CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

761347Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 140100

MEETING PRELIMINARY COMMENTS

Genentech, Inc.
Attention: Sili Liu, Ph.D.
Associate Program Director, Regulatory Affairs
1 DNA Way
South San Francisco, CA 94080

Dear Dr. Liu:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Tecentriq subcutaneous (atezolizumab and hyaluronidase coformulation).

We also refer to your correspondence, dated and received July 22, 2022, requesting a meeting to discuss the clinical results from Part 2 of Study BP40657 (IMscin001), and acceptability of the data package for submission of a Biologics License Application for Tecentriq subcutaneous for all the approved Tecentriq intravenous indications.

Our preliminary responses to your meeting questions are enclosed.

You should provide, to the Regulatory Project Manager, a hardcopy or electronic version of any materials (i.e., slides or handouts) to be presented and/or discussed at the meeting.

In accordance with FDA policy, you should not make audio or visual recordings of the discussion at this meeting. Consistent with 21 CFR 10.65(e), the official record of this meeting will be the FDA-generated minutes.

[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.

If you have any questions, call me at 301-796-1755 or email me at Raniya.Al-Matari@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Raniya Al-Matari, Ph.D.
Regulatory Health Project Manager
Division of Regulatory Operations – Oncologic Diseases for DO2
Office of Regulatory Operations
Office of New Drugs
Center for Drug Evaluation and Research

ENCLOSURE:
Preliminary Meeting Comments

U.S. FOOD & DRUG ADMINISTRATION

PRELIMINARY MEETING COMMENTS

Meeting Type:	B
Meeting Category:	Pre-BLA
Meeting Date and Time:	September 26, 2022; 12:00 PM – 1:00 PM, EST
Meeting Location:	Videoconference
Application Number:	IND 140100
Product Name:	Tecentriq subcutaneous (atezolizumab and hyaluronidase coformulation).
Indications:	the same indications as approved for Tecentriq IV
Applicant Name:	Genentech, Inc.
Regulatory Pathway:	351(a) of the Public Health Service Act

FDA ATTENDEES

Erin Larkins, M.D., Supervisory Associate Director (Acting), Division of Oncology 2 (DO2)
Nicole Drezner, M.D., Cross-Disciplinary Team Lead, DO2
Satinder Choudhary, Pharm D., Clinical Reviewer, DO2
Hong Zhao, Ph.D., Clinical Pharmacology Team Leader, Division of Clinical Pharmacology II (DCPII)
Miao Zhao, Ph.D., Clinical Pharmacology II Reviewer, DCPI
Brian Roelofs, Ph.D., CMC Team Leader, Division of Biotechnology Review and Research II (DBRRII)
Yetao Jin, Ph.D., CMC Reviewer, DBRRII
Anup Amatya, Ph.D., Biostatistics Team Leader, Division of Biostatistics V (DBV)
Chi Song, Ph.D., Biostatistics Reviewer, DBV
Raniya Al-Matari, Ph.D., Regulatory Health Project Manager, Division of Regulatory Operations

SPONSOR ATTENDEES

Luis Herraez-Baranda, Ph.D., Senior Clinical Scientist, Product Development Oncology
Nadia Tosti, Ph.D., Lead Clinical Scientist, Product Development Oncology
Stephanie Liu, Pharm.D., Clinical Pharmacology Lead, gRED Clinical Pharmacology
Benjamin Wu, Ph.D., Senior Principal Scientist, Clinical Pharmacology
Phyllis Chan, Ph.D., Modeling & Simulation Lead, Clinical Pharmacology
Victor Osho, MPharm., Associate Director, Product Development Safety
Esther Shearer-Kang, Ph.D., Safety Director, Product Development Safety
Xiaoyan Liu, Ph.D., Senior Statistical Scientist, Data Science
Mahesh Shivhare, Ph.D., Principal Statistical Scientist, Data Science
Jim Zanghi, Principal Scientist, Bioanalytical Sciences
Ivy Lin, Senior Regulatory Program Director, Pharma Technical Regulatory
Yi Yang, Senior Scientist, Pharma Technical Development
Michael Kim Scientist, Pharma Technical Development

Brooke Aghajani, Lifecycle Leader
Gladys Ingle, Program Director, Regulatory Affairs
Sabrina Werby, Ph.D., Program Manager, Regulatory Affairs
Sili Liu, Ph.D., Associate Program Director, Regulatory Affairs

Introduction:
This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for September 26, 2022, 12:00 PM – 1:00 PM, EST between Genentech, Inc. and the Division of Oncology 2. We are sharing this material to promote a collaborative and successful discussion at the meeting. The meeting minutes will reflect agreements, important issues, and any action items discussed during the meeting and may not be identical to these preliminary comments following substantive discussion at the meeting. However, if these answers and comments are clear to you and you determine that further discussion is not required, you have the option of cancelling the meeting (contact the regulatory project manager (RPM)). If you choose to cancel the meeting, this document will represent the official record of the meeting. If you determine that discussion is needed for only some of the original questions, you have the option of reducing the agenda and/or changing the format of the meeting (e.g., from face to face to teleconference). It is important to remember that some meetings, particularly milestone meetings, can be valuable even if the pre-meeting communications are considered sufficient to answer the questions. Contact the RPM if there are any major changes to your development plan, the purpose of the meeting, or the questions based on our preliminary responses, as we may not be prepared to discuss or reach agreement on such changes at the meeting.

BACKGROUND

Meeting Purpose

On July 22, 2022, Genentech, Inc., sent a meeting request to discuss the clinical results from Part 2 of Study BP40657 (IMscin001) and the acceptability of the data package for submission of a Biologics License Application (BLA) for Tecentriq subcutaneous for all the approved Tecentriq IV indications.

Regulatory

On August 27, 2018, Genentech submitted a meeting request to discuss their plan to develop a new fixed combination drug (atezolizumab and rHuPH20) to be administered by the subcutaneous (SC) route of administration in support of a marketing application for this new drug product. Genentech states that they will seek the same indications for which Tecentriq administered by the intravenous (IV) route is approved.

On November 13, 2018, a teleconference was held between FDA and Genentech to discuss proposed study, IMscin001. FDA agreed with the overall proposed study design for Part 1 of IMscin001 and recommended changes to the proposed design of Part 2 of IMscin001, to incorporate a randomized trial design to establish pharmacokinetic (PK) comparability based on C_{trough} after single dose and at steady state and to evaluate the risks of anti-drug antibody (ADA) and its potential impact on efficacy.

On December 10, 2019, a Type C meeting was held to discuss the proposed statistical non-inferiority comparison of PK based on the observed C_{trough} after Cycle 1 and enrollment of immunotherapy-naïve second-line (2L) patients with non-small cell lung cancer (NSCLC) for Part 2 of IMscin001. FDA agreed with the overall plan but noted that immunotherapy (IO) naïve 2L patients would be difficult to enroll in U.S., given that IO as part of first-line therapy had become standard of care treatment.

On June 3, 2020, Genentech submitted a request for clinical pharmacology feedback, following up to the December 10 2019 meeting, and FDA provided a response on August 19, 2020, indicating there was no objection to the proposed atezolizumab SC dosing regimen of 1875 mg SC Q3W for use in Part 2 of IMscin001 based on the results of Part 1 of IMscin001. FDA stated that dose selection should take into consideration of the observed large PK inter-subject variability (124%) in bioavailability of atezolizumab with SC administrations to ensure that there is no substantial difference in a proportion of patients with extreme atezolizumab PK values for SC compared to IV administration. FDA additionally recommended that both AUC0-tau and C_{trough} at Cycle 1 be the primary PK endpoints for comparability and assessment and that AUC0-tau and C_{trough} at steady-state should also be provided.

Clinical

Genentech is developing atezolizumab for SC injection, a ready to use, (b) (4) formulation of atezolizumab co-formulated with rHuPH20, a human recombinant hyaluronidase. Genentech intends to submit a BLA for this new dosage form and formulation for all currently approved adult indications of atezolizumab IV. BLA submission is anticipated in November 2022.

A summary of the studies that comprise the development program for atezolizumab SC is provided in the table below.

Table 1. Overview of studies of atezolizumab SC

Study Name	Patient population/Description	Key Endpoints	Status/ Notes
BP40657 (IMscin001)	Previously treated locally advanced or metastatic NSCLC Dose finding portion followed by non-inferiority randomized study of SC atezolizumab vs IV atezolizumab	Part 1: Serum atezolizumab trough concentration (C_{trough}) at C1. Part 2: i) Serum atezolizumab C_{trough} at C1 ii) Model-predicted AUC $_{0\text{-}21\ days}$ at Cycle 1	Part 1: ongoing N=67 Part 2: enrollment complete N=371 (2:1 randomized; 247, 124)
MO43576 (IMscin002)	PD-L1+ NSCLC Randomized, open-label crossover study	Patient and healthcare professional reported preference for SC vs IV based on responses to Patient Preference Questionnaire.	Ongoing

Study BP40657 (IMscin001): An ongoing, ex-U.S., multiregional, open label, two-part, study evaluating the PK, efficacy and safety of atezolizumab SC in patients with metastatic NSCLC who have received prior platinum-based chemotherapy and are IO-naïve.

The dose finding portion of the study (Part 1) enrolled 67 patients in three cohorts defined by dose level:

- Cohort 1 (n=13): single dose of atezolizumab SC 1800 mg followed by atezolizumab 1200 mg IV Q3W
- Cohort 2 (n=15): atezolizumab SC 1200 mg Q2W for 3 cycles followed by atezolizumab 1200 mg IV Q3W
- Cohort 3 (n=39): atezolizumab SC 1800 mg Q3W for 3 cycles followed by atezolizumab 1200 mg IV Q3W

Based on a primary analysis of Part 1 and modeling and simulation data, a dosage of 1875 mg Q3W SC was selected for further evaluation.

The dose confirmation portion of the study (Part 2) was a randomized (2:1), non-inferiority study of atezolizumab SC 1875 mg Q3W or atezolizumab 1200 mg IV Q3W in approximately 355 patients with advanced NSCLC who had received prior platinum-based chemotherapy and were checkpoint inhibitor naïve. The primary objective was to demonstrate the non-inferiority of PK exposure of the atezolizumab SC formulation versus the atezolizumab IV formulation based on the co-primary endpoints of Cycle 1 observed serum C_{trough} (predose Cycle 2) and model-predicted $AUC_{0–21\ day}$. Secondary

endpoints included progression-free survival (PFS) and overall survival (OS) in the Full Analysis Set (FAS) and overall response rate (ORR) in the response-evaluable set, which included all patients in the FAS who had measurable disease at baseline.

The null hypotheses of inferiority of the SC dose of atezolizumab to IV dose will be rejected and non−inferiority will be concluded if the lower bound of the 90% CI of C_{trough} SC/C_{trough} IV geometric mean ratio (GMR) and $AUC_{0-21\ d}$ SC/$AUC_{0-21\ d}$ IV GMR are ≥ 0.8. Secondary endpoints are descriptive.

As of the data cutoff date for the primary analysis, 377 patients were randomized, including 247 to the atezolizumab SC arm and 124 to the atezolizumab IV arm. The median follow-up time was 4.6 months. The median age was 64 years; 67% of patients were White, 22% were Asian, and 69% were male. A total of 48% of patients were enrolled in Europe or the Middle East, 28% were enrolled in Central or South America, and 21% were enrolled in the Asia-Pacific regions.

Eighty percent of patients received one prior line of anti-cancer therapy; the remaining 20% of patients received two or more lines of prior anti-cancer therapy. PD-L1 expression ≥ 1% was reported in 40% of patients. There was a higher percentage of PD-L1 positive patients in the atezolizumab SC arm (45%) vs. the atezolizumab IV arm (32%).

Study results

A geometric mean ratio (GMR) of 1.05 (90% CI 0.88-1.24) was observed for the observed serum C_{trough} at Cycle 1 (predose Cycle 2) and a GMR of 0.88 (90% CI 0.83-0.93) was observed for model-predicted $AUC_{0-21\ days}$ at Cycle 1.

A summary of the clinical efficacy results is provided in the table below.

	Atezolizumab SC N=247	Atezolizumab IV N=124
Inv-assessed PFS, mos. (95% CI)	2.8 (2.1, 3.1)	2.9 (1.7, 4.2)
HR (95% CI)	1.08 (0.82, 1.41)	
Inv-assessed ORR*, % (95% CI)	9 (5, 13)	8 (4, 14)
Median DOR, mos. (95% CI)	NE (5.2, NE)	11.2 (4.2, NE)

*Based on response-evaluable patients; N=245 in the atezo SC arm and N=124 in the atezo IV arm

According to Genentech, the safety data for atezolizumab SC was consistent with the known safety profile of atezolizumab IV. Two patients (0.8%) had a fatal adverse event (AE) considered related to study treatment on the atezolizumab SC arm versus no patients on the atezolizumab IV arm. The rates of serious AEs (SAEs) were similar between arms (15% vs. 18%), and there was a slightly higher incidence of Grade 3-4

AEs in the atezolizumab IV arm (26% vs. 18%). A total of 1.6% and 3.2% of patients on the atezolizumab SC and IV arms, respectively, had an AE resulting in drug discontinuation. Rates of immune-related AEs (imAEs) were similar between arms and the only AEs with a difference of ≥ 5% between arms were hyperglycemia (8% in the atezolizumab IV arm and 2.8% in the atezolizumab SC arm) and increased creatinine (7% in the atezolizumab IV arm and 1.2% in the atezolizumab SC arm). Injection site reactions with atezolizumab SC occurred at a rate of 4.5%; most events were Grade 1 in severity.

Proposed plan for BLA submission:

- Data from Part 2 of IMscin001 will comprise the primary PK and clinical safety and efficacy data in support of the application.
- Additional safety data from the following pooled populations will be provided:
  - Atezo Mono 1: Pooled data from patients with mixed solid tumor types who received atezolizumab IV as a single agent (n=3178)

(b) (4)

- A safety update for IMscin001 will be submitted within 120 days after the BLA submission that includes approximately 4 months of additional data from the primary analysis data cutoff date of April 26, 2022.
- Genentech plans for the Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) in Module 5 to cross-reference the Summary of Clinical Efficacy (SCE) and Summary of Clinical Safety (SCS) in Module 2.

SPONSOR QUESTIONS AND FDA RESPONSES

1. Does the Agency agree that the PK and clinical data provided from Part 2 of IMscin001 adequately support the use of atezolizumab SC in patients with metastatic NSCLC who progressed during or following a platinum-containing regimen?

   FDA Response:
   The PK comparisons provided in the current meeting package appear to support the establishment of PK non-inferiority for atezolizumab SC administration compared with atezolizumab IV administration. However, a final determination on the adequacy of the data to support the approval of atezolizumab SC will be made at the time of BLA review. In the BLA submission, provide the following information:
   - Observed PK metrics such as AUC in cycle 1 and C_{trough} at steady state,
   - Assessment for extreme PK values with the SC administration compared to that with the IV administration (e.g., patients with extreme low exposures with the SC administration that was not adequately covered by the 1200 mg Q3W IV dosing).

   The descriptive clinical efficacy and safety results appear comparable between arms. A final determination on the adequacy of the totality of the data included in the

BLA submission to support the approval of atezolizumab SC will be made at the time of BLA review.

We reiterate that the proposed indication cited in Question 1 (e.g., for the treatment of patients metastatic NSCLC who progressed during or following a platinum-containing regimen) is not relevant to U.S. patients or medical practice, given that inclusion of an anti-PD-(L)1 agent as a single agent or in combination with chemotherapy is standard first-line treatment for patients with metastatic NSCLC in the U.S.

2. Does the Agency agree the data package provides sufficient evidence to allow bridging of atezolizumab SC to all the approved TECENTRIQ IV indications?

   FDA Response:
   Insufficient evidence was provided to support the bridging of atezolizumab SC to all the approved TECENTRIQ IV indications. In the BLA submission, provide the following assessment:
   - Effect of tumor types on the PK of atezolizumab.
   - Effect of ADA status on the PK of atezolizumab in Study BP40657 (IMscin001).

3. Does the Agency agree that the proposed contents and format of the dossier supports the submission of the planned BLA application for TECENTRIQ?

   FDA Response:
   Yes, we agree. However, please clarify whether you intend to include results of Study IMscin002 in the planned BLA as supportive data.

Safety

4. Does the Agency agree with the Applicant's proposal to submit a 120-day safety update?

   FDA Response:
   Yes, we agree.

Chemistry, Manufacturing, and Controls (CMC)

5. (b) (4)

(b) (4)

FDA Response:

No. We do not agree that you classify (b) (4), as non-CQAs from a product quality perspective. You proposed to classify (b) (4), as non-CQAs from the pharmacokinetic perspective. Although the provided rationale and new study support that (b) (4), may not have significant clinical impact to PK, you did not provide sufficient information to justify the impact of these attributes on the product quality, safety, and potency. Your risk consideration should include, but not be limited to, information on the following:

- The effect of (b) (4) during manufacture, shipment, and storage.
- The effect of the (b) (4) on the antibody-target interaction.
- The relevance of the content of (b) (4) in the manufacturing process.

ADDITIONAL FDA COMMENTS

CMC

6. You propose to market a vial presentation of the drug product (DP). Please include a release specification for the DP called "gross content" to ensure that the excess liquid filled into vials is appropriate to deliver the labeled content and avoid an excessive overfill that may be misused. Refer to the Agency's MAPP 5019.1 *"Allowable Excess Volume/Content in Injectable Drug and Biological Products"* (Effective Date: January 28, 2022).

7. You propose to cross reference specific vorhyaluronidase alfa (rHuPH20) sections in Rituxan Hycela BLA 761064 for 3.2.S and 3.2.A with the cross reference information in Module 1.4.4. You should submit CMC information of rHuPH20 DS specific to this proposed BLA, including but not limited to, rHuPH20 DS shipping validation from the DS manufacturer to the atezolizumab SC manufacturer.

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.

We acknowledge receipt of your February 11, 2022, amendment containing your Agreed Initial Pediatric Study Plan (Agreed iPSP-1) for the SC administration of Tecentriq for all the previously approved Tecentriq IV indications; in addition to issuance of our the March 9, 2022 Initial Agreement.

For the latest version of the molecular target list, please refer to FDA.gov.[2]

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

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

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 the guidance for industry, *Formal Meetings Between the FDA and Sponsors or Applicants*, 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.[3]

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[4] and Pregnancy and Lactation Labeling Final Rule[5] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the

[3] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[4] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[5] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

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.

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

To optimize the output of this meeting, submit the following documents for review as part of the briefing package:

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.

- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).

- For a phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).

- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

When requesting this meeting, clearly mark your submission "**DISCUSS SAFETY ANALYSIS STRATEGY FOR THE ISS**" in large font, bolded type at the beginning of the cover letter for the Type C meeting request.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[6]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[7]

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

[6] http://www.fda.gov/ectd
[7] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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)				

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[8] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[9]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

OFFICE OF SCIENTIFIC INVESTIGATIONS (OSI) REQUESTS

The Office of Scientific Investigations (OSI) requests that the items described in the draft guidance for industry, *Standardized Format for Electronic Submission of NDA and BLA Content for the Planning of Bioresearch Monitoring (BIMO) Inspections for CDER*

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

Submissions, and the associated conformance guide, *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*.[10]

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[11]: In general, the data submission should be fully CDISC-compliant to

[10] https://www.fda.gov/media/85061/download
[11] https://www.fda.gov/about-fda/oncology-center-excellence/real-time-oncology-review-pilot-program

facilitate efficient review.

- Assessment Aid[12]

NONPROPRIETARY NAME

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

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

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

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.

[12] https://www.fda.gov/about-fda/oncology-center-excellence/assessment-aid-pilot-project

---

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/

RANIYA A AL-MATARI
09/23/2022 10:51:54 PM