CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761325Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 136342

MEETING MINUTES

Sanofi US Services Inc.
Attention: Selina Feng, MBS, RAC
Senior Manager, Global Regulatory Affairs
55 Corporate Drive
Mail Stop: 55C-300
Bridgewater, New Jersey 08807

Dear Ms. Feng:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for SAR341402.

We also refer to the teleconference between representatives of your firm and the FDA on January 24, 2022. The purpose of the meeting was to discuss the following for the planned Biologics License Application (BLA) submission:

1. The overall data provided to support licensure of SAR341402 as an interchangeable biosimilar with U.S.-licensed NovoLog.

2. Chemistry Manufacturing and Controls (CMC), nonclinical, and clinical data to support review of the BLA for the proposed indications, including the following CMC topics:

    a) Introduction of the tighter action limit for the content of bacterial endotoxin for drug product.

    b) Proposal of pre-approval inspection (PAI) related to planned shutdown of the drug substance facility.

3. The Proposed content plan and eSubmission package for the planned BLA.

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

If you have any questions, contact Michael Oyewole, Regulatory Project Manager, at (301) 796-3897.

Sincerely,

{See appended electronic signature page}

Patrick Archdeacon, M.D.
Associate Director for Therapeutics
Division of Diabetes, Lipid Disorders, and Obesity
Office of Cardiology, Hematology, Endocrinology, and Nephrology
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

MEMORANDUM OF MEETING MINUTES

Meeting Type:	Biosimilar
Meeting Category:	BPD Type 4
Meeting Date and Time:	Monday, January 24, 2022, 12:00 PM – 1:00 PM ET
Meeting Location:	Teleconference
Application Number:	IND 136342
Product Name:	SAR341402
Proposed Indication:	SAR341402 is being developed for the same indications as those approved for US-licensed Novolog
Sponsor Name:	Sanofi US Services Inc.
Regulatory Pathway:	351(k) of the Public Health Service Act
Meeting Chair:	Patrick Archdeacon, M.D.
Meeting Recorder:	Michael Oyewole, Pharm.D.

FDA ATTENDEES

Division of Diabetes, Lipid Disorders, and Obesity

Patrick Archdeacon, M.D.	Associate Director for Therapeutics
Dolly Misra, M.D.	Clinical Reviewer

Division of Pharmacology/Toxicology for Cardiology, Hematology, Endocrinology, and Nephrology

C. Lee Elmore, Ph.D.	Deputy Director
Patty Brundage, Ph.D.	Nonclinical Team Lead
Elena Braithwaite, Ph.D., DABT	Nonclinical Reviewer

Office of Regulatory Operations, Division of Regulatory Operations for Cardiology, Hematology, Endocrinology, and Nephrology

Liz Godwin, M.S.H.S.	Chief, Project Management Staff
Michael Oyewole, Pharm.D.	Regulatory Project Manager
Georgia Rogers, Ph.D.	Regulatory Project Manager

Office of Clinical Pharmacology, Division of Cardiometabolic & Endocrine Pharmacology

Jaya Vaidyanathan, Ph.D.	Associate Director for Therapeutic Review
Lin Zhou, Ph.D.	Clinical Pharmacology Reviewer

Office of Biostatistics, Division of Biometrics II

Yoonhee Kim, Ph.D.	Biometrics Team Leader
Jade (Yu) Wang, Ph.D.	Biometrics Reviewer

Office of Pharmaceutical Quality, Office of Biotechnology Products, Office of Pharmaceutical Manufacturing Assessment

Anjali Shukla, Ph.D.	Product Quality Team Leader
Qiong Fu, Ph.D.	Product Quality Reviewer
Marlene Schultz-DePalo, MS, MA, RAC	Biosimilar Program and Policy Analyst
Maria Gutierrez-Hoffmann, Ph.D.	Staff Fellow Microbiologist
Virginia Carroll, Ph.D.	Senior Microbiologist

Center for Devices and Radiological Health (CDRH), Office of Health Technology 7

Joshua Balsam, Ph.D.	CDRH Reviewer
Yiduo Wu, Ph.D.	Diabetes Branch Chief

Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Ariane O. Conrad, Pharm.D.	Safety Evaluator

Office of Therapeutic Biologics and Biosimilars

Stacey Ricci, M.Eng, Sc.D.	Director, Scientific Review Staff
Michelle Luo, MD, Ph.D.	Scientific Reviewer
Cristina Ausin, Ph.D.	Scientific Reviewer
Carol Kim, Pharm.D.	Scientific Reviewer
Sarah Brown, Pharm.D.	Science Policy Analyst
Jessica Greenbaum, J.D.	Regulatory Counsel
Shelley Skibinski, Pharm.D.	Project Coordinator
Ruby (Chi-Ann) Wu, Pharm.D., M.P.H	Labeling Reviewer
Sarah Schrieber, Pharm.D.	Scientific Reviewer
Angela LaPier, J.D.	Regulatory Counsel

Office of Combination Products

Patricia Love, M.D., MBA	Deputy Director

Office of Scientific Investigations

Ling Yang, M.D.	Medical Officer

SPONSOR ATTENDEES

Anne Doisy, Pharm D, PhD.	Principle Medical Writer
Baerbel Rotthaeuser, PhD.	Global Project Head, Clinical Development
Caroline Seiz, PhD.	Head ICF API Bio2020 Prog. Ops.
Catherine Lelouet, PhD.	Programming Project Leader
Chetan Somaiya, B.Pharm, MBA	Director Regulatory Affairs, GRTL
Christoph Dette, PhD.	CMC Business Development Leader
Cornelia Wihler, PhD.	Project Leader API

Don Gieseker, PhD.	US Regulatory Affairs
Erich Frese	Head of Quality IA GenMed Cluster Insulins Emerging Markets
Lenore Teichert, PhD.	Team Lead, Early Clinical Biostatistics
Marcus Korn, PhD.	Lab Head SFB&O QC Bioanalytics I
Mayme Cui, MS	Senior Manager Reg Affairs CMC Biologics
My-Liên Nguyên-Pascal, MD, MSc	Clinical Research Director
Niels Porksen, PhD.	Head of DCV Development, Development Innovation
Paulus Wohlfart, PhD.	Head of Preclinical Assays & Compliance
Robyne Kelemen, PhD.	Director Glob Regulatory Affairs CMC Biologics
Selina Feng, MBS, RAC	Senior Manager, Global Regulatory Affairs
Suzanne Pierre, MSc	Statistical Project Leader
Wolfgang Schmider, PhD.	Head of Pharmacokinetics/ Pharmacodynamics

1.0 BACKGROUND

On November 14, 2018, Sanofi US Services Inc. (Sanofi) submitted an IND to support the development of SAR341402 (insulin aspart-xxxx) injection, which is being developed as (b) (4) biosimilar to US-licensed NovoLog (insulin aspart) injection. Sanofi plans to submit the BLA application under section 351(k) of the Public Health Service Act.

Meetings held with the Agency regarding the development of SAR341402 as (b) (4) (b) (4) biosimilar product have included: a multi-disciplinary BPD Type 2 meeting on November 7, 2017; BPD Type 2 written responses issued on January 18, 2019; a multi-disciplinary BPD Type 2 meeting on July 1, 2019; CMC-only BPD Type 2 meeting on December 11, 2019; and a CMC-only BPD Type 2 meeting on May 4, 2021.

On November 23, 2021, Sanofi submitted a BPD Type 4 meeting request, along with the briefing package, to discuss the BLA submission for this product.

FDA sent Preliminary Comments to Sanofi on January 19, 2022.

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 Sanofi 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

General Comments:

We note that in your review of key FDA interactions (Table 1) in your meeting background package, you did not include the Advice Letter from the Division issued to you on November 25, 2019, in which the Division relayed the Agency's updated scientific thinking pertaining to your comparative clinical study proposal and switching study proposal. The letter references the draft guidance for industry *Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products*[1]. As described in the guidance, FDA's thinking is that a comparative clinical immunogenicity study generally would be considered unnecessary to support a demonstration of biosimilarity or (b) (4) for your proposed insulin product if the comparative analytical assessment (CAA) for SAR341402 with US-licensed NovoLog supports a demonstration of "highly similar" as part of a demonstration of biosimilarity such that there is little or no residual uncertainty regarding immunogenicity. For your proposed product, based on our previous communications regarding your development program, we expect that you will submit (among other things) a comparative pharmacokinetic/pharmacodynamic (PK/PD) study (e.g., euglycemic clamp study). A comparative clinical immunogenicity study may still be necessary to support licensure, for example, if there are differences in certain impurities or novel excipients that give rise to questions or residual uncertainty related to immunogenicity.

If you believe that data from a comparative clinical immunogenicity study may not be necessary, we recommend that your 351(k) BLA submission for SAR341402 include an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not needed to support a demonstration of biosimilarity for SAR341402. This justification may reference other data and information in the application, e.g., a CAA that supports a demonstration of "highly similar" with very low residual uncertainty regarding immunogenicity. Your justification need not necessarily include any clinical data.

If you intend to submit the findings of your comparative clinical studies EFC15081 and EFC15178 as data necessary to support licensure in your BLA, then your submission should include the data sets and SAS programs for all analyses of your clinical studies. Analysis to demonstrate PK/PD similarity between the SAR341402 and US-licensed NovoLog based on data from Study PDY12695 will also be an important review topic; therefore, the data sets and SAS programs for analyses conducted for study PDY12695 should be submitted with your BLA. In addition, you should confirm that the drug product tested in Study

[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.

PDY12695 is still the to-be-marketed formulation and confirm that US-licensed NovoLog was used as one of the comparator products.
In order to obtain an indication for improvement in glycemic control for the broad diabetic population for which US-licensed NovoLog has been previously approved (i.e., adults and pediatric patients with diabetes mellitus), you must provide scientific justification for the extrapolation of the necessary clinical data relied upon to demonstrate biosimilarity to SAR 341402 to those populations not studied, but for which you are seeking biosimilarity (b) (4) If the only clinical data you rely on to demonstrate biosimilarity of SAR341402 to US-licensed NovoLog is the finding of PK/PD similarity from Study PDY12695, an acceptable scientific justification is that the finding of PK similarity of the two products in adults may be extrapolated to children because the same scientific factors that determine absorption, distribution, metabolism, and elimination in adults determine absorption, distribution, metabolism, and elimination in children and that the finding of PD similarity of the two products in adults may be extrapolated to children because the assessed PD endpoints evince the binding and activation of insulin receptors, which is the pertinent mechanism of action for all conditions of use of U.S.-licensed NovoLog (to the extent known). If the determination of biosimilarity (b) (4) of SAR341402 to US licensed-NovoLog in your submission relies on clinical data beyond the PK and PD data from the euglycemic clamp study (e.g., if your submission also relies on clinical data from EFC15081 and EFC15178 in adult patients with diabetes mellitus), include additional scientific justification for how those clinical data may be extrapolated to the pediatric population.

Finally, based on the proposed formulation of SAR341402, the data necessary to support (b) (4) use will in part be dependent upon the review of the data from the bench studies previously requested to be submitted to IND 136342 for SAR341402. Note that there are additional comments related to (b) (4) as it relates to (b) (4) below.

We have provided preliminary comments to the questions which you included as topics of discussion below. Your questions are repeated with our responses followed in bold. Your responses to our preliminary comments are copied below with the meeting discussion followed in italics.

2.1. Chemistry Manufacturing and Controls

Question 1: The Sponsor is proposing to reduce the (b) (4) (b) (4) EU/ 100 Insulin Aspart Units for cartridge and (b) (4) EU/ 100 Insulin Aspart Units for vials) to ensure that the finished product meets the USP Acceptance criteria of (b) (4) EU/ 100 Insulin Aspart Units because despite intensive investigations the developed (b) (4) does not completely circumvent the (b) (4) (b) (4) effect.

Does Agency agree with the Sponsor's proposal?

FDA Response to Question 1: We do not agree with your proposal. It is premature to make changes to the [redacted] for the drug product because the [redacted] results provided in the meeting package are inconsistent. For example, the formulation of the vial and cartridge presentation are the same, however [redacted] (Figure 5). We recommend repeating the [redacted] studies to demonstrate consistent results between testing sites and operators. We also recommend continuing to develop an alternative [redacted] test method to mitigate [redacted] he [redacted] test method proposed for drug product release should reliably det [redacted] over process-relevant time and temperature.

Sponsor's Pre-meeting Response: The Sponsor acknowledges the Agency's response.

[redacted]

Based on FDA feedback and timing considerations, the Sponsor intends to include compendial rabbit pyrogen testing in the BLA, and a fully validated endotoxin method (utilizing ENDOLISA®), if complete at the time of BLA submission.

No further discussion is planned.

Discussion: *No further discussion occurred.*

Question 2: The Sponsor plans to submit a BLA for SAR341402 solution for injection in the US in May 2022. [redacted] However, the drug product facility would be available for physical inspection.

Does the Agency agree with the Sponsor's proposal?

FDA Response to Question 2: We do not agree with your proposal, as the [redacted]

(b) (4)
(b) (4) **in accordance with 21 CFR 600.21 and 601.20(b)(2). Refer to Additional CMC Microbiology Comments and section 7.0 below for further information.**

Sponsor's Pre-meeting Response: The Sponsor acknowledges FDA's comments. The manufacturing facilities will be ready for inspection and drug substance will be manufactured during the review period. The original submission package will include a production schedule. The drug product and drug substance production will occur (b) (4) (b) (4) from the date of submission.

No further discussion is planned.

Discussion: *No further discussion occurred.*

2.2. Clinical

Question 3: Does the Agency agree that the proposed clinical data package is sufficient to support the filing and review of the BLA for the proposed indication?

FDA Response to Question 3: Your meeting package states that the clinical studies that you intend to submit with your application include the following:

a) **PDY12695 - A randomized, double-blind, controlled, single-dose, 3-treatment, 3-period, 6-sequence cross-over study to compare exposure and activity of SAR341402 to NovoRapid and NovoLog using the euglycemic clamp technique, in subjects with type 1 diabetes mellitus (T1DM).**

b) **EFC15081 - A six-month, randomized, open-label, parallel-group comparison of SAR341402 to NovoLog/NovoRapid in adult patients with diabetes mellitus also using insulin glargine, with a 6-month safety extension period.**

c) **PDY15083 – A safety assessment of SAR341402 and NovoLog used in (b) (4) in adult patients with T1DM.**

d) **EFC15178 – A randomized, open-label, parallel-group study comparing the pharmacokinetics and immunogenicity of alternating use of SAR341402 and NovoLog versus continuous use of NovoLog in patients with T1DM also using insulin glargine.**

We agree that the data from your clinical program may be submitted in support of your BLA for biosimilarity (b) (4). We refer you to the Advice Letter issued to you by the Division on November 25, 2019, and also the draft guidance for industry, *Clinical Immunogenicity Considerations*

for Biosimilar and Interchangeable Insulin Products. Although you may submit all of the data you believe supports your BLA, not all of the clinical data you have generated may be necessary to support a conclusion of biosimilarity [redacted] (b) (4) In your submission, you should specify the proposed purpose of the data you include in support of your BLA. The adequacy of your BLA, including the clinical data, will be a review issue.

Your proposed submission package includes a CAA of SAR341402 and US-licensed NovoLog and PK/PD findings from PDY12695 (euglycemic clamp study). If you believe that the data from your CAA adequately supports a demonstration of "highly similar" as part of a demonstration of biosimilarity and you believe the PK/PD findings from PDY12695 demonstrate PK/PD similarity, then your submission may include an immunogenicity assessment justifying why a comparative clinical study to assess immunogenicity is not needed to support a demonstration of biosimilarity for SAR341402. This justification may reference other data and information in the application, e.g., a CAA with very low residual uncertainty. Your justification need not necessarily include any clinical data. See also General Comments above.

In order to obtain an indication for improvement in glycemic control for the broad diabetic population for which US-licensed NovoLog has been previously approved (i.e., adults and pediatric patients with diabetes mellitus), you must provide scientific justification for the extrapolation of the necessary clinical data relied upon to demonstrate biosimilarity to all indications in the adult and the pediatric populations for which you are seeking biosimilarity and [redacted] (b) (4) See General Comments above for advice regarding an adequate scientific justification to extrapolate a finding of PK/PD similarity in PDY12695 between SAR341302 and US-licensed NovoLog in adults to children. If you rely on clinical data other than a finding of PK/PD similarity in PDY12695, provide additional scientific justification.

See also our response to Question #10 (regarding [redacted] (b) (4) for additional advice concerning the data necessary for the determination of [redacted] (b) (4) of SAR341402 and US-licensed NovoLog.

[redacted] (b) (4)

In addition, confirm that the drug product tested in Study PDY12695 is still the to-be-marketed formulation. Also confirm that US-licensed NovoLog was used as one of the comparator products in Study PDY12695.

Sponsor's Pre-meeting Response: Sanofi considers that quality, nonclinical and Phase 1 PK/PD data support high similarity between SAR341402 and the reference product. The comparative clinical efficacy, safety and immunogenicity Phase 3 study EFC15081 further confirms biosimilarity between products and that there is no residual uncertainty regarding immunogenicity.

The Sponsor would like to clarify if the justification to support (b) (4) (b) (4) (b) (4) The Sponsor would like to know if the FDA has any recommendations for elements to be included in the justification to request for (b) (4)

In order to obtain an indication for improvement in glycemic control for the broad diabetic population for which US-licensed NovoLog has been previously approved (i.e., adults and pediatric patients with diabetes mellitus), the Sponsor will submit the agreed iPSP with a scientific justification for the extrapolation of the necessary clinical data relied upon to demonstrate biosimilarity to all indications in the adult and the pediatric populations for which we are seeking biosimilarity (b) (4)

(b) (4)

The Sponsor is not developing a separate (b) (4) for SAR341402. (b) (4) is only used under medical supervision and not at pharmacy level. The Sponsor is willing to perform comparative testing with SAR341402 with NovoLog Insulin (b) (4) but at this time testing has not been performed due to availability concerns of NovoLog Insulin (b) (4) The Sponsor propose to remove (b) (4) ection from the label. Would this label change impact on the (b) (4) biosimilar designation?

The Sponsor confirms the drug product tested in Study PDY12695 is still the to-be-marketed formulation. NovoLog was used as one of the comparator products in Study PDY12695.

Discussion: *The Sponsor noted that they embarked on conducting study EFC15081 prior to the publication of the draft guidance for industry* Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products, *which discusses the clinical data necessary to support a demonstration of biosimilarity or interchangeability. The Sponsor requested clarification regarding how to address study EFC15081 in its future 351(k) BLA submission. The Agency stated that the Sponsor could elect to submit the clinical data from study EFC15081(and/or any other study) to support a demonstration of biosimilarity and/or interchangeability if they believed the data from study EFC15081 address a source of residual uncertainty not adequately addressed by other data and information. If, after consideration of the aforementioned guidance, the Sponsor determines that the*

clinical data from study EFC15081 are not necessary to support its BLA, the Agency indicated that the Sponsor need not submit the full datasets from study EFC15081. Rather, a clinical study report or other summary data could be submitted to support a conclusion that the results of study EFC15081 do not conflict with a demonstration of biosimilarity and/or interchangeability based on other data and information.

(b) (4)

[redacted]

Question 4: Does the Agency agree with the Sponsor's proposal for the provision of patient narratives and case report forms?

FDA Response to Question 4: We agree with your proposed selection criteria, content, and organization of patient narratives and case report forms. Also include the patient narratives of subjects who discontinued study participation.

Sponsor's Pre-meeting Response: Patient narratives for safety events are all available in Section 15.3.3 of each final Clinical Study Report located in Module 5 of the CTD.

For the patients who discontinued study participation, the Sponsor's proposal is to provide for each study an individual listing for patients who discontinued the study with the reason for study discontinuation, with a link to the corresponding individual Case Report Form. The listings will be provided in Module 5.3.5.3.

Does the Agency agree with the Sponsor's proposal?

Discussion: *Regarding patients who discontinued study participation, the Sponsor proposed to provide for each study, an individual listing for patients who discontinued the study, along with the reason for study discontinuation. The Sponsor will also provide a link to the corresponding individual Case Report Form. The Agency agreed with the Sponsor's proposal.*

(b) (4)

Discussion: *No further discussion occurred.*

2.3. Statistical

Question 6: Does the Agency Agree with the Sponsor's proposal to submit datasets and related documentation as described in the Study Data Standardization Plan (SDSP), and below proposal for program submission to support the filing and review of the BLA for registration?

FDA Response to Question 6: Analysis to demonstrate PK/PD similarity between the proposed biosimilar product and the reference product, based on data from Study PDY12695, will be an important review topic. Therefore, submit the SAS program for analysis conducted for study PDY12695.

As described in General Comments above (and in accordance with the draft guidance for industry, *Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products*), data from EFC15081 and EFC15178

may not be necessary to support your 351(k) BLA application. If you do not choose to rely on the data from EFC15081 and EFC15178, you do not need to submit full datasets and SAS programs as part of your application. However, should you choose to rely on the data from EFC15081 in your 351(k) BLA application, your proposal to submit SAS programs used to create the derived dataset for the primary efficacy endpoint (change from baseline to Week 26 in HbA1c) and SAS programs used of the primary efficacy endpoint analysis appears reasonable, in general. If you choose to rely on data from EFC15081 in your 351(k) application, also include the SAS analysis programs on immunogenicity data for evaluating immunogenicity between SAR341402 and U.S.-licensed NovoLog.

Analysis to demonstrate PK/PD similarity between the proposed biosimilar product and the reference product, based on data from Study PDY12695, will be an important review topic. Therefore, submit the SAS program for analysis conducted for study PDY12695.

Sponsor's Pre-meeting Response: The Sponsor acknowledges the Agency's comments. We will submit SAS programs for primary and key secondary PK and PD analyses conducted for Study PDY12695.

If the Sponsor chooses to rely on data from Study EFC15081, SAS programs used to create the derived datasets for immunogenicity endpoints and SAS programs used for key immunogenicity analyses of the 12-month data will also be included in the BLA. Immunogenicity analysis results will be stored in an analysis dataset which will be submitted in addition to the analysis datasets containing immunogenicity parameters. No statistical programs are planned to be submitted for Study EFC15178 (should the Sponsor choose to rely on data from this study) and Study PDY15083. Does the Agency agree with this approach?

Discussion: *The Sponsor agreed to submit SAS programs for primary and key secondary PK and PD analyses conducted for study PDY12695. However, the Sponsor stated that they do not intend to submit statistical programs for study PDY15083. The Agency agreed with the plan not to submit statistical programs (e.g., SAS) for study PDY15083 and stated that submitting a clinical study report for study PDY15083 was sufficient. The sponsor indicated that they plan to include individual patient data for study PDY15083, and The Agency did not object to the inclusion of individual patient data for study PDY15083. With regard to study EFC15178, the Sponsor also asked the Agency which analyses of interest to submit. The Agency reiterated the points made during the discussion of Question #3: The Agency directed the Sponsor to draft guidance for industry* Clinical Immunogenicity Considerations for Biosimilar and Interchangeable Insulin Products*, which discusses the clinical data necessary to support a demonstration of biosimilarity or interchangeability. The Agency noted that the Sponsor could elect to submit the clinical data from study EFC15178 to support a demonstration of biosimilarity and/or interchangeability if they believed the data from study EFC15178 address a source*

of residual uncertainty not adequately addressed by other data and information. If the Sponsor elects to rely on clinical data from study EFC15178, the BLA should include a fulsome explanation of their view of the purpose served by the data from study EFC15178 in supporting a conclusion regarding biosimilarity and/or interchangeability. The analyses and statistical programming submitted for study EFC15178 should be informed by the purpose that the Sponsor proposes for the clinical data from study EFC15178. If, after consideration of the aforementioned guidance, the Sponsor determines that the clinical data from study EFC15178 are not necessary to support its BLA, The Agency indicated that the Sponsor need not submit the full data for full FDA review. Rather, a clinical study report or other summary data could be submitted to support the conclusion that the results of study EFC15178 do not conflict with a finding of biosimilarity and/or interchangeability based on other data and information.

2.4. Regulatory

Question 7: Does the Agency agree with the Sponsor's proposal to submit a request for a waiver to 21 CFR 314.50(d)(5)(vi)(b)(1), i.e., 120-day safety update report?

FDA Response to Question 7: Given that all clinical trials for SAR341402 are completed, we agree with your proposal to submit a waiver for 120-day safety update report.

Sponsor's Pre-meeting Response: No further discussion is needed.

Discussion: *No further discussion occurred.*

Question 8: Does the Agency agree with the Sponsor's proposal for the Bioresearch Monitoring (BIMO) program?

FDA Response to Question 8: We are in agreement with your proposal not to include study PDY12695 in the BIMO program/site selection tool.

For studies EFC15081, PDY15083 and EFC15178, we are in agreement with your proposal not to include subject-level data line listings for sites with fewer than 5 subjects enrolled with the option for the BIMO reviewer to request the subject-level data line listings for the other sites, if needed.

Note that if Studies EFC15081 and EFC15178 are not necessary to support your 351(k) BLA for SAR341402, those studies will not be subject to the BIMO program for purposes of your BLA.

Sponsor's Pre-meeting Response: No further discussion is needed.

Discussion: *No further discussion occurred.*

Question 9: Does the Agency agree with the Sponsor's proposal for the overall table of content (ToC) and format of the proposed BLA submission?

FDA Response to Question 9: We agree with your proposed table of contents and format of your planned submission. However, if applicable, Module 1, Section 1.4 *References* in the BLA table of contents, should contain Letters of Authorization from Drug Master File (DMF) holders for applicable DMFs. Letters of Authorization should clearly identify referenced components and location of relevant information within the DMF.

Sponsor's Pre-meeting Response: The Sponsor acknowledges the Agency's comments. DMF information will be included in the BLA. No further discussion is needed.

Discussion: *No further discussion occurred.*

Question 10:

(b) (4)

2 Page(s) have been Withheld in Full as b4 (CCI/TS) immediately following this page

(b) (4)

[redacted]

Question 11: Does the Agency agree with the Sponsor's plan to reference only NovoLog and NovoLog FlexPen, Product 001 and 003 (purple book), respectively, under BLA 020986 to rely on FDA's finding in safety and effectiveness to support the BLA under section 351(k) pathway?

FDA Response to Question 11: We agree with your plan to seek licensure of SAR341402 10 mL vial (b) (4) **with US-licensed Novolog 10 mL vial and SAR341402 3 mL prefilled pen** (b) (4) **with US-licensed NovoLog 3 mL FlexPen.**

Sponsor's Pre-meeting Response: No further discussion is needed.

Discussion: *No further discussion occurred.*

2.5. Additional Comments

Nonclinical Comment:

The completed mitogenicity assay in the human breast adenocarcinoma cell line, MCF-7 and the human osteosarcoma cell line, SAOS-2 which preferentially express the insulin-like growth factor-1 receptor (IGF-1R), adequately assesses IGF-1R-dependent mitogenesis. However, assessments of insulin receptor-A (IR-A) binding and IR-A phosphorylation alone are not considered sufficient to evaluate the insulin receptor-dependent mitogenicity. Therefore, you should conduct a second mitogenicity assay using a cell line that preferentially expresses the insulin receptor over the IGF-1 receptor (e.g., L6-hIR, H4IIE) with SAR341402 compared to US-licensed NovoLog. The mitogenicity assays along with the other in vitro assays comparing the IR-A and IR-B and IGF-1R binding kinetics, IR and IGF-1R activation (via phosphorylation), and metabolic activity (via insulin-stimulated glucose uptake and inhibition of lipolysis) of SAR341402 and U.S.-licensed NovoLog

should be sufficient for the evaluation of biosimilarity from a nonclinical perspective.

Sponsor's Pre-meeting Response: The Sponsor agrees that measuring insulin dependent mitogenicity (without a significant IGF-1R contribution) is highly needed for new insulin analogs, based on the findings with Insulin-B10-Asp, for which the clinical development was discontinued because of increased tumor incidences in rat toxicity studies at low pharmacological doses. Insulin-B10-Asp, the only insulin analog with proven carcinogenic activity, binds with increased affinity to both, insulin receptor isoforms and IGF-1 receptor and importantly has a delayed dissociation rate upon binding to the insulin receptor. In our submission package we plan to include for this reason comparison of kinetic binding data to the human insulin receptor A and B and the human IGF-1 receptor, raised by Biacore technology, in order to assess whether dissociation rates are delayed compared to the marketed US-licensed NovoLog with its known safety profile.

In addition, the Sponsor has assessed antigen Ki-67, a marker that is associated with cellular proliferation, in the toxicity studies in rat. There was no increase in proliferation activity in the mammary gland tissue different from concurrent vehicle controls and was at the most at the same level compared to the already marketed product NovoLog. Therefore, the Sponsor does not consider it necessary to conduct a second in vitro mitogenicity assay. Does Agency agree with Sponsor's approach?

Discussion: *The Sponsor did not consider it necessary to conduct an additional in vitro cell-based mitogenicity assay that was recommended by the Agency in preliminary meeting comments to assess insulin receptor-dependent mitogenicity. The sponsor provided their rationale for why their completed evaluations were adequate, which was based primarily on establishing similarity to US-Novolog in binding kinetic properties thought to drive the mitogenic liability (as demonstrated by e.g., Insulin (Asp)B10). The Agency agreed that the binding kinetics of the insulin receptor (IR) were valuable for the evaluation of IR-dependent mitogenicity with respect to the putative mechanism of Insulin (Asp)B10. However, the Agency strongly recommended that a single additional mitogenicity assay using a cell line that preferentially expresses the insulin receptor over the IGF-1 receptor (e.g., L6-hIR, H4IIE) be conducted as part of a fully comprehensive in vitro comparison of mitogenic risk between SAR341402 and US-licensed Novolog irrespective of any specific mechanism. The Sponsor and the Agency agreed that in vivo studies evaluating proliferation (via assessment of the biomarker ki-67) in mammary tissue after one month of exposure in the rat lacked the sensitivity required to identify meaningful differences between SAR341402 and US-Novolog, due primarily to the short duration of the study. The Agency suggested that should the comprehensive battery of in vitro assays (including the cell-based IR-dependent mitogenicity assay) support a demonstration of highly similar between the SAR341402 and US-licensed Novolog, additional in vivo animal studies would not be warranted.*

Comments for Human Factors (HF):

(b) (4)

With regard to human factors considerations for your proposed (b) (4) SAR341402 SoloStar pen, in addition to the HF differentiation study, we remind you that appropriate data (b) (4) may be collected (b) (4) (b) (4) (b) (4) (b) (4)

Submit the information from your analyses to your IND so that we can reach agreement on whether additional data are needed to support your application (b) (4) Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

We request that you submit your comparative analyses for review as soon as possible.

Sponsor's Pre-meeting Response: The Sponsor will provide the comparative analyses for review when completed, no later than the time of BLA submission, which was agreed on May 4, 2021, to seek interchangeability to US-licensed NovoLog.

This data package is not limited to but will include threshold analyses (b) (4) (b) (4) (b) (4) in addition to the HF differentiation study. No further discussion is planned.

Discussion: *The Agency clarified that the Sponsor should submit their comparative analyses to the IND for review prior to the submission of the BLA so that agreement regarding HF data requirements is reached before the application is submitted. There is no formal timeline for DMEPA to complete review of comparative analyses, but we aim to complete reviews within 90 days if resources allow. If the BLA is submitted before the Agency has completed review of the comparative analyses, the Sponsor risks a delay in approval of the BLA should we determine that additional human factors data are needed.*

Clinical Pharmacology Comments:

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 guidance for industry *Bioanalytical*

Methods Templates Guidance for Industry Technical Specifications Document **to provide the information regarding the bioanalytical methods for PK and/or PD 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 Section 2.7.1.**

Sponsor's Pre-meeting Response: No further discussion needed.

Discussion: *No further discussion occurred.*

CMC Comments:

The comparative analytical assessment between SAR341402 and the reference product submitted to eCTD Section 3.2.R Regional Information should include data from the analytical tests listed in Table 11 of your meeting package, as well as data from the comparative in vitro assays described in Section 18.2.1 Nonclinical pharmacology of your meeting package.

Sponsor's Pre-meeting Response: The Sponsor will include a summary of data from the analytical tests listed in Table 11 in Section 3.2.R Regional Information, in addition to cross-reference to the nonclinical CTD module. Nonclinical CTD module will contain pharmacology studies and toxicity studies. Does Agency agree with Sponsor's proposal?

Discussion: *The Sponsor proposed that they would include a summary of data from the analytical tests listed in Table 11 in Section 3.2.R Regional Information, in addition to cross-reference to the nonclinical CTD module. The Sponsor also described that the Nonclinical CTD module will contain pharmacology studies and toxicity studies. Regarding the Sponsor's proposal to cross reference to the nonclinical CTD module, the Agency advised that at least a summary of the data from the comparative in vitro assays described in Section 18.2.1 of the meeting package should be submitted by the Sponsor as part of the comparative analytical assessment (CAA) in Section 3.2.R Regional Information, and that a cross-reference may be provided to the non-clinical CTD module for detailed information on these in-vitro studies. These comparative in-vitro studies should be performed using the same CAA approach as that used for the other attributes, including criticality risk ranking, lots of SAR341402 and U.S.-licensed NovoLog used, and statistical analyses.*

CMC Microbiology Comments:

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:

a) **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).**

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

c) **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).**

d) **Chromatography resin and ultrafiltration/diafiltration (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).**

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

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

g) **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 guidance for industry *Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products*.

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

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

b) **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.**

c) **Parameters for filling and plunger placement for the cartridges.**

d) **Parameters for filling and capping for the vials.**

e) **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.**

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

g) **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:

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

b) 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.

c) 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.

d) Isolator decontamination summary data and information, if applicable.

e) 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.

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

g) Validation of capping parameters, using a container closure integrity test.

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

a) 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 pen injector 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.

b) 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.

c) **Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b). A request to waive the Rabbit Pyrogen Test may be made for insulin products by providing scientifically justifiable rationale.**

d) **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.**

e) **Specification for the concentration of preservative by chemical analysis and the method used to quantify the preservative concentration. Preservative concentration should be tested at release and on stability at all test intervals.**

f) **Antimicrobial effectiveness testing (APET) in accordance with USP <51>. The study should be performed with the lowest concentration of preservative indicated by the specification. APET should be conducted on the first three commercial lots of drug product placed on stability, at the beginning and end of the stability period.**

Discussion: No further discussion occurred.

Combination Product General Comment

1. **For location of information on the device constituent part (the SAR341402 pen injector) see the FDA 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*[2]*".***

2. **The SAR341402 (insulin aspart-xxxx) pen injector appears to be a combination product under 21 CFR 3.2(e). Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. For further information on 21 CFR Part 4, the final rule is accessible at the Current Good Manufacturing Practice**

[2] https://www.fda.gov/media/93818/download

Requirements for Combination Products website[3]. Also, refer to the guidance for industry *Current Good Manufacturing Practice Requirements for Combination Products*.

Discussion: *No further discussion occurred.*

3.0 DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.

  All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.

- A preliminary discussion regarding the approach to developing the content for a REMS, where applicable, patient labeling (e.g., Medication Guide and Instructions for Use) and, where applicable, the development of a Formal Communication Plan was held and it was concluded that no formal communication plan is necessary.

- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

4.0 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

[3] https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products

recommends that you allow adequate time to reach agreement with FDA on the proposed iPSP prior to initiating your comparative clinical study.

Sections 505B(e)(2)(C) and 505B(e)(3) of the FD&C Act set forth a process lasting up to 210 days for reaching agreement with FDA on an iPSP. FDA encourages the sponsor to meet with FDA to discuss the details of the planned development program before submission of the iPSP. You must address PREA for every indication for which you seek licensure, and we encourage you to submit a comprehensive iPSP that addresses each indication. For additional information on how you may fulfill the requirement for pediatric assessments or investigations under PREA, see question and answer I.16 in the guidance for industry, *Questions and Answers on Biosimilar Development and the BPCI Act*.

After the iPSP is submitted, a sponsor must work with FDA to reach timely agreement on the plan, as required by section 505B(e)(2)-(3) of the FD&C Act. For additional guidance on the timing content, and submission of the iPSP, including an iPSP Template, please refer to the guidance for industry, *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*[4]. 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.

5.0 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)[5] and 201.57[6] 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[7] and Pregnancy and Lactation Labeling Final Rule[8] websites, which include:

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[4] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/pediatric-study-plans-content-and-process-submitting-initial-pediatric-study-plans-and-amended
[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.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
[7] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/LawsActsandRules/ucm084159.htm
[8] 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.
- 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*.[9]

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.

6.0 NONPROPRIETARY NAME

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

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.

7.0 MANUFACTURING FACILITIES

All facilities should be registered with FDA at the time of the 351(k) BLA submission and ready for inspection in accordance with 21 CFR 600.21 and 601.20(b)(2). Manufacturing and testing facilities will be subject to the CGMP standards as described in 21 CFR 601.20, including but not limited to the good manufacturing practice requirements set forth in 21 CFR 210, 211, and 600 of this chapter.

Manufacturing facilities should be in operation and manufacturing the product under review during the inspection, 2-7 months after the submission of the BLA. A manufacturing schedule for the drug substance and the drug product should be provided in Module 1 of the BLA to facilitate planning of pre-license/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[10] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[11]. 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.

8.0 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*

[10] https://www.fda.gov/media/84223/download
[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and

Submissions (February 2018) and the associated Bioresearch Monitoring Technical Conformance Guide Containing Technical Specifications be provided to facilitate development of clinical investigator and sponsor/monitor/CRO inspection assignments, and the background packages that are sent with those assignments to the FDA ORA investigators who conduct those inspections. This information is requested for all major trials used to support safety and efficacy in the application (i.e., phase 2/3 pivotal trials). Please note that if the requested items are provided elsewhere in submission in the format described, the Applicant can describe location or provide a link to the requested information.

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

9.0 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[12] 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.

10.0 ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

11.0 ACTION ITEMS

There were no action items identified at the meeting.

12.0 ATTACHMENTS AND HANDOUTS

There were no slides presented at the meeting.

[12] 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/

PATRICK ARCHDEACON
02/23/2022 03:09:17 PM