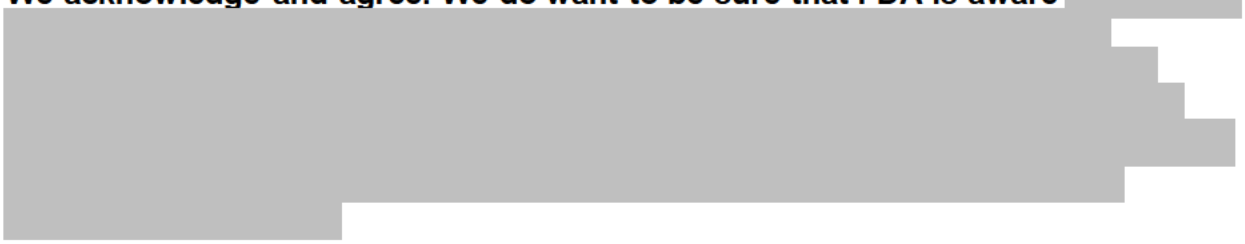
See Slides 6 and 7.

The FDA replied that Alvotech's proposal is acceptable.

5. *Submit the data from clinical studies in CDISC SDTM and ADaM format. All datasets should be submitted in SAS Transport format (.xpt). The datasets should be accompanied by adequate and clear documentation.*

6. *Your submission should include all clinical study protocols (including all amendments), SAPs, and annotated case report forms. Include statistical programs for the more complex analysis models and missing data imputation models.*

Sponsor's Pre-Meeting Response to no. 6:
We acknowledge and agree. We do want to be sure that FDA is aware (b) (4)



Discussion:

See Slide 7.

The FDA had no objections and stated that as long as Alvotech provides all the requested information for the studies that will be supporting the application, the proposal will be acceptable.

Question 2:
Does FDA have any feedback on the proposed locations for both the analytical methods/validations for release testing and on the proposed approach for presenting characterization method summaries in 3.2.R.3?

FDA Response to Question 2:
Your proposals to submit method validation reports for all non-compendial release testing methods in Section 3.2.R.2 Method Validation Reports, and characterization method summaries in Section 3.2.R.3 are acceptable. In addition to the method validation reports in Section 3.2.R.2, provide summaries of the analytical procedure validation results for release methods in Sections 3.2.S.4.3 or 3.2.P.5.3. Characterization method summaries provided in Section 3.2.R.3 should include sufficient data and information to support that each method is scientifically fit for its intended use. We recommend providing information on sensitivity, specificity, and precision of the characterization assays, as appropriate, to support that the methods provide results that are reproducible and reliable. Additionally, we recommend including information on the number of technical replicates within each lot tested for characterization methods. This information may be necessary to support our assessment of comparative analytical results.

Discussion:
No discussion took place.

Question 3:
The applicant intends to claim an initial shelf life of 24 months. It is intended to include all available stability data (up to 18 months) for AVT02 drug product at the point of filing (Table 7). An additional 6 months of stability data for all studies will provided during BLA review at Day 120 post-submission, to ensure data up to 24 months is available. The shelf life assignment data for (b) (4) 0.4 mL (b) (4) (b) (4) will be based on that available from the 0.4 mL presentation. Comparability data between the quality attributes of the 0.4 mL fill (b) (4) batches will be presented in the dossier to support this approach. Does the Agency agree that this approach will be acceptable?

FDA Response to Question 3:
We agree that your approach to use available biochemical stability data from the AVT02-PFS with 0.4 mL fill to support the shelf life for (b) (4) 0.4 mL (b) (4) is acceptable, provided that adequate data and information are submitted to support comparability (b) (4) as proposed in the meeting package. We also agree with your approach to submit 18 months stability data at initial BLA submission, and additional 6 months stability data during BLA review at Day 120. The updated 6 months stability data should be from the same drug product batches using the same stability protocols and analytical methods as in the original BLA submission.

Also, see response to Question 4 regarding acceptable device data package for proposed shelf life.

Discussion:
No discussion took place.

Question 4: ***Stability of AVT02 drug product assembled with*** [redacted] ***an autoinjector (AI)***

Does the Agency agree that this approach will be acceptable?

FDA Response to Question 4:
You propose to leverage the stability data generated from the pre-assembled AVT02 drug product (AVT02-DP PFS) to support the shelf life [redacted] *AVT02-AI with 0.4 mL fill). We agree that it is acceptable to leverage the biochemical stability results from the pre-assembled AVT02 drug product to support the shelf life* [redacted] *provided that adequate data and information are provided to support that the safety device and autoinjector assembly operations have no adverse impact on product quality attributes.*

All device essential performance requirements (EPR's) should be tested through end of shelf life at the intended storage temperature on 3 final finished batches in order to ensure that your product performs within the specification limits through the end of shelf life. If the complete data is not yet available at the time of submission, you should include accelerated temperature data in addition to your real time testing. The accelerated temperature data should be collected through a timepoint which correlates with end of shelf life at the intended storage temperature.

For the AI device, you propose submitting the following functionality data:

a. 12 months for 2 batches at 5°C
b. 6 months for 1 batch at 5°C
c. 6 months for 1 batch at 5°C
d. 6 months for 4 batches at 25°C

Sponsor's Pre-Meeting Response:

Alvotech would like to clarify the availability of device stability data

a. 12 months for 2 batches at 5°C
b. 9 months for 1 batch at 5°C
c. ~~6 months for 1 batch at 5°C~~
d. 6 months for 3 batches at 25°C

APPEARS THIS WAY ON ORIGINAL

Discussion**:**

See Slide 8.

Regarding the EPR's, Alvotech stated that they will have 3 batches and listed the availability of the device stability data as noted above.

Regarding the stability plan, Alvotech stated that they had discussed the plan with the FDA in previous meetings and they were being consistent with the guidance but have not yet made any specific correlation plans and asked FDA for guidance in how much of the collation should be presented. The FDA stated that their preliminary response was based on Alvotech not providing the complete shelf-life data on the device and using some accelerated data to support the proposed shelf-life. FDA explained that Alvotech will need to show correlation with the in-house data or can re-standardize.

Overall the FDA stated that from the rough calculation, Alvotech's approach and amount of data is acceptable for now. The FDA also referred to the discussion captured in the October 30, 2018, BPD2 meeting minutes where advice was previously provided.

The FDA also referred Alvotech to the ASTM F1980-16 to determine the amount of data needed to support shelf life. Alvotech agreed to provide justification in reference to the standard and discuss internally about their available data and commit to the recommendation on end of the shelf-life; overall, this was agreed as a suitable approach.

> *In order to accept the AI data, you should show that the 6 months at 25°C data correlates with 24 months at 5°C. If you are unable to show the correlation with this amount of data, additional data at 5°C and/or accelerated temperature should be included at the time of submission.*

Sponsor's pre-meeting response to FDA's above preliminary comment:

PIND136459 Type 2 meeting in OCT 2018 resulted in the following conclusion (meeting minutes):

To support a shelf-life claim, the Sponsor proposed to submit stability data of 6 months 25°C and at least 6 months 2-8°C for the auto-injector presentation. The FDA had no objections and accepted their proposal, provided that the Sponsor committed to continue testing until the end of the shelf-life.

Alvotech has followed this advice, which is also in keeping with CDRH guidance. Alvotech would be open to input about presentation of correlation of data coming from the standard (5°C, 24m) and accelerated (25°C, 6m) conditions.

Discussion:

See slide 9.

Refer to the above discussion under Question 4.

(b) (4)

Question 5:
Can the Agency confirm that this presentation and format is adequate or if anything else will be required?

FDA Response to Question 5:
We do not agree that your proposed comparative analytical similarity data format is adequate. We recommend including a column with the minimum to maximum range of AVT02 batch results for each quality attribute tested in your table formats shown in Appendix 3. In addition to representative images and tabular format described in the meeting package, you should provide quantitative comparative analytical results in easy-to-read graphical formats. For quality attributes assessed by quality range, we recommend providing graphs with AVT02 results compared against the quality range from U.S.-licensed Humira and EU-approved Humira, as well as EU-approved Humira results compared against the quality range from U.S.-licensed Humira. For non-quantitative quality attributes, qualitative comparisons should be provided.

Discussion:

No further discussion took place.

Question 6: Batch Manufacturing Records

Will this be sufficient for BLA?

FDA Response to Question 6:
In addition to executed batch manufacturing records from the fully developed process of one batch of AVT02 drug substance and one batch of AVT02 drug product, include non-

executed batch manufacturing records from the fully developed process of AVT02 drug substance and AVT02 drug product in 3.2.R.

Sponsor's pre-meeting response*:*

In line with FDA recommendation, Alvotech plans to provide executed and non-executed batch records related to all process steps except media and buffer preparation, Does the Agency agree with Alvotech approach?

Discussion*:*

See Slide 10.

The FDA replied that Alvotech's proposal is acceptable.

Question 7: Facilities requirements

Refer to Appendix 1: Draft Manufacturing Flow Chart, provided with the background information and find below a summary of the manufacturing, packaging and testing facilities. Further to this, upon filing the relevant 3.2.A.1 Facilities summaries for manufacturing sites will be included.
Can the Agency clarify if any further information will be required for BLA submission or for inspection planning?

FDA Response to Question 7:
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. Refer to the additional CMC Microbiology comments.

Sponsor pre-meeting response:
Alvotech Reykjavik, Iceland manufacturing facility is not in routine commercial production, Alvotech would like to work with the Agency on batch scheduling to fit PAI in Q1-2021.

Discussion:

See Slide 11.

The FDA stated that in general the proposal is acceptable as the scheduled inspection usually takes 2-6 months after the receipt of the original BLA submission. The FDA reiterated that AVT02 DS should be manufactured for the pre-approval inspection as well. Alvotech was in agreement.

The FDA added that once Alvotech submits the manufacturing schedule, the FDA will reach out to Alvotech to discuss some potential dates of scheduling the inspection.

Alvotech stated that since they're not currently in commercial manufacturing from September 2020 on, therefore no further plans have been made for manufacturing, but they plan to manufacture the extra batch when FDA is on-site. The FDA replied that first quarter of 2021 may be an acceptable time frame for the inspection.

The FDA added that the inspection can usually take a month to review and complete, and FDA prefers that the inspection occur near the mid-cycle time frame. Alvotech acknowledged the feedback. Alvotech will provide a target date of manufacturing when submitting the original BLA.

Question 8: Medical device content

Does the FDA agree that this content is sufficient for BLA submission?

FDA Response to Question 8:
In addition to the data that you specified, also submit verification data for both the AI and PFS filled with drug, since test results may be impacted by the drug. For EPR testing not impacted by drug, you may provide device testing free of drug, only if acceptable justification is provided.

Discussion:

No further discussion took place.

Question 9: Assembly process qualification

Does the Agency agree with proposed approach?

FDA Response to Question 9:
We do not agree with your proposed approach to submit process performance qualification (PPQ) reports for assembly of AI (b) (4) *during BLA review cycle (as part of 120-day update). All PPQ results should be submitted at the time of BLA submission. To support a determination that the application is complete for filing, we expect you to provide all CMC information in the original application, with the exception of the simple stability updates described for Question 5 of this meeting package.*

Discussion:

No further discussion took place.

Question 10: submission of long-term safety of studies AVT02-GL-301 (b) (4) ***during the BLA review process***

Does the FDA agree that the proposed content of the 120-day data update is in line with FDA expectation for review and approval of AVT02 per Section 351(k) of the PHS Act?

FDA Response to Question 10:
You propose to submit the reports from two studies AVT02-GL-301 (a 48-week efficacy and safety study in subjects with psoriasis) (b) (4) (b) (4) *as follows:*

Table 10: AVT02 long-term safety data submission to the FDA

Study Identifier	Initial BLA	120-Day Update	Q2 2021
AVT02-GL-301	*Efficacy, safety, and immunogenicity double-blinded data up to Week 24 (Primary CSR)*	*Full Data Set (Final CSR)*	*N/A*
(b) (4)			

Yes, we agree with your proposal.

Discussion:

No further discussion took place.

Question 11: during the BLA review process

Does the agency concur with the Sponsor's proposal to not include an ISS and ISE?

FDA Response to Question 11:
Yes, we agree.

Discussion:

No further discussion took place.

Question 12: agreement on Human Factor validation study plan for AVT02-PFS (b) (4)

Does the FDA agree with Sponsor's proposed approach on the conduct of HF validation study and the inclusion of the study report as part of 120-day update post submission of AVT02 BLA would facilitate review?

FDA Response to Question 12:
We acknowledge your threshold analysis/comparative analysis and use-related risk analysis submission dated June 1, 2020, to support your determination (b) (4) *We are currently reviewing your submission and will notify you if we concur with your determination. If we do not agree with your determination, you will need to submit HF validation study results at the time of your BLA submission. Thus, we do not agree with your proposed approach on the inclusion of the study report as part of the 120-day update post submission of your BLA.*

Discussion:

No further discussion took place.

Question 13: electronic data submission (b) (4)

Does FDA agree with the proposed (b) (4) ***Study of the AVT02-BLA?***

FDA Response to Question 13:
Yes, we agree.

Discussion:

No further discussion took place.

Question 14: Risk Evaluation and Mitigation Strategies (REMS) for AVT02

Does the FDA concur with the proposed REMS strategy for AVT02?

FDA Response to Question 14:
Your proposal to provide patient counseling information and a Medication Guide for AVT02 appears reasonable. Based on the information currently available, we do not believe that a REMS will be necessary. We will make a final determination for the need for a REMS during the review of your application.

Discussion:

No further discussion took place.

Question 15: AVT02 Prescribing Information

Does the FDA have any feedback on the proposed location of AVT02 specific data in the prescribing information and overall concept for the prescribing information?

FDA Response to Question 15:
Your proposal is generally acceptable. However, we note that you propose to include a statement as follows: TRADENAME" is a biosimilar to Humira (adalimumab) for the indications listed." We refer you to Guidance for industry – Labeling for Biosimilar Products (July 2018) for recommendations on the biosimilarity statement.

Discussion:

No further discussion took place.

Question 16: AVT02-AI HF validation plan to support interchangeability

Does the Agency concur with the proposed approach on HF validation of AVT02-AI to support interchangeability claim, and if not, could the agency provide guidance on any supplementary data that would likely be required?

FDA Response to Question 16:
This question is outside the scope of this meeting; however, we do not agree with your proposed approach to use the human factors validation study to support an application seeking interchangeability and have the following comments:

With regards to considerations for developing presentations, container closure systems, and delivery device constituent parts for your proposed interchangeable product, appropriate data to support a demonstration of interchangeability may be collected from comparative task analysis, labeling comparison (including the Instructions for Use [IFUs]), and physical comparison between each presentation for US-licensed Humira to its corresponding presentation for which you intend to seek licensure for your proposed interchangeable product.

Should you find that these analyses suggest that any identified differences in the designs of your presentation(s) are minor, we recommend that you provide these data for our review and concurrence.

We may view the design differences of your proposed presentation(s) as not being minor if any aspect of the analyses suggests that the design differences in the design of the presentation of the proposed interchangeable product as compared to the reference product may impact a critical task that can affect patient use or caregiver administration of the product. In such cases, comparative use human factors studies may be needed to characterize any impact of the differences on the appropriate use of your proposed

interchangeable product and evaluate whether the design difference between the presentation of the proposed interchangeable product and the reference product is acceptable to support a demonstration of interchangeability.

We encourage you to submit the data from your analyses to your IND when they become available so that we can reach agreement on whether additional data are needed to support your application requesting interchangeability. If the comparative analyses data suggest that the differences in your design may not be minor, we also encourage you to discuss with us your plans for a comparative use human factors study so that we can reach agreement on a study that could provide additional data to support your application requesting interchangeability. An assessment of interchangeability will be made based on the totality of data and information you submit to support a demonstration of interchangeability.

Refer to our draft guidance titled Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications[1] for the content of a threshold (comparative) analyses submission.

Additional Comments

Center for Devices and Radiological Health (CDRH)

Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications"
(https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf).
When submitting a marketing application for the final finished combination product, provide the following information related to your device:

1) Device Description Documentation

a) Provide a description of your device constituent design, including any novel features and/or functionalities. This should include drawings / diagrams of the device, descriptions of device components, or any other available information to explain the device design.
b) Describe the principles of operation of your device.
c) Describe any accessories or other devices labeled for use with your device.

[1] 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

2) *Design Control (21 CFR 820.30) – The application should include design documentation. The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about design control documentation, we recommend that you reference the FDA Design Control Guidance for Medical Device Manufacturers, https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070642.pdf. We recommend that the design control information provided in your application include the following:*

   a) *Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)*
   b) *Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)*
   c) *Design Verification Plan/Summary Report, supporting data and traceability*
   d) *Design Validation Plan/Summary Report, supporting data and traceability*
   e) *Risk Management File*

3) *Essential Performance – Identify essential performance requirements (EPR) for the device.*

   For each identified essential performance requirement, your marketing application should include verification and validation information of EPR specifications. While the final set of essential performance requirements should be based on your design control process, we are providing the following example EPRs for your device type. This is not an exhaustive list and product specific factors should influence your EPR selection.

   Example auto- injector EPRs:
      a. *Delivered Volume Accuracy*
      b. *Activation Force*
      c. *Injection Time*
      d. *Extended Needle Length*

   Example prefilled syringe EPRs:
      a. *Delivered Volume Accuracy*
      b. *Break loose & Extrusion Force*

4) *Stability (ICH Q1) – Your stability program should include endpoints to verify that device essential performance is maintained at expiry. You may exclude certain EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time.*

5) *Shipping - Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.*

6) *Control Strategy – Provide a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, in-process, control of incoming materials, purchasing controls, etc.*

7) *Quality System*

   The marketing application should contain a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf).

Chemistry, Manufacturing, and Control (CMC) Microbiology

We are 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.

Information and data for CMC product quality microbiology should be submitted in the specified sections indicated below.

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:

1. *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).*

2. *Bioburden and endotoxin data obtained during manufacture of three process qualification (PPQ) lots (3.2.S.2.5).*

3. *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).

4. *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).*

5. *Information and summary results from the shipping validation studies (3.2.S.2.5).*

6. *Drug substance bioburden and endotoxin release specifications (3.2.S.4).*
7. *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.

1. *Identification of the manufacturing areas and type of fill line (e.g. open, RABS, isolator), including area classifications.*

2. *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.*

3. *Parameters for filling and plunger placement for the pre-filled syringes.*

4. *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.*

5. *Processing and hold time limits, including the time limit for sterilizing filtration and aseptic filling.*

6. *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:

1. *Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.*

2. *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.*

3. *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.*

4. *Isolator decontamination summary data and information, if applicable.*

5. *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.*

6. *Information and summary results from shipping validation studies. For prefilled syringes, autoinjectors, the effects of varying air pressure on pre-filled syringe plunger movement and potential breaches to the integrity of the sterile boundary during shipment should be addressed. Include data demonstrating that the pre-filled syringe plunger movement during air transportation does not impact product sterility.*

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

1. *Container closure integrity testing. System integrity should be demonstrated initially and during stability. Data demonstrating the maintenance of container closure integrity after the assembly of the pre-filled syringe and autoinjector*

should be included. 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.

Sponsor pre-meeting response:

Alvotech acknowledges the FDA guidance "Container and Closure System Integrity Testing in Lieu of Sterility Testing as a Component of the Stability Protocol for Sterile Products" and the reasons why CCI is preferable to sterility testing.

Steps taken to develop CCI method for this specific product (AVT02-AI):

Discussion:

See Slide 14.

Alvotech sought FDA's feedback on whether or not the sterility testing proposed is acceptable instead of the Container and Closure Integrity (CCI) testing. The FDA did not agree to Alvotech's proposal and stated that they require CCI testing annually and at expiry. The FDA added that they may consider some flexibility on the timeline in submitting the data and it may be submitted 8 months after submitting the original BLA. However, FDA encouraged Alvotech to submit the data sooner than later.

Alvotech discussed Slide 16 to back up their justification regarding CCI testing.

The FDA stated that there's no preferred method in evaluating the CCI testing. The FDA added that for evaluating CCI either by dye or helium leak detection/testing are common methods for AI systems, as there's ways in reconstructing the AI and evaluate/preventing dye-leakage into the syringe.

Alvotech discussed some of the challenges [redacted] (b) (4) but they plan to revisit the topic and see how FDA's recommendation can be considered.

Alvotech asked if the FDA would be open to a further discuss the challenges and ways [redacted] (b) (4) The FDA was open in having further discussion [redacted] (b) (4)

The FDA stated that even though they're open in having further discussion with Alvotech to also consider the timelines and current resources.

2. *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.*

3. *Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b).*

Sponsor pre-meeting response to no. 3:

No pyrogen test has been performed. Alvotech uses the LAL test for endotoxin testing at release and during stability of AVT02. The method has been verified according to USP <85> and Ph. Eur. 2.6.14 and the specifications set in accordance with the guidelines. AVT02 is developed as a global programme.

The EMA guidelines on BET testing states that a manufacturer should work towards using an alternative test to the RPT. (https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-replacement-rabbit-pyrogen-testing-alternative-test-plasma-derived-medicinal-products_en.pdf). This can be done by establishing a validated manufacturing process with special consideration of a bioburden programme, which Alvotech has done.

The manufacturing process is designed as single use wherever possible. A risk assessment has been performed and experience from clinical studies do not indicate a pyrogen issue with AVT02.

Does the Agency agree to this approach?

Discussion**:**

See Slide 12.

The FDA did not agree with Alvotech's approach on the pyrogen testing. The FDA stated that per the regulation rabbit pyrogen testing should be completed using three batches of drug product. Alvotech acknowledged the feedback and stated that testing will be under way and further analysis will be initiated. The FDA stated that the pyrogen testing has to be submitted when submitting the original BLA and cannot be submitted during the review cycle.

Alvotech asked if they can submit the pyrogen testing protocol with the original submission and then have the data available at a later date before the mid-cycle review. The FDA responded to include the protocol in the original submission and have the data available before filing date (prior to day 60) and not at a later time. Alvotech will check on the timing and will re-visit the topic.

4. *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.*

3.0 OTHER INFORMATION

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 FDA.gov.[2]

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain a pediatric assessment to support dosing, safety, and effectiveness of the product for the claimed indication unless this requirement is waived, deferred, or inapplicable.

Section 505B(l) of the FD&C Act, added by section 7002(d)(2) of the Affordable Care Act, provides that a biosimilar product that has not been determined to be interchangeable with the reference product is considered to have a "new active ingredient" for purposes of PREA, and a pediatric assessment is required unless waived, deferred, or inapplicable.

FDA encourages prospective biosimilar applicants to submit an initial pediatric study plan (iPSP) as early as practicable during product development. FDA recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For 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

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

pediatric information from the reference product to your proposed product (see question and answer I.16 in the draft guidance for industry, *New and Revised Draft Q&As on Biosimilar Development and the BPCI Act*. 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.

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 draft guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[3]. In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov It should be noted that requested deferrals or waivers in the initial PSP will not be formally granted or denied until the product is licensed

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d)[4] and 201.57[5] including the Pregnancy and Lactation Labeling Rule (PLLR) (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[6] and Pregnancy and Lactation Labeling Final Rule[7] websites, which include:

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

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

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

[6] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm_084159.htm

[7] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

- 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*.[8]

In addition, you should review the FDA guidance for industry *Labeling for Biosimilar Products* (July 2018).

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

NONPROPRIETARY NAME

[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.

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) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Manufacturing and testing facilities will be subject to the CGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection 2-7 months after the submission of the BLA. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the BLA to facilitate planning of pre-approval inspections during the review cycle. For a BLA submission, when providing the preliminary manufacturing schedule, we encourage you to bear in mind the anticipated time frame for the late-cycle meeting for applications subject to "the Program" under BSUFA II.

To facilitate our inspectional process, we request that you clearly identify *in a single location*, either on the Form FDA 356h, or an attachment to the form, all manufacturing facilities associated with your application. Include the full corporate name of the facility and address where the manufacturing function is performed, with the FEI number, and specific manufacturing responsibilities for each facility.

Also provide the name and title of an onsite contact person, including their phone number, fax number, and email address. Provide a brief description of the manufacturing operation conducted at each facility, including the type of testing and DMF number (if applicable). Each facility should be ready for GMP inspection at the time of submission.

Consider using a table similar to the one below as an attachment to Form FDA 356h. Indicate under Establishment Information on page 1 of Form FDA 356h that the information is provided in the attachment titled, "Product name, BLA 012345, Establishment Information for Form 356h."

Site Name	Site Address	Federal Establishment Indicator (FEI) or Registration Number (CFN)	Drug Master File Number (if applicable)	Manufacturing Step(s) or Type of Testing [Establishment function]
(1)				
(2)				

Corresponding names and titles of onsite contact:

Site Name	Site Address	Onsite Contact (Person, Title)	Phone and Fax number	Email address
(1)				
(2)				

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 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.

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[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

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

Please refer to the draft guidance for industry *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER Submissions* (February 2018) and the associated *Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications*.

RECOMMENDATIONS FOR FORMATTING OF CLINICAL PHARMACOLOGY SUBMISSIONS FOR APPLICATIONS

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

1. As it relates to clinical pharmacology-related sections of the application, apply the following advice when preparing the 351(k) BLA:
   a. Include the rationale for the selected dose used in the PK (and PD similarity, when applicable) study(ies) in the BLA (e.g., eCTD Module 2.7.2 Summary of Clinical Pharmacology).
   b. Include a summary evaluation of the impact of immunogenicity on the activity (e.g., efficacy/PD), safety, and pharmacokinetics, as is applicable, for the 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. Submit the tables in the Appendix of the Summary of Biopharmaceutics located in eCTD 2.7.1.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None

5.0 ACTION ITEMS

None

6.0 ATTACHMENTS AND HANDOUTS

See attached slides

17 Page(s) have been Withheld in Full as B4 (CCI/TS) immediately following this page

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

This is a representation of an electronic record that was signed electronically. Following this are manifestations of any and all electronic signatures for this electronic record.

/s/

SADAF NABAVIAN
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