CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761196Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 126138

MEETING MINUTES

ADC Therapeutics SA
c/o ADC Therapeutics America Inc.
Attention: Rupal Patel
Associate Director, Global Regulatory Affairs
430 Mountain Avenue, Suite 404 (4th Floor)
Murray Hill, NJ 07974

Dear Ms. Patel:[1]

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for ADCT-402.

We also refer to the teleconference between representatives of your firm and the FDA on April 17, 2020. The purpose of the meeting was to discuss the content and presentation of data to be included in your planned BLA submission.

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, contact Jennifer Lee, Senior Regulatory Health Project Manager, at (240) 402-4622.

Sincerely,

{See appended electronic signature page}

Nicholas Richardson, DO, MPH
Acting Clinical Team Leader
Division of Hematologic Malignancies II
Office of Oncologic Diseases
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: Type B
Meeting Category: Pre-BLA

Meeting Date and Time: Friday, April 17, 2020; 9:00 AM – 10:00 AM (ET)
Meeting Location: Teleconference

Application Number: IND 126138
Product Name: ADCT-402
Proposed Indication: Relapsed or refractory diffuse large B-cell lymphoma (DLBCL)
Sponsor Name: ADC Therapeutics SA
Regulatory Pathway: 505(b)(1) of the Food, Drug, and Cosmetics Act and 351(a) of the Public Health Service Act

Meeting Chair: Nicholas Richardson, DO, MPH
Meeting Recorder: Jennifer Lee, PharmD, RAC-US

FDA ATTENDEES

Office of Oncologic Diseases (OOD)
Elizabeth Everhart, MSN, RN, ACNP – Acting Program Manager for Safety

OOD/Division of Hematologic Malignancies II
Nicole Gormley, MD – Acting Director
Nicholas Richardson, DO, MPH – Acting Clinical Team Leader
Maryam Yazdy, MD – Clinical Reviewer

Office of Regulatory Operations/Division of Regulatory Operations for Oncologic Diseases
Theresa Carioti, MPH – Chief, Project Management Staff
Jennifer Lee, PharmD, RAC-US – Senior Regulatory Health Project Manager

Office of Hematology and Oncology Products/Division of Hematology, Oncology, Toxicology
Haleh Saber, PhD – Deputy Director
Brenda Gehrke, PhD – Acting Team Leader
Natalie Simpson, PhD – Pharmacologist

Office of Biostatistics/Division of Biometrics IX
Yu-te Wu, PhD – Biometrics Team Leader
Qing Xu, PhD – Biometrics Reviewer

Office of Clinical Pharmacology/Division of Clinical Pharmacology V
Ruby Leong, PharmD, BCOP – Clinical Pharmacology Team Leader
Hisham Qosa, PhD – Clinical Pharmacology Reviewer

Office of Pharmaceutical Quality (OPQ)/Office of Biotechnology Products/Division Of Biotechnology Review and Research IV
Haoheng Yan, MD, PhD – Lead Chemist
Rukman De Silva, PhD – Chemist

OPQ/Office of Pharmaceutical Manufacturing Assessment/Division of Biotechnology Manufacturing, Branch I
Dupeh Palmer-Ochieng, PhD – Microbiologist

OPQ/Office of New Drug Products/Division of New Drug API
Sherita McLamore, PhD – Chemist
Rohit Tiwari, PhD – Chemist

SPONSOR ATTENDEES

Jay Feingold MD, PhD, Senior Vice President and Chief Medical Officer, ADCT
Jens Wuerthner MD, PhD, Vice President, Head of Global Clinical Development Oncology, Clinical, ADCT
David Ungar MD, Head of US Oncology Clinical Development, ADCT
Joe Boni PhD, Head of Global Clinical Pharmacology, ADCT
David Ellis PhD, Vice President, Regulatory Affairs, ADCT
Rupal Patel, Associate Director, Regulatory Affairs, ADCT
Shui He PhD, Vice President, Global Biometrics, ADCT
Karthik Mani, Associate Director, CMC Regulatory Affairs, ADCT
(b) (4)
Karin Havenith, Principal BioAnalytical Scientist, R&D, ADCT
Esohe Idusogie PhD, Head of Process Quality and CMC Analytical, ADCT
Michael Mulkerrin, PhD, Vice President, Head of CMC, ADCT

1.0 BACKGROUND

Loncastuximab tesirine (ADCT-402) is an antibody drug conjugate composed of a proposed CD19 targeting humanized monoclonal immunoglobulin (IgG1) conjugated via a linker to SG3199, a pyrrolobenzodiazepine (PBD) dimer cytotoxin, currently under development by ADC Therapeutics SA for the treatment of CD19-positive B cell hematologic malignancies.

The Sponsor is currently targeting a 3rd quarter 2020 submission of an original Biologics License Application (BLA) to propose the registration of ADCT-402 for the treatment of patients with relapsed or refractory DLBCL. Results from the ongoing Phase 2 Study

ADCT-402-201, entitled "*A Phase 2 Open-Label Single-Arm Study to Evaluate the Efficacy and Safety of Loncastuximab Tesirine in Patients with Relapsed or Refractory Diffuse Large B-Cell Lymphoma (DLBCL)),"* will provide the basis for the planned application.

On February 4, 2020, the Sponsor requested a Pre-BLA meeting with the Agency to discuss the content and presentation of data to be included in the planned BLA. A revised list of meeting questions was received on February 7, 2020.

FDA sent Preliminary Comments to ADC Therapeutics SA on April 9, 2020.

2.0 DISCUSSION

2.1. Chemistry, Manufacturing, and Controls

Question 1: *Does the Agency have any comments on the proposed list of CMC/Quality documents to be included in 3.2.R Regional Information of the BLA?*

FDA Response to Question 1: We do not agree with the proposed submission of the CMC/Quality information listed on page 12 of the Type B meeting package in Section 3.2.R Regional Information of the BLA. The following information should be included in the Section 3.2.R Regional Information:

a) The SOPs and method validation reports for the drug substance monoclonal antibody intermediate, drug linker intermediate, antibody-drug conjugate drug substance and drug product release and stability assays.

b) The master batch records and at least one of the executed batch records for the PPQ runs/lots for the drug substance monoclonal antibody intermediate, drug linker intermediate, antibody-drug conjugate drug substance and drug product.

Note that the descriptions of analytical methods and summaries of the method validation data should be included in the corresponding sections of 3.2.S.4.2 or 3.2.P.5.2 Analytical Procedures, and 3.2.S.4.3 or 3.2.P.5.3 Validation of Analytical Procedures.

Discussion: **No discussion occurred.**

Question 2: *Does the Agency agree that the intravenous (IV) compatibility and microbial challenge study designs, and that the package to be provided in the BLA are sufficient to support in-use physiochemical and microbiological attributes of the commercial product?*

FDA Response to Question 2: In general, the proposed IV compatibility study to support the commercial use of diluted drug product in IV administration appears to be reasonable. We have the following comments regarding the proposed IV compatibility study:

a) You propose to measure drug product recovery by Size Exclusion Chromatography (SEC). It is not clear whether the SEC method can accurately assess the product recovery at the proposed concentrations (b) (4) (b) (4). For instance, protein absorption to the SEC column matrix may cause low protein recovery (Reference: Arakawa T. et al. J Pharm Sci. 2010 April;99(4):1674-92). Therefore, in the BLA submission, provide method qualification data to demonstrate the proposed SEC method can accurately measure protein content at the proposed concentrations.

b) It is unclear if there is any change in the free drug content during the use of the ADCT-402 drug product. The Agency recommends including the test for free drug in the IV bag compatibility study.

c) We agree that the microbiological challenge study outlined on page 13 of the Type B meeting package is adequately designed to provide data to support transfer and storage of the reconstituted drug product diluted in 5% dextrose in the IV bag for up to 8 hours at room temperature or up to 24 hours at 2-8°C prior to patient administration. We recommend that you also include positive controls (i.e., 5% dextrose without the product) that demonstrate the viability of the challenge organisms over the duration of the test period in the study.

Discussion: **The Agency stated that overall, the plan to address the comments above appears reasonable. However, in the absence of any data at this stage, the adequacy for the exclusion of free drug linker test from in-use stability study will be assessed at the time of BLA review. The Agency recommended providing the forced degradation study data for SG-3249 linker to assess the structural integrity of the payload-linker. Regarding using the SEC method for product recovery, the Agency suggested the Sponsor to include method LOQ (limit of quantification) in the method qualification and follow the ICH Q2(R1) guideline.**

2.2. Clinical

Question 3: *Does the Agency agree with the efficacy and safety data analysis strategy as well as the proposed method of inclusion of the ISS information in the BLA?*

FDA Response to Question 3: The proposed approach appears reasonable.

Discussion: **No discussion occurred.**

Question 4: *Does the Agency agree with the datasets and programs planned to be submitted with the BLA?*

FDA Response to Question 4: Yes. We agree with the datasets and programs planned to be submitted with the BLA. In addition, we have the following comments:

a) Datasets should have one and only one unique subject ID for each patient among all trials.

b) There should be instructions for the reviewer regarding the use of variables and flags to identify the set of patients on which the primary analysis is performed. Provide flags to identify the analysis population, for example, (1) Intent-to-Treat patients set, (2) safety population set.

c) Include an Analysis Data Reviewer's Guide (ADRG) and Study Data Reviewer's Guide (SDRG), an important part of a standards-compliant study and analysis data submission, to be prepared and submitted for each dataset in the BLA. Please refer to the "Study Data Technical Conformance Guide: Technical Specifications Document."[2]

d) The define.pdf file should contain the descriptions (how coded, which value stands for what) of variable names on SAS datasets. The same variable name should be used for all datasets (i.e., one definition, well-annotated, per one variable).

e) Provide the SAS programs (with adequate comments) used to create all ADaM datasets along with the tables and figures associated with primary and secondary efficacy analyses in order to help reviewers to better understand how the datasets, tables, and figures are created. The main purpose of requesting the submission of these programs is to understand the process by which the variables for the respective analyses are created and to confirm the analysis algorithms.

f) Provide documentation of any correspondence (written documents or meeting minutes) with FDA regarding pivotal study of ADCT-402-201.

Discussion: **No discussion occurred.**

Question 5: *Does the Agency agree with the approach to comparing the PK for the two different loncastuximab tesirine drug products used in study ADCT-402-201?*

FDA Response to Question 5: Yes, we agree with your approach to comparing the PK for the two loncastuximab tesirine formulations used in study ADCT-402-201. We

[2] https://www.fda.gov/media/131872/download

also recommend submitting a comparison of the efficacy and safety of the two formulations.

Discussion: **No discussion occurred.**

Question 6: *Given that only a limited amount of supplemental PK data will be forthcoming in the month prior to the final safety/efficacy database cut, does the Agency agree with use of a PK database cut for study ADCT-402-201 that is different (earlier) than the safety/efficacy cut? Does the Agency agree with suitability of a PPK analysis model structure that is defined from mock analysis using the aforementioned PK database cut?*

FDA Response to Question 6: Yes. The use of an early cutoff date of the PK dataset appears acceptable. With regards to the exposure-response (E-R) analyses for efficacy and safety, perform analyses for the unconjugated SG3199 in addition to the conjugated antibody. Further, we recommend that you evaluate exposure metrics for the first dose/cycle in the E-R analyses.

Discussion: **The Agency acknowledged that there may be limitations of the E-R analysis for SG3199 due to low systemic concentrations. The methodology of the bioanalytical assays and results of the E-R analysis will be a review issue.**

Question 7: *Does the Agency agree with the proposed approach for the 120-day safety update?*

FDA Response to Question 7: Yes, the proposed approach is acceptable.

Discussion: **No discussion occurred.**

Question 8: *Does the Agency agree with the proposed approach to patient narratives and CRFs to be included in the BLA?*

FDA Response to Question 8: Yes, the proposed plan for narratives and CRFs is acceptable.

Discussion: **No discussion occurred.**

Question 9: *Does the Agency agree with the proposed plan to use the characterization and neutralization assays qualified under R&D and not fully validated [Guidance for Industry entitled: "Immunogenicity Testing of Therapeutic Protein Products – Developing and Validating Assays for Anti-Drug Antibody Detection (January 2019)], would ADA positivity be found late during the pivotal study? Does the Agency agree that a separate Integrated Summary of Immunogenicity is not required and that results summarized in 2.7.4 Summary of*

Clinical Safety (SCS) and 2.7.2 Summary of Clinical Pharmacology (SCP) are acceptable?

FDA Response to Question 9: No. Samples derived from pivotal studies should be tested with fully validated immunogenicity assays. At the time of license application, the sponsor should provide data demonstrating that the assays are fully validated. We advise you to store samples obtained from completed and ongoing studies under suitable storage conditions for future analysis once a validated ADA neutralizing assay is fully characterized and validated.

Your proposal to not include a separate summary is not acceptable. To facilitate the review of immunogenicity data, we recommend providing an Integrated Summary of Immunogenicity (ISI) that includes (1) Immunogenicity Risk Assessment, (2) Tiered Bioanalytical Strategy and Assay Validation Summaries, (3) Clinical Study Design and Detailed Immunogenicity Sampling Plans, (4) Clinical Immunogenicity Data Analysis, and (5) Conclusions and Risk Evaluation and Mitigation Strategies (REMS). An integrated immunogenicity summary report will allow the sponsor to update the immunogenicity information of loncastuximab at regular intervals during the clinical development and even at post-approval stages.

Complete and include the tables (Table 1 - Bioanalytical Method Life Cycle Information, and Tables 2a-b - Summary Method Performance of Each Bioanalytical Method) in your 351(a) BLA submission to provide the information regarding the bioanalytical methods for pharmacokinetic and/or immunogenicity assessments used in pivotal clinical pharmacology studies and its life-cycle information pertaining to the submission. Do not delete any rows from the tables. We recommend that these tables be included as an Appendix in the Summary of Biopharmaceutics located in eCTD 2.7.1. In addition to including in the Appendix, we request you also submit both tables in docx format. Include any other additional bioanalytical information that might be relevant for review in your BLA submission. Finally, refer to additional clinical pharmacology comments below. Refer to the FDA guidance for industry for detailed information on ISI, *Immunogenicity Testing of Therapeutic Protein Products — Developing and Validating Assays for Anti-Drug Antibody Detection*.[3]

Table 1. Summary life cycle information of bioanalytical method(s) used in submission of BLA xxxxxx to measure analyte X in matrix

	Method validation #1	Method validation #2	Clinical Study x	Clinical Studies y-z
Analyte	Drug name	Drug x, Drug y	Drug x, and Drug y	Drug x, Drug z
Validation type	Full	Partial validation of method xx	NA	NA
	Ref # in eCTD	x0000.0xxxxxx	x0000.0xxxxxx	x0000.0xxxxxx

[3] https://www.fda.gov/media/119788/download

• CTD ref # • method ID • BA site	Method ID xx (version)	SOP xxxx or Method xxx (v 1.0)	SOP xxxx or Method xxx (v 1.0)	SOP xxxx or Method xxx (v 1.0)
	Name of BA test facility	US Lab 1	US lab 1	Other lab
• Matrix	Serum/ Plasma/Urine/ whole blood			
• Platform	LC/MS, ELISA, ECL			
• Format	A validated sandwich format using x as capture and y as detection, a bridging format using z as both capture and detection, competitive assay using x as a capture and b as a competitor			
Stock reference & lot (expiry)	Drug 1, lot 1	Drug 1, lot 2 Drug 2, lot 1		
Calibration range (LLOQ -ULOQ) and levels validated	x- x000 ng/mL (E.g., 2, 5, 50, 250, 1000, 1500, 2000 ng/mL)	x- x000 ng/mL	x- x000 ng/mL	x- x000 ng/mL
Matrix/ study population	Normal or x diseased serum	Normal serum	Normal serum	x Diseased population
Relevant reference and applicable report amendment (s) and links -Amendment 1 -Amendment 2				
Amendment history				

The bioanalytical method performance summary table (**Table 2a**) is recommended in describing PK and/or biomarker methods. Please use one method per analyte per table. This table is not applicable for anti-drug antibody methods. Do not delete any rows or columns from the table. State "not applicable" if certain rows or columns are not applicable. Include any additional bioanalytical data that may be relevant to the submission.

Table 2a. Summary method performance of a bioanalytical method to measure [analyte] in [matrix]

Bioanalytical method validation report name, amendments, and hyperlinks	
Method description	
Materials used for calibration curve & concentration	
Validated assay range	
Material used for QCs & concentration	
Minimum required dilutions (MRDs)	

Source & lot of reagents (LBA)			
Regression model & weighting			
Validation parameters	**Method validation summary**		**Source location**
Calibration curve performance during accuracy & precision	Number of standard calibrators from LLOQ to ULOQ	x	
	Cumulative accuracy (%bias) from LLOQ to ULOQ Product A Product B and/or Product C	 x to y% x to y% x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	
QCs performance during accuracy & precision	**<u>Cumulative accuracy (%bias) in 5 QCs</u>** QCs: Product A Product B and/or Product C	 x to y% x to y% x to y%	
	<u>Inter-batch %CV</u> QCs: Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	
	<u>Total error</u> QCs: Product A Product B and/or Product C	 ≤ x% ≤ x% ≤ x%	
Selectivity & matrix effect	Number of total lots tested. Range of observed bias. State any issue		
Interference & specificity	Number of total lots tested. Range of observed bias. State any issue		
Hemolysis effect	Number of total lots tested. Range of observed bias. State any issue		
Lipemic effect	Number of total lots tested. Range of observed bias. State any issue		
Dilution linearity & hook effect	Describe data here		
Bench-top/process stability	Describe data here Product A Product B and/or Product C		
Freeze-Thaw stability	Describe data here Product A Product B and/or Product C		
Long-term storage	Describe data here Product A		

	Product B and/or Product C	
Parallelism	Describe data here	
Carry over	Describe data here	
Method performance in study number (In addition to the report name, also provide hyperlink to the report)		
Materials used for calibration curve & QC		
Assay passing rate	(including incurred sample reanalysis (ISR))	
Standard curve performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV	
QC performance	• Cumulative bias range: x to y% • Cumulative precision: ≤ x% CV • TE: ≤ x% (LBA only)	
Method reproducibility	Incurred sample reanalysis was performed in x% of study samples and x % of samples met the pre-specified criteria	
Study sample analysis/ stability	Describe storage stability coverage for standard/QC and samples	

If the method above was modified, describe the modification(s) and cross-validation results, with any additional information in **Table 2b** below.

Table 2b. Summary of method [x] modification(s) and cross-validation results

Bioanalytical method validation report name and hyperlink			
Changes in method			
New validated assay range if any			
Validation parameters	**Cross-validation performance**		**Source location**
Calibration curve performance during accuracy & precision	Cumulative accuracy (%bias) in standard calibrators from LLOQ to ULOQ	x to y%	
	Cumulative precision (%CV) from LLOQ to ULOQ	≤ x%	
QCs performance during accuracy & precision	Cumulative accuracy (%bias) in 5 QCs	x to y%	
	Inter-batch %CV	≤ x%	
	Percent total error (TE)	≤ x%	
Cross-validation	Numbers of spiked or incurred samples analyzed and result		
List other parameters			

Discussion: **The Agency stated that samples identified as ADA positive should be further characterized in neutralization assay, as per the guidance. We acknowledge that the immunogenicity risk for loncastuximab tesirine is theoretically low. However, you have not completed testing clinical samples and the Agency cannot agree with your approach of not testing nAb without fully reviewing your ADA method and the complete clinical ADA data. The Agency agrees that ADCT should retain clinical samples under suitable conditions until a validated nAb assay is available. The Agency recommended that the ADA analysis be completed prior to submission of the BLA. The lack of an nAb analysis may not affect filing of the BLA, however could be considered a major amendment if submitted during the BLA review cycle.**

The Sponsor clarified that they will provide information regarding ADA for the linker-payload and the antibody.

Question 10: *Does the Agency agree that the renal and hepatic function limited to mild impairment criteria as governed by inclusion in studies ADCT-402-101 and ADCT-402-201 are sufficient to guide labeling for loncastuximab tesirine?*

FDA Response to Question 10: The acceptability of the data to support the labeling recommendation in patients with mild hepatic or renal impairment will be a review issue. To use the popPK approach to assess the effect of renal and hepatic impairment, sufficient numbers of subjects that fall in each category of hepatic or renal impairment should be included in the analysis, otherwise the labeling recommendation will be limited to the hepatic or renal impairment categories that have data from clinical studies to support the labeling recommendations. In addition, identify the means by which SG3199 is metabolized and excreted. Based on the contribution of hepatic and renal pathways to SG3199 elimination, you should assess the need to conduct a dedicated hepatic and/or renal impairment study or justify why a dedicated study is not needed in support of the BLA.

Discussion: **No discussion occurred.**

Question 11: *Does the Agency agree with the proposed approach to comply with the Bioresearch Monitoring (BIMO) Program?*

FDA Response to Question 11: The proposed approach appears reasonable.

Discussion: **No discussion occurred**

2.3. General

Question 12: *Does the FDA agree that the proposed BLA contains all major components for a complete application?*

For the BLA submission, ADCT anticipates that the CMC and Nonclinical modules will be complete and ready for submission in June 2020 and remaining modules of the BLA submission are anticipated to be ready for submission in September 2020. Does the Agency agree with the proposal for a rolling review submission of the complete CMC and Nonclinical modules prior to submission of the full modules 1 and 5 (Clinical) and related M2 Clinical summaries?

FDA Response to Question 12: Based on the nonclinical information provided in the meeting package, we have the following comment:

a) We refer you to the EOP1 meeting minutes from March 28, 2018, regarding the completeness of the Nonclinical modules to support the BLA submission. In this meeting, the Division agreed that fertility and carcinogenicity studies are not warranted; however, we noted that we do not have all of the information needed to waive reproductive toxicology studies. Submit data with your BLA clearly demonstrating the genotoxicity of SG3199; alternatively, you can reference data in another application if you have right to reference the data.

At this time, submission of the CMC module at an early timepoint may be acceptable, followed by submission of a complete marketing application. To be eligible for a rolling review, your product must have received fast track or breakthrough therapy designation.

Discussion: **The Agency communicated to the Sponsor that if upon review of genetic toxicology studies we conclude that the ADCT-402 and/or the payload are genotoxic, we agree that reproductive toxicology studies will not be needed per ICH S9.**

The Agency stated that in the absence of fast track or breakthrough therapy designation, the Applicant may submit only Module 3 in eCTD format via the Electronic Submission Gateway ahead of the complete application. If the Agency accepts a portion of an application, this does not necessarily mean that review will commence or proceed before the complete application is submitted.

For information on how to obtain a pre-assigned application number via the CDER NEXUS Portal, please refer to the following link: https://www.fda.gov/drugs/electronic-regulatory-submission-and-review/requesting-pre-assigned-application-number. For submission-related questions please contact esub@fda.hhs.gov.

Additional Product Quality Comments

1) To facilitate the Agency's review of the drug substance monoclonal antibody intermediate, antibody drug conjugate drug substance, and drug product

manufacturing processes for ADCT-402, provide the information for process parameters and in-process control, as applicable, in the following tabular format. Please provide a separate table for each unit operation. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R.

Process Parameter/ Operating Parameter/ In-Process Control	Proven Acceptable Range/ Control Limits/ Targets[1] for Commercial Manufacturing Process	Criticality Classification[2]	Characterized Range/ Control Limits/Targets[1] tested in Process Development Studies	Manufactured Range/ Control Limits/Targets[1] used for Pivotal Clinical Study Lots	Manufactured Range/ Control Limits/Targets[1] used in Process Validation	Justification of the Proposed Commercial Acceptable Range[3]	Comment[4]

[1]As applicable.
[2]For example, critical process parameter, key process parameter, non-critical process parameter, as described in module 3.
[3]This could be a brief verbal description or links to the appropriate section of the eCTD.
[4]Optional.

2) To facilitate the Agency's review of the control strategy for ADCT-402, provide information for quality attributes and process and product related impurities for the drug substance monoclonal antibody intermediate, antibody drug conjugate drug substance, and drug product in the following tabular format. The tables should summarize information from Module 3 and may be submitted either to Module 1 or Module 3R.

Quality Attributes and Process and Product Related Impurities for CI, DS and DP	Criticality Classification[1]	Impact[2]	Source[3]	Analytical Method [4]	Proposed Control Strategy[6]	Justification of the Proposed Control Strategy[6]	Comment[7]

[1]For example, critical quality attribute or non-critical quality attribute.
[2]What is the impact of the attribute, e.g. contributes to potency, immunogenicity, safety, efficacy.
[3]What is the source of the attribute or impurity, e.g. intrinsic to the molecule, fermentation, protein A column.
[4]List all the methods used to test an attribute in-process, at release, and on stability. For example, if two methods are used to test identity then list both methods for that attribute.
[5]List all the ways the attribute is controlled, for example, in-process testing, validated removal, release testing, stability testing.
[6]This could be a brief verbal description or links to the appropriate section of the eCTD.
[7]Optional.

Additional Product Quality Microbiology Comments

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

All facilities should be registered with the FDA at the time of the 351a 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 antibody intermediate, 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.

For facilities handling potent or toxic products, a risk assessment should be conducted to identify risks of cross-contamination between the products. Please refer to ICH Q9 and ISPE (2010), "Risk Based Manufacture of Pharmaceutical Products" (Risk-MaPP) for guidance. The quality risk management report and the segregations and controls implemented to mitigate the identified risks will be evaluated during the pre-license inspection. Cleaning validation limits of shared equipment should be science-based, e.g., based on Acceptable Daily Exposure (ADE) of products.

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

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

- Bioburden and endotoxin levels at critical manufacturing steps should be monitored using qualified bioburden and endotoxin tests. Bioburden sampling should occur prior to any 0.2 µm filtration step. The pre-established bioburden and endotoxin limits should be provided (3.2.S.2.4).

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

- Microbial data from three successful product intermediate hold time validation runs at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided (3.2.S.2.5).

- Chromatography resin and UF/DF membrane lifetime study protocols and acceptance criteria for bioburden and endotoxin samples. During the lifetime studies, bioburden and endotoxin samples should be taken at the end of storage prior to sanitization (3.2.S.2.5).

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

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

- Summary reports and results from bioburden and endotoxin test method qualification studies performed for in-process intermediates and the drug substance. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers (3.2.S.4).

The CMC Drug Product section of the 351a 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.*[4] The following information should be provided in Sections 3.2.P.3.3 and/or 3.2.P.3.4, as appropriate.

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

- Description of the sterilizing filter (supplier, size, membrane material, membrane surface area, etc.); sterilizing filtration parameters (pressure and/or flow rate), as validated by the microbial retention study; wetting agent used for post-use integrity testing of the sterilizing filter and post-use integrity test acceptance criteria.

- Parameters for filling and capping for the vials.

- A list of all equipment and components that contact the sterile drug product (i.e., the sterile-fluid pathway) with the corresponding method(s) of sterilization and depyrogenation, including process parameters. The list should include single-use equipment.

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

[4] http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm072171.pdf

- Sampling points and in-process limits for bioburden and endotoxin. Bioburden samples should be taken at the end of the hold time prior to the subsequent filtration step. Pre-sterile filtration bioburden limits should not exceed 10 CFU/100 mL.

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

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

- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.

- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.

- Isolator decontamination summary data and information, if applicable.

- Three successful consecutive media fill runs, including summary environmental monitoring data obtained during the runs. Describe the environmental and personnel monitoring procedures followed during media fills and compare them to the procedures followed during routine production.

- Information and summary results from shipping validation studies.

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

- Lyophilizer sterilization validation summary data and information.

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

- Container closure integrity testing. System integrity should be demonstrated initially and during stability. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.

- Summary report and results for qualification of the bioburden, sterility, and endotoxin test methods performed for in-process intermediates (if applicable) and the finished drug product, as appropriate. If compendial test methods are used, brief descriptions of the methods should be provided in addition to the compendial reference numbers. Provide full descriptions and validation of non-compendial rapid microbial methods.

- Summary report and results of the Rabbit Pyrogen Test conducted on three batches of drug product in accordance with 21 CFR610.13(b). In accordance with 21 CFR610.9, an alternative pyrogen test may be submitted in lieu of the rabbit pyrogen test (such as a Monocyte Activation Test). Full supporting test validation data should be submitted to support the use of a non-compendial pyrogen test.

- 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.

- Microbiological studies in support of the post-reconstitution and/or post-dilution storage conditions storage conditions. Describe the test methods and results that employ a minimum countable inoculum (10-100 CFU) to simulate potential microbial contamination that may occur during dilution. The test should be run at the label's recommended storage conditions, be conducted for twice the recommended storage period, bracket the drug product concentrations that would be administered to patients, and use the label-recommended solutions and diluents. Periodic intermediate sample times are recommended. Challenge organisms may include strains described in USP <51> *Antimicrobial Effectiveness Testing*, plus typical skin flora or species associated with hospital-borne infections. *In lieu* of this data, the product labeling should recommend that the post-reconstitution and/or post-dilution storage period is not more than 4 hours.

The CMC Drug Product section of the BLA (Section 3.2.P) for the water for injection (WFI) that is co-packaged with the drug product should contain validation data summaries to support the terminal sterilization process from a sterility assurance perspective. 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*.

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

- Description of the terminal sterilization process, loading patterns, methods used to monitor and control production cycles, and the performance specifications. The autoclaves used for WFI sterilization should be identified and the requalification program should be described.

- Processing/hold time limits prior to terminal sterilization. Bioburden and endotoxin should be monitored at the end of a hold prior to terminal sterilization.

- Depyrogenation process parameters for the primary container closure system components that contact the drug product.

The following study protocols and validation data summaries for the WFI drug product should be included in Section 3.2.P.3.5:

- Depyrogenation of the drug product container closure system. Provide summary data for the three validation studies and describe the depyrogenation process revalidation program.

- In-process microbial controls and hold times prior to terminal sterilization. Three successful product intermediate hold time validation runs should be performed at manufacturing scale. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.

- Terminal sterilization process validation. Provide summary data and reports for the three validation studies. Validation summary reports should include heat distribution, heat penetration, and microbial challenge studies (including a description of the type of biological indicators used in the microbial challenge studies). Adequate justification should be provided for the validation approach taken (e.g., overkill or bioburden-based).

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

- Container closure integrity testing. System integrity (including maintenance of the microbial barrier) should be validated initially following terminal sterilization and should be demonstrated during stability. Initial validation should be performed with units capped and terminally sterilized under worst-case processing conditions. Container closure integrity method validation should demonstrate that the assay is sensitive enough to detect breaches that could allow microbial ingress (≤ 20 microns). Container closure integrity testing should be performed *in lieu* of sterility testing for stability samples every 12 months (annually) until expiry.

- Summary report and results for qualification of the bioburden, sterility and endotoxin test methods performed for in-process intermediates and the WFI 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.

Discussion: **No discussion occurred.**

Additional Clinical Pharmacology Comments

1) Recommendation about labeling:

We recommend that the content and format of information found in the Clinical Pharmacology section (Section 12) of labeling submitted to support this application be consistent with FDA guidance for industry, *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products – Content and Format*.[5] Consider strategies to enhance clarity, readability, and comprehension of this information for health care providers through the use of text attributes, tables, and figures as outlined in the above guidance.

2) Address the following questions in the Summary of Clinical Pharmacology:
   a) What is the basis for selecting the doses and dosing regimen used in the registration trials to support your marketing application? Identify individuals who required dose modifications and provide time to the first dose modification and reasons for the dose modifications in support of the proposed dose and administration.

   b) What are the exposure-response relationships for efficacy, safety and biomarkers?

   c) How do extrinsic (e.g., other drugs) and intrinsic factors (such as sex, race, body weight, organ dysfunctions, and disease) influence the exposure, efficacy, or safety of your drug? What dose modifications are recommended?

   d) What is the impact of immunogenicity on exposure, efficacy and safety?

3) Apply the following advice in preparing the clinical pharmacology sections of the original submission:

   a) Submit bioanalytical methods and validation reports for all clinical pharmacology and biopharmaceutics trials.

[5] https://go.usa.gov/xn4qB

b) Provide final study report for each clinical pharmacology trial. Present the pharmacokinetic parameter data as geometric mean with coefficient of variation (and mean ± standard deviation) and median with range as appropriate.

c) Provide complete datasets for clinical pharmacology and biopharmaceutics trials. The subjects' unique ID number in the pharmacokinetic datasets should be consistent with the numbers used in the clinical datasets.

   i) Provide all concentration-time and derived pharmacokinetic 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.

   ii) Identify individual subjects with dose modifications; the time to the first dose reduction, interruption or discontinuation; the reasons for dose modifications in the datasets.

d) Submit the following for the population pharmacokinetic analysis reports:

   i) Standard model diagnostic plots.
   ii) Individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual prediction line and the population prediction line.

   iii) Model parameter names and units in tables.

   iv) Summary of the report describing the clinical application of modeling results.

   Refer to the pharmacometrics data and models submission guidelines.[6]

e) Submit the following information and data to support the population pharmacokinetic analysis:

   i) SAS transport files (*.xpt) for all datasets used for model development and validation.

   ii) A description of each data item 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.

[6] http://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm180482.htm

iii) Model codes or control streams and output listings for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. Submitted these files as ASCII text files with *.txt extension (e.g.: myfile_ctl.txt, myfile_out.txt).

f) Submit a study report describing exploratory exposure-response (measures of effectiveness, biomarkers and toxicity) relationships in the targeted patient population. Refer to the guidances for industry for population PK[7] and exposure-response relationships.[8]

4) Apply the following advice in preparing the QTc study report:

a) For exposure-response analysis, we recommend the analysis and reporting of results follow the recommendations described in "Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2017; doi 10.1007/s10928-017-9558-5) and "Correction to: Scientific white paper on concentration-QTc modeling" (Garnett, C. et al., J Pharmacokinet Pharmacodyn 2018; doi 10.1007/s10928-017-9565-6). Use concentration-QTc analysis as the supportive analysis.

b) When you submit your QT study report, please include the following items:

i) Study report(s) for any other clinical studies of the effect of product administration on the QT interval that have been performed.

ii) Study report.

iii) Statistical analysis plan.

iv) Clinical study protocol.

v) Investigator's Brochure.

vi) A completed Highlights of Clinical Pharmacology and Cardiac Safety Table.

vii) Annotated CRF.

viii) A data definition file which describes the contents of the electronic data sets.

[7] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072137.pdf
[8] http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072109.pdf

ix) Electronic data sets as SAS.xpt transport files (in CDISC SDTM and ADAM format – if possible) and all the SAS codes used for the primary statistical and exposure-response analyses. Please make sure that the ECG raw data set includes at least the following: Subject ID, treatment, period, ECG date, ECG time (down to second), nominal day, nominal time, replicate number, heart rate, intervals QT, RR, PR, QRS and QTc (including any corrected QT, e.g., QTcB, QTcF, QTcN, QTcI, along with the correction factors for QTcN and QTcI), Lead, and ECG ID (link to waveform files, if applicable).

x) Data set whose QT/QTc values are the average of the above replicates at each nominal time point.

xi) Adverse Event analysis using the MedDRA SMQ "Torsade de pointes/QT Prolongation" and include the preferred term "Seizure" by treatment and dose level.

xii) Narrative summaries and case report forms for any:

- Deaths.
- Serious adverse events.
- Episodes of ventricular tachycardia or fibrillation.
- Episodes of syncope.
- Episodes of seizure.
- Adverse events resulting in the subject discontinuing from the study.

c) We are also interested in the effects of the test substance on other ECG intervals and changes in waveform morphology. Please submit PR and QRS interval data with the study report and descriptive waveform morphology changes.

d) Submit all related ECG waveforms to the ECG warehouse.[9]

Discussion: **The Agency stated the QT evaluation proposal appears reasonable. When the QT evaluation report is submitted, please include a completed version of the "QT Evaluation Report Submission Checklist" located at the IRT website (https://www.fda.gov/about-fda/center-drug-**

[9] www.ecgwarehouse.com

evaluation-and-research-cder/interdisciplinary-review-team-cardiac-safety-studies-formerly-qt-irt).

3.0 OTHER IMPORTANT MEETING INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed. The Sponsor communicated the following estimated submission timeline for their proposed BLA:
  - CMC Module 3 – July 2020
  - Full BLA submission – September 2020
- 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 was held on the need for a REMS, other risk management actions and, where applicable, the development of a Formal Communication Plan and it was concluded that at this time the Agency had insufficient information to determine whether a REMS will be necessary to ensure that the benefits of loncastuximab tesirine outweigh the risks, and if it is necessary, what the required elements will be. The Agency will determine the need for a REMS during the review of the application.
- 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.

Discussion: **The Agency acknowledged submission of the iPSP for loncastuximab tesirine and the submission of the proposed Phase 3 study ADCT-402-311. The Agency acknowledged the current challenges with initiating and conducting clinical trials in the current coronavirus pandemic, *March 2020 FDA Guidance on Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*** https://www.fda.gov/media/136238/download.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (codified at section 505B of the Federal Food, Drug, and Cosmetic Act (FD&C Act), 21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new

indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived or deferred (see section 505B(a)(1)(A) of the FD&C Act). Applications for drugs or biological products for which orphan designation has been granted that otherwise would be subject to the requirements of section 505B(a)(1)(A) are exempt pursuant to section 505B(k)(1) from the PREA requirement to conduct pediatric assessments.

Title V of the FDA Reauthorization Act of 2017 (FDARA) amended the statute to create section 505B(a)(1)(B), which requires that any original marketing application for certain adult oncology drugs (i.e., those intended for treatment of an adult cancer and with molecular targets that FDA has determined to be substantially relevant to the growth or progression of a pediatric cancer) that are submitted on or after August 18, 2020, contain reports of molecularly targeted pediatric cancer investigations. See link to list of relevant molecular targets below. These molecularly targeted pediatric cancer investigations must be "designed to yield clinically meaningful pediatric study data, gathered using appropriate formulations for each age group for which the study is required, regarding dosing, safety, and preliminary efficacy to inform potential pediatric labeling" (section 505B(a)(3)). Applications for drugs or biological products for which orphan designation has been granted and which are subject to the requirements of section 505B(a)(1)(B), however, will not be exempt from PREA (see section 505B(k)(2)) and will be required to include plans to conduct the molecularly targeted pediatric investigations as required, unless such investigations are waived or deferred.

Under section 505B(e)(2)(A)(i) of the FD&C Act, you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End of Phase 2 (EOP2) meeting, or such other time as agreed upon with FDA. (In the absence of an EOP2 meeting, refer to the draft guidance below.) The iPSP must contain an outline of the pediatric assessment(s) or molecularly targeted pediatric cancer investigation(s) that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation; and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

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*.

For the latest version of the molecular target list, please refer to FDA.gov.[10]

[10] https://www.fda.gov/about-fda/oncology-center-excellence/pediatric-oncology

FDARA REQUIREMENTS

Sponsors planning to submit original applications on or after August 18, 2020 or sponsors who are uncertain of their submission date may request a meeting with the Oncology Center of Excellence Pediatric Oncology Program to discuss preparation of the sponsor's initial pediatric study plan (iPSP) for a drug/biologic that is intended to treat a serious or life-threatening disease/ condition which includes addressing the amendments to PREA (Sec. 505B of the FD &C Act) for early evaluation in the pediatric population of new drugs directed at a target that the FDA deems substantively relevant to the growth or progression of one or more types of cancer in children. The purpose of these meetings will be to discuss the Agency's current thinking about the relevance of a specific target and the specific expectations for early assessment in the pediatric population unless substantive justification for a waiver or deferral can be provided. Meetings requests should be sent to the appropriate review division with the cover letter clearly stating "**MEETING REQUEST FOR PREPARATION OF iPSP MEETING UNDER FDARA.**" These meetings will be scheduled within 30 days of meeting request receipt. The Agency strongly advises the complete meeting package be submitted at the same time as the meeting request. Sponsors should consult FDA's Guidance on Formal Meetings Between the FDA and Sponsors or Applicants[11] to ensure open lines of dialogue before and during their drug development process.

In addition, you may contact the OCE Subcommittee of PeRC Regulatory Project Manager by email at OCEPERC@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[12]

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[13] and Pregnancy and Lactation Labeling Final Rule[14] 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

[11] See the guidance for industry *"Formal Meetings Between the FDA and Sponsors or Applicants."*
[12] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[13] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[14] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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*.

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

MANUFACTURING FACILITIES

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

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

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

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

Corresponding names and titles of onsite contact:

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

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

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

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

Specifications.[15]

ONCOLOGY PILOT PROJECTS

The FDA Oncology Center of Excellence (OCE) is conducting two pilot projects, the Real-Time Oncology Review (RTOR) and the Assessment Aid. RTOR is a pilot review process allowing interactive engagement with the applicant so that review and analysis of data may commence prior to full supplemental NDA/BLA submission. Assessment Aid is a voluntary submission from the applicant to facilitate FDA's assessment of the NDA/BLA application (original or supplemental). An applicant can communicate interest in participating in these pilot programs to the FDA review division by sending a notification to the Regulatory Project Manager when the top-line results of a pivotal trial are available or at the pre-sNDA/sBLA meeting. Those applicants who do not wish to participate in the pilot programs will follow the usual submission process with no impact on review timelines or benefit-risk decisions. More information on these pilot programs, including eligibility criteria and timelines, can be found at the following FDA websites:

- RTOR[16]: In general, the data submission should be fully CDISC-compliant to facilitate efficient review.

- Assessment Aid[17]

NONPROPRIETARY NAME

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

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

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

[15] https://www.fda.gov/media/85061/download
[16] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program
[17] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

biological products) and the considerations that support the convention.

To the extent that your proposed 351(a) BLA is within the scope of this guidance, FDA will assign a four-letter suffix for inclusion in the proper name designated in the license at such time as FDA approves the BLA.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

There are no issues requiring further discussion.

5.0 ACTION ITEMS

There were no action items identified.

6.0 ATTACHMENTS AND HANDOUTS

The Sponsor's response document is appended to these meeting minutes.

11 Page(s) have been Withheld in Full as B4 (CCI/TS)
Immediately Following this Page

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

/s/

NICHOLAS C RICHARDSON
04/20/2020 12:17:35 PM