

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761127Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND129198

MEETING MINUTES

Revance Therapeutics, Inc.
Attention: Sita Malhi
Manager, Regulatory Affairs
7555 Gateway Blvd
Newark, CA 94560

Dear Ms. Malhi:

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

We also refer to the meeting between representatives of your firm and the FDA on December 05, 2018. The purpose of the meeting was to discuss the format and content for future marketing application to support the proposed indication of treatment for temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults.

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

If you have any questions, call Barbara Gould, Chief, Project Management at 301 796-4224.

Sincerely,

{See appended electronic signature page}

Jill A. Lindstrom, MD, FAAD
Deputy Director
Division of Dermatology and Dental Products
Office of Drug Evaluation III
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's Comments to FDA Responses



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: December 20, 2018 @ 11:00
Meeting Location: White Oak Campus, Silver Spring, Maryland

Application Number: IND 129198
Product Name: daxibotulinumtoxinA

Proposed Indication: For the treatment of glabellar lines
Sponsor Name: Revance Therapeutics, Inc.

Meeting Chair: Jill Lindstrom, MD
Meeting Recorder: Barbara Gould

FDA ATTENDEES

Jill Lindstrom, MD, Deputy Director, Division of Dermatology and Dental Products (DDDP)
Gordana Diglicic, MD, Clinical Team Leader, DDDP
Melinda McCord, MD, Clinical Reviewer, DDDP
Mohamed Alesh, PhD, Biometrics Team Leader, Division of Biometrics III
Rebecca Hager, PhD, Biometrics Reviewer, DB III
Lin Zhou, PhD, Clinical Pharmacology Reviewer, Division of Clinical Pharmacology (DCP) 3
Ramesh Potla, PhD, Product Quality Team Leader, Office of Biotechnology Products (OBP)
Rong Wang, PhD, Product Quality Reviewer, OBP
Maria Candauchacon, PhD, Microbiology Team Leader, Division Monoclonal Antibody (DMA)
Virginia Carroll, PhD, Microbiology Reviewer, DMA
Teresa McMillan, PharmD, Team Leader, Division of Medication Errors, Prevention, & Analysis (DMEPA)
Madhuri R. Patel, PharmD, Safety Evaluator, DMEPA
Barbara Gould, MBAHCM, Chief, Project Management Staff, DDDP

SPONSOR ATTENDEES

Azita Nejad, Vice President, Quality and Validation, Revance Therapeutics, Inc.
Roman Rubio, Senior Vice President, Clinical Development, Revance Therapeutics, Inc.
Sita Malhi, Manager Regulatory Affairs, Revance Therapeutics, Inc.

Susanne Fors, Vice President, Regulatory Affairs, Revance Therapeutics, Inc.
Todd Gross, Vice President, Biostatistics and Data Management, Revance Therapeutics, Inc.

1.0 BACKGROUND

The purpose of this Pre-BLA meeting is to discuss the format and content for future marketing application to support the proposed indication of treatment for temporary improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults.

Regulatory Correspondence History:

We have had the following meetings/teleconferences with you:

- 10/03/2017 Final Written Response
- 06/08/2016 PreIND Meeting

We have sent the following correspondences:

- 03/05/2018 Advice Letter
- 07/14/2017 Pediatric Study Plan – Initial Agreement
- 04/18/2017 Pediatric Study Plan – Written Response
- 03/16/2017 Advice/Information Request Letter
- 10/28/2016 Study May Proceed Letter
- 10/07/2016 Information Request

2.0 DISCUSSION

Introductory Comments

You conducted 5 clinical trials in the development of daxibotulinumtoxinA for injection (DAXI) for the proposed indication of the ^{(b) (4)} *improvement in the appearance of moderate to severe glabellar lines with corrugator and/or procerus muscle activity in adults*” (page 128). You enrolled 3139 subjects age 18-86 years. A total of 2839 subjects were exposed to DAXI at the proposed to-be-marketed dose of 40 U. You intend to provide data from the following trials to support your BLA:

- RT002-CL001: Phase 1/ 2 double-blind, dose escalation trial to evaluate the tolerability of single doses of DAXI (IM 25, 50, 75, 100 U) in 48 subjects from Mexico age 30 to 60 years.
- RT002-CL002: Phase 2 double-blind, placebo-controlled, dose -finding trial to evaluate the safety and efficacy of single doses of DAXI (20,40, 60 U) in 268 subjects from Canada age 30 to 65 years

- SAKURA-1: Phase 3 double-blind, placebo- controlled, single dose trial of 40 U DAXI for injection, single in 303 subjects from the United States age 18-75 years.
- SAKURA-2: Phase 3 double-blind, placebo- controlled, single dose trial of 40 U DAXI for injection in 306 subjects from the United States and Canada age 18-75 years.
- SAKURA-OLS: Phase 3 open label, single and repeat dose trial of 40 U DAXI for injection to evaluate long- term safety in 2691 subjects age 18 years and older.

2.1. Regulatory

Question 21:

- a) Does the Agency agree on the overall content and format of our proposed ToC?
- b) Does Agency agree with the proposed organization of the ISS and ISE in Module 2 and Module 5?
- c) Does Agency agree that the proposed documentation for the pediatric waiver in the BLA will satisfy the requirements for a BLA?
- d) Does the Agency agree to provide the photo assessment upon request?
- e) Does the Agency agree on the content and format of the interim psychometric study dossier in support of the primary endpoint?
- f) Does the FDA agree that a summary of the ECG results will be included in the BLA, with ECG tracings available upon request?
- g) Does the Division agree on the content and format for proposed draft mock-up of the carton and vial labels? Does the Agency agree that for each strength, two different presentations will be acceptable; one box containing one vial, and a second box containing two vials?

FDA Response to Question 21:

- a) The overall Table of Contents (TOC) appears reasonable. However, we have the following comments below:
 - Section 1.6 Meetings-submit meeting minutes for all meetings with the Agency regarding the proposed product (PIND, Guidance, Pre-BLA.)

- Section 1.16.2 Risk Evaluation Mitigation Strategy (REMS)-see Additional Comments

Insufficient information has been provided for the evaluation. Section 3.2.P.5.3 Validation of Analytical Procedures should include method validations for all non-compensial QC analytical methods, including sterility, endotoxin, and container closure integrity testing. See additional CMC microbiology comments at the end of the document for CMC microbiology information and data which should be provided in different sections of the BLA.

- b) Yes. Your proposal to provide the text portion of the ISS and ISE in Module 2 and the appendices and datasets in Module 5 with cross references appears reasonable.

For additional information about the location of ISS and ISE in the CTD, refer to the guidance for industry: *Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document* at:

<http://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm136174.pdf>

- c) Yes, we agree. In Section 1.9 Pediatric Administrative Information in the BLA, provide your Agreed Pediatric Study Plan.
- d) We request that you submit images obtained at Baseline and Week 4 (timepoint for the primary efficacy evaluation) for subjects enrolled in the pivotal Phase 3 trials. In addition, provide images to document adverse events in the eye disorders system organ class (SOC) including ptosis.
- e) In principle, the content and format of the interim psychometric study dossier appears reasonable.

For more details on what components should be included in an evidence dossier for clinical outcome assessments (e.g., Clinician-reported outcome and Patient-reported outcome assessments), you may refer to the Appendix of the Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims

(<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm193282.pdf>).

- f) Yes, we agree. However, for this class of products, there are reports of adverse events related to the cardiovascular system (e.g. arrhythmia, myocardial infarction, hypertension and decreased heart rate). Therefore, to support cardiovascular safety, provide an analysis of the results of the cardiovascular safety monitoring from the Phase 3 trials and narratives for all subjects who

experience major adverse cardiovascular events (MACE) and significant changes in cardiovascular parameters from baseline (e.g. heart rate.)

- g) The content and format of all labels and labeling and your proposed packaging will be a review issue. Please note, in September 2018, FDA released draft guidance on product identifiers required under the Drug Supply Chain Security Act¹. The Act requires manufacturers and repackagers, respectively, to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction in(to) commerce beginning November 27, 2017, and November 27, 2018, respectively. We recommend that you review the draft guidance.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 1:

Does FDA agree on the content planned to be included in the BLA to support the proposed specifications for:

- a) DAXI drug substance?
- b) DAXI for injection 50 U/vial?
- c) DAXI for injection 100 U/vial?

FDA Response to Question 1:

In general, the planned content to support the proposed drug substance (DS) and drug product (DP) specifications appear reasonable. Address the following in the BLA submission:

- a) If there are any changes in the manufacturing process of the different DS and DP lots used to support the proposed specifications, provide appropriate data to demonstrate comparability of the pertinent DS and DP lots with regards to their purity, potency, and safety.
- b) To ensure the specificity of the ELISA identity test, demonstrate that the antibody used in the ELISA assay only recognizes botulinum toxin Type A and is not cross-reactive with other botulinum toxins.
- c) Reporting of endotoxin results in EU/mL is recommended for drug substance and drug substance intermediates to reflect the readout of the endotoxin test. Reporting of endotoxin results in EU/μg is not recommended due to variability in protein concentration.

Adequacy of the proposed DS and DP specifications will be determined during review of the BLA.

¹ The draft guidance is available from: <https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-drugs-gen/documents/document/ucm621044.pdf>

Question 2:

Does FDA agree that the proposed stability studies will be adequate to facilitate FDA's review of the BLA for DAXI drug substance?

FDA Response to Question 2:

In general, the proposed stability strategy appears reasonable. Note that expiration dating for biotechnology products is based on real-time, real-temperature data. To support the proposed dating period in your BLA application, provide appropriate real-time stability data from studies conducted on drug substance and drug product batches representative of the manufacturing scale and packaged in container closure systems representative of those proposed for marketing. DS and DP shelf life will be determined during review of the BLA. Refer to ICH Q5C for additional information.

Question 3:

Does FDA agree that the proposed stability data package will be adequate to facilitate FDA's review of the proposed retest period at the recommended storage conditions for DAXI drug substance?

FDA Response to Question 3:

Refer to FDA Response to Question #2.

Question 4:

Does FDA agree that the stability package will be adequate to facilitate FDA's review of the proposed shelf-life for DAXI for injection (lyophilized drug product) for the:

- a) 50U/vial?
- b) 100 U/vial?
- c) reconstituted product in vials and in syringes?

FDA Response to Question 4:

Your proposed stability package is not adequate for DAXI for injection.

Address the following in your BLA submission:

- a) For 50 U/vial and 100 U/vial presentations, provide data to demonstrate comparability of process performance qualification (PPQ) lots manufactured using the updated filling equipment in the DP manufacturing process versus other stability lots manufactured using a pre-change process.
- b) For reconstituted product in vials and in syringes, you propose to monitor the following quality attributes during in-use stability: appearance, pH, toxin content by ELISA, and relative potency by mouse LD50. In addition to the above quality attributes, the in-use stability assessment should include evaluation of particulate matter (e.g., USP <788>).

- c) In addition to the biochemical stability data, microbiological data in support of the post-reconstitution storage conditions in vials or syringes should be provided for post-reconstitution storage time greater than 4 hours. For more information, see additional CMC microbiology comments at the end of the document.

Meeting Discussion:

The sponsor clarified that the proposed post-reconstitution storage condition is (b) (4) hours at 2-8°C, not room temperature. The Agency stated that microbiological data is required to support a total storage time of greater than 4 hours, regardless of storage temperature (refrigerated or room temperature) and referenced the additional CMC microbiology comments for details on study design. The sponsor agreed to provide appropriate microbiological data to support the proposed storage time.

Question 5:

Does the Agency agree with the proposed bracketing strategy for process validation of the 50 U/vial and 100 U/vial DAXI for injection?

FDA Response to Question 5:

In general, you proposed (b) (4) bracketing approach (b) (4) appears reasonable. (b) (4)

Note that the adequacy and acceptability of (b) (4) bracketing approach will be determined during review of the BLA.

Question 6:

Does FDA agree that the planned content to support the proposed specification for RTP004 excipient is adequate to facilitate FDA's review of the BLA?

FDA Response to Question 6:

The specifications for the RTP004 appear reasonable. We remind you that acceptance criteria for impurities should be justified and toxicologically qualified by appropriate nonclinical studies.

Question 7:

Does FDA agree that the stability data package will be adequate to facilitate FDA's review of the proposed retest period at the recommended storage condition for RTP004 excipient?

FDA Response to Question 7:

Your proposed stability plan for RTP004 appears reasonable.

Question 8:

Does FDA agree that the planned content in the BLA to support the manufacturing equipment upgrade is adequate?

FDA Response to Question 8:

We do not agree that the planned content is adequate to support the manufacturing process upgrade. In your BLA provide:

- a) Data to demonstrate comparability between the post-change batches and the pre-change batches. In addition, provide a formal risk assessment to show that the upgraded equipment in the DP manufacturing process do not pose a negative risk from potential extractables and leachables.
- b) Additional information to support the (b) (4) operations on the upgraded fill line. In section 3.2.P.3.5 of the BLA include media fill data and sterilization validation summaries for sterile-product contact equipment and the lyophilizer used for the commercial manufacturing. In addition, validate capping parameters with a container closure integrity test. For more information on the type of information to be submitted, refer to the 1994 FDA Guidance for Industry “Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products” and additional CMC microbiology comments at the end of the document.

Meeting Discussion:

The Agency stated that, in addition to the standard drug product process validation data, the sponsor needs to provide release and stability data from both pre-change and post-change batches to demonstrate comparability in the quality, purity, and potency of commercial drug product against the clinical batches. The sponsor stated they would provide both release and 3 months stability data (real-time and accelerated) in the BLA submission, and that the additional supportive stability data will be submitted within 30 days of receipt of the application.

Question 9:

Does the FDA agree with the proposed transition plan from LD50 to CBPA for potency determination of DAXI and DAXI for injection?

FDA Response to Question 9:

Yes, your proposed plan appears reasonable. Note that, for LD50 and cell-based potency assay (CBPA), the adequacy of method validation will be determined during review of the BLA.

Meeting Discussion:

The sponsor proposed the LD50 potency assay in the BLA submission. The Agency found the proposal acceptable.

2.3. Nonclinical

Question 10a:

Does the Agency agree that the completed, nonclinical studies with DAXI for injection constitute a complete nonclinical safety program that would support the BLA and the registration for the improvement of the appearance of moderate to severe glabellar lines indication?

FDA Response to Question 10a:

Yes, we agree that the completed nonclinical studies conducted with DAXI for injection constitute a complete nonclinical safety program that would support the BLA submission.

Question 10b:

Does the Agency agree that the data from the nonclinical studies conducted with DAXI (RT001 formulation) administered topically do not need to be included with the BLA for DAXI for injection?

FDA Response to Question 10b:

Yes, we agree that the data from the nonclinical studies conducted with DAXI (RT001 formulation) administered topically do not need to be included with the BLA for DAXI for injection.

Question 11:

In accordance to guidance document (Dec 2014), "Providing Regulatory Submissions in Electronic Format – Standardized Study Data", the nonclinical data being submitted to support DAXI for injection market application are not within the scope of SEND.

Revance does not intend to submit any nonclinical data in SEND format. Does the FDA agree with Revance's proposal?

FDA Response to Question 11:

Yes, we agree with your proposal that SEND datasets are not required to support a BLA submission for DAXI for injection.

2.4. Clinical Pharmacology

Question 12:

Does the Agency agree to include Waivers for conducting human bioavailability studies for DAXI and for the novel excipient RTP004 and their location in the BLA?

FDA Response to Question 12:

Yes, we agree. We will review your submission to determine whether the waiver requests would be granted or not for your proposed dose and indication.

2.5. Clinical/Biostatistics

Question 13:

Does FDA agree with the following proposal:

- To exclude safety and efficacy data from clinical studies evaluating (b) (4)
[REDACTED]
- To exclude safety and efficacy data from clinical studies evaluating (b) (4)
[REDACTED]
- To include AE Line Listings in the 4-Months Safety Update, with a safety database cut-off of 4-6 months, from the on-going phase 2a clinical studies, one in Forehead Lines and a second one (b) (4), as these studies will have FPI less than 6 months before BLA submission.

FDA Response to Question 13:

Provide safety and efficacy data for your proposed product in the target population with moderate to severe glabellar lines. We recommend that you include a summary of the safety data related to other indications (b) (4) and forehead lines with glabellar lines) and other dosage forms. If you plan to submit data from ongoing or recently completed trials in other indications, provide your analysis of the data and conclusions regarding the safety of your product in these populations.

Question 14:

Revance is seeking feedback on our responses to comments from the Division on the statistical analysis plan of the two Phase 3 registration studies. We want to ensure that the analyses are reported in the BLA in accordance with the Division's expectations. On March 5, 2018, the FDA provided feedback to which Revance responded on 06 July 2018.

- a) Does the Agency agree that the analyses performed will appropriately characterize potential variability in efficacy across centers?
- b) Does the Agency acknowledge Revance's agreement to provide data analysis and results in the BLA for the primary endpoint?
- c) Does the Agency agree with our proposal of formal hypothesis testing of secondary efficacy endpoints?
- d) Does the Agency agree with our proposal to report the results of best/worst imputation of missing data, and the sensitivity analyses for the MCMC as an alternative method?

FDA Response to Question 14:

- a) These analyses appear reasonable for the BLA submission.
- b) We acknowledge your agreement. The format of the results appears reasonable for the BLA submission.
- c) The meeting package states that the proposed secondary endpoints that are adjusted for multiplicity evaluate (i) the proportion of subjects rated “none” or “mild” by the investigator on the IGA-FWS and (ii) the proportion of subjects rated “none” or “mild” by both the patient (PFWS) and investigator (IGA-FWS). The meeting package specifies that these endpoints were analyzed sequentially (IGA-FWS first, then the composite) at 7 sequential study time points at Weeks 2, 4, 8, 12, 16, 20 and 24. We reiterate our comments from the Advice Letter dated 3/5/2018 that formal testing of endpoints at timepoints after the primary timepoint (i.e., Week 4) is not required; however, a descriptive analysis including plots may be presented in labeling. The determination of which endpoints appear in labeling will be a review issue. We note that results were not provided for the secondary endpoint of the proportion of subjects rated “none” or “mild” by both the patient (PFWS) and investigator (IGA-FWS) at timepoints other than Week 4.

We also note that the sequential testing stated in the meeting package differs from that in the last SAP submitted to the Agency on 11/22/2017. Ensure that the BLA submission contains all previous versions of the protocols and SAPs with dates and a summary of changes.

- d) These analyses appear reasonable for the BLA submission.

Meeting Discussion for Response to Question 14c:

The sponsor acknowledged, as stated in their response to the Agency’s comments related to Question 14c, the discrepancy in the secondary endpoints and the statistical testing for the timepoints of Week 2 and Week 4; the sponsor stated that the section on secondary endpoints in the SAP states that secondary endpoints would be tested sequentially across the specified timepoints starting at Week 2. The Agency noted that after re-evaluation of the section on secondary endpoints in the SAP, sequential testing of the secondary endpoints was not specified in this section. The Agency further clarified that a distinction should be made between efficacy data after the designated primary timepoint (i.e., Week 4) versus efficacy data at timepoints earlier than the primary timepoint. As the Agency pointed out in previous communications, efficacy data from timepoints after Week 4 may appear descriptively through plots in labeling as done with other applications without the need for formal statistical testing. As for efficacy data at earlier timepoints than the primary timepoint, the Agency stated that (i) testing needs to be pre-specified, and (ii) the definition of treatment response should be the same as that used for establishing efficacy (i.e., achieving a rating of 0 or 1 [none or mild] and at least a 2-grade improvement from baseline on both investigator [IGA-FWS] and patient

[PFWS] assessments). The Agency noted that the endpoints tested at Week 2 and 4 are not the same as that used to establish efficacy.

Question 15:

Does the Agency agree that analysis of time to relapse could inform prescribers and patients of expected time to retreatment?

FDA Response to Question 15:

To characterize the maintenance of response, you evaluated time to relapse to “moderate” or “severe” glabellar lines status as assessed by both investigator and subject and time to return to Baseline glabellar line severity. In consultation with their patients, prescribers may determine that retreatment is needed at loss of success where success is defined as 0 or 1 (none or mild) with at least 2-grade improvement from baseline on both IGA-FWS and the PFWS assessments. We reiterate our comments from the written response dated 10/3/2017 that the proportion of subjects who remain a success (responders on both the IGA-FWS and the PFWS) at each time point is clinically meaningful and will inform labeling.

Meeting Discussion:

The sponsor inquired about the approach for testing the duration of the treatment effect and proposed several endpoints evaluating the “expected time to retreatment”. In response, the Agency noted that testing of time-to-event endpoints is appropriate when the event is well-defined (e.g., death in oncology trials). The Agency further stated that for the proposed indication, there are different criteria that may be used to define the “need for retreatment”, as there is an investigator assessment and a patient assessment and defining the need for retreatment may differ from subject to subject. Therefore, it would be difficult to come to concurrence about the criteria for retreatment. The Agency noted that the sponsor’s data on the proportion of subjects who remain 0 or 1 over time conveys meaningful information.

Question 16:

Does the Agency have any comments on the proposed presentation of the results to support inclusion in the USPI?

FDA Response to Question 16:

It is premature to provide agreements regarding proposed labeling. The content of labeling depends on the results of the review of the submitted data. We agree that the proposed USPI should be informed by precedents from other approved botulinum toxin products which are indicated for the treatment of glabellar lines.

Question 17:

Our OLS study (1620303) includes subjects who will receive up to three consecutive treatments. The SAP for this study was submitted to the IND on September 5, 2018 [Reference IND 129198, SN0038]

a) Does FDA have any feedback on the efficacy analyses described in the SAP?

b) Does FDA have any feedback on the safety analyses described in the SAP?

FDA Response to Question 17:

a) See FDA Response to Question 18 c.

b) Your approach to the safety analysis appears reasonable. Also, see FDA Response to Question 18.

Question 18:

a) Does the Agency agree with pooling strategy for the ISE and ISS?

b) Does the Agency agree on the imputation strategy for the ISE?

c) Does the Agency agree with proposal to present efficacy and safety by treatment cycle?

d) Does the Agency agree on the proposed subgroups analysis for the ISE and ISS?

e) Does the Agency agree on Revance's definition of AESI (AESI) that is planned to be analyzed across the phase 3 program and presented in the BLA?

FDA Response to Question 18:

a) No, we do not agree. The primary basis for the safety evaluation will be pooled data from the two placebo-controlled Phase 3 trials (SAKURA-1 and SAKURA-2). Because of differences in study design and study population, we do not recommend pooling data from the open-label, long-term safety trial (SAKURA-OLS) with data from the placebo-controlled trials for the ISE and ISS.

Provide the following in your ISS:

- Analyses of treatment emergent adverse events (TEAEs) in the pooled dataset to include all TEAEs, treatment-related TEAEs, serious TEAEs, discontinuations due to TEAEs, and possible spread of toxin TEAEs.
- Adverse event tables $\geq 1\%$ regardless of causality.
- Adverse reaction tables (adverse reactions defined as those AEs with possible or probable causality) $\geq 1\%$. We recommend that you pool related preferred terms in your table (e.g. upper respiratory tract infection, nasopharyngitis, viral upper respiratory tract infection etc.)

- Electronic links to Case report forms (CRFs) and narratives as discussed below in Additional Comments.
- Line listings for all abnormal safety findings (e.g. adverse events, vital signs etc.)
- Shift tables for all laboratory values. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.
- Shift tables for all vital signs
- An analysis of ECG data. See FDA Response to Question 21 f).
- A worldwide safety update in addition to safety update report, if the product is approved in any other jurisdiction, provide.
- A discussion of any differences in the safety monitoring among the pooled trials and a comparison of safety results from the individual trials and pooled data.
- Evaluation of uncommon, rare or unexpected events that may be possibly related to the study drug

The objective of the ISE is to support the analysis results obtained from the individual trials and not to establish a new efficacy claim based on pooling data from the individual trials. Therefore, while analyses based on pooled data may be performed for the ISE, such analyses are considered exploratory. Establishing an efficacy claim will be based on efficacy data from the individual Phase 3 trials to provide replication of study findings.

Meeting Discussion:

In addition to the endpoints proposed by the sponsor for inclusion in the ISE, the Agency requested that the sponsor submit results in the ISE from the following endpoints at all timepoints:

- *The proportion of subjects who achieve a rating of 0 or 1 (none or mild) and at least a 2-grade improvement from baseline on the investigator assessment (IGA-FWS)*
- *The proportion of subjects who achieve a rating of 0 or 1 (none or mild) and at least a 2-grade improvement from baseline on the subject assessment (PFWS)*

- *The proportion of subjects who achieve a rating of 0 or 1 (none or mild) and at least a 2-grade improvement from baseline on both the investigator (IGA-FWS) and patient (PFWS) assessments*

The Agency also reiterated that analyses in the ISE are considered exploratory. The sponsor inquired whether there is utility in submitting data from Pool 2 which includes data from the pivotal trials and the open-label extension study, taking into account that Pool 1 includes data from the pivotal trials only. In response, the Agency noted that for interpretation of pooled data, one needs to take into account whether the populations and response rates across the trials are similar.

- b) Whether the imputation strategy is reasonable for the ISE would depend on the regulatory intent of any analyses of such pooled data. For Pool 1, use of the same method of handling missing data for the ISE as that which was pre-specified for the individual trials is reasonable.
- c) We agree. In addition to providing overall incidence rates of safety variables, you may conduct an analysis of the safety data from SAKURA-OLS by treatment cycle. Also, you may conduct an exploratory analysis of treatment effect over time by treatment cycle.
- d) We recommend that you conduct safety analyses in the following subgroups:
 - Race categories include Caucasian, African American, Asian and Other
 - Age categories (18 to 45, >45 to 75), age group (<65 and ≥65)
 - Ethnicity (Hispanic/Latino or not Hispanic/Latino)
 - Sex
 - Baseline severity
 - Any prior exposure to botulinum toxin products
- e) Yes, your definition of adverse events of special interest (systemic effects of botulinum toxins) is reasonable.

Additional Comments:

- Per the Table of Contents (TOC), you propose to submit electronic Case Report Forms (eCRFs) in the Clinical Study Reports (CSR) for the Phase 2 and Phase 3 clinical trials. This strategy is reasonable. Provide CRF for all deaths, serious adverse events, hypersensitivity reactions, discontinuations due to adverse events, moderate/severe injection site reactions and possible spread of toxin (PSOT) events. Other eCRFs should be readily available upon request. However, if the eCRFs are located in the CSR, then provide links to the eCRFs in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety.

- In addition, provide narratives for all deaths, serious adverse events (SAEs), subjects who discontinued the study agent due to adverse events (AEs), and AEs of special interest, anaphylaxis/hypersensitivity reactions, adverse events of ptosis and pregnancies. Narratives may be included in the CSRs with links to these narratives provided in the relevant sections of the Overview of Clinical Safety, Summary of Clinical Safety and Integrated Summary of Safety
- In the 4-month safety update report (SUR), per section 505(i) of the act, you should update the BLA application with new safety information learned about the drug that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. Provide narratives in the SUR for all subjects who died, experienced SAEs, pregnancies and AEs of special interest. See Response to Question 13.
- Based on summary of safety information contained in your meeting package, a Medication Guide and product labeling may be sufficient to ensure the safe use of your product in the treatment of moderate to severe glabellar lines. However, our final determination regarding the need for REMS will be based on the overall risk benefit assessment for your product at the time of the BLA review.
- Submit the coding dictionary used for mapping investigator verbatim terms to preferred terms. The “coding dictionary” consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim preferred and preferred -> verbatim). The Agency can provide recommendations regarding the pooling of certain preferred terms (e.g. viral upper respiratory tract infection and upper respiratory tract infection) to enhance your safety analysis if you submit your coding dictionary prior to completion of the safety analysis for your BLA.
 - As we will conduct an issue-based review of the safety of your product, provide a list and discussion of key potential safety issues associated with the class of products or identified during the development of your product. In addition, discuss any factors which impacted the appropriateness of the data and conclusions supported by your safety assessment, e.g., design issues, degree of missing data/handling of dropouts (if there is a targeted safety outcome), frequency/intensity of monitoring, and exposure in at-risk populations.
- Include the full text version of any referenced articles.
- As part of our review of your original biologic, the Agency will conduct a comprehensive assessment of the benefits and risks of your drug product. The information needed to complete this analysis is described in the Structured

Approach to Benefit-Risk Assessment in Drug Regulatory Decision-Making Draft PDUFA V Implementation Plan which is available at:

<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm>. In your BLA submission, we recommend that you consider/discuss why your product provides an advantage with regard to benefit/risk compared with other FDA approved products indicated for the treatment of glabellar lines.

To facilitate review of the data, we recommend that your BLA submission include a summary of the trials in tabular form such as the following:

Trial Identity	Trial Design	Regimen/schedule/route	Study Endpoints	Treatment Duration/Follow Up	No.of subjects enrolled	Study Population	No.of Centers & Countries
<i>Controlled Studies to Support Efficacy and Safety</i>							
<i>Studies to Support Safety</i>							
<i>Other studies pertinent to the review of efficacy or safety (e.g., clinical pharmacological studies)</i>							

2.6. eSub/eData

Note that FDA Response to Questions 19 and 20 are included as final post meeting comments.

Question 19:

Does the Agency agree on the scope of the datasets?

FDA Response to Question 19:

[Study Data Technical Conformance Guide v. 4.2](#) is the important FDA guide for preparing the data for the submission. It should be added to the list of the guidelines.

Question 20:

Does the Agency agree with the proposed SDSP (Appendix 8)?

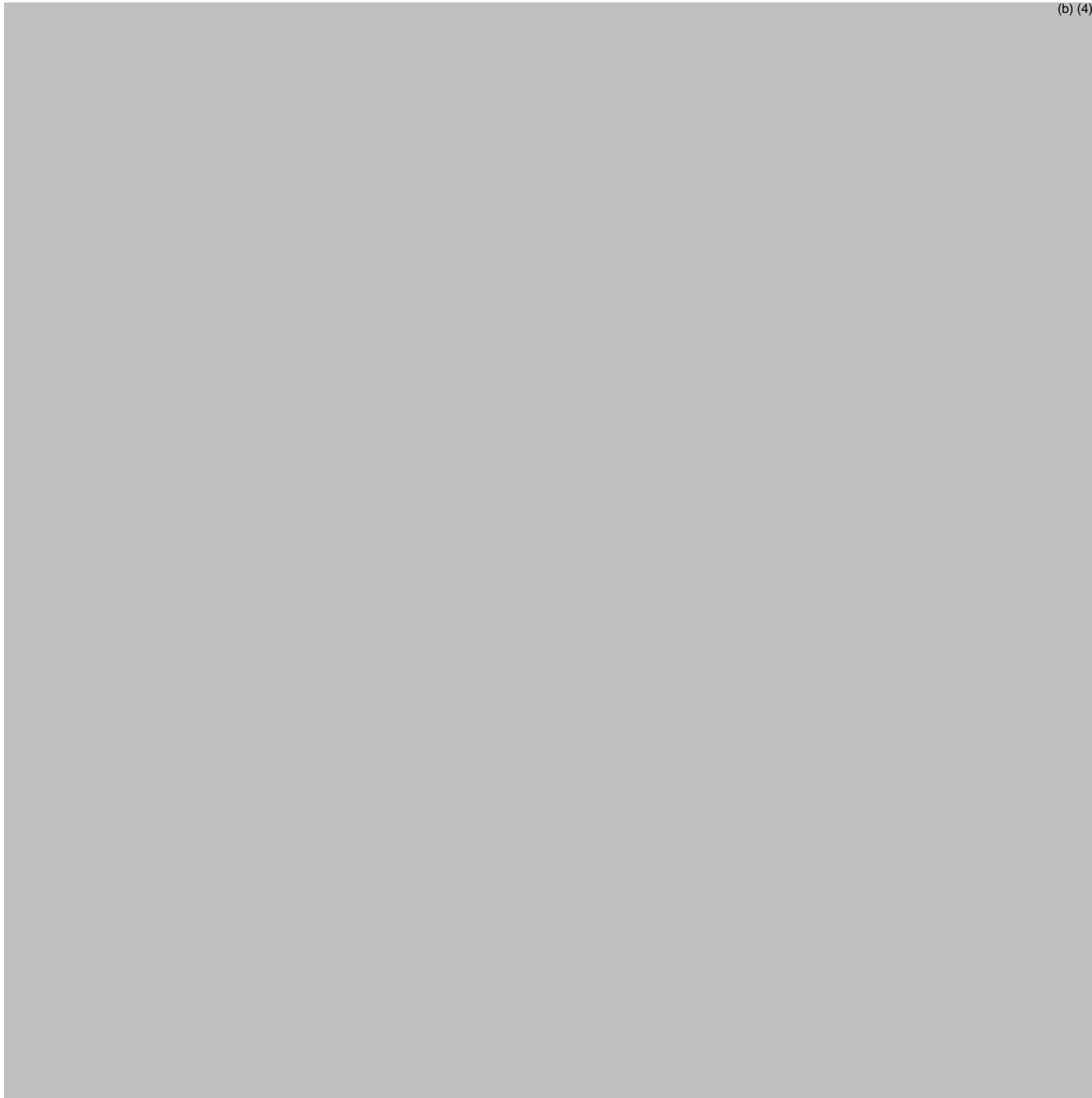
FDA Response to Question 20:

From a technical standpoint SDSP is acceptable. Analysis Data Reviewer's (ADRG) for the analysis datasets were not mentioned in SDSP. Please provide ADRGs to the studies listed and the pooled datasets.

CMC 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 351(a) BLA submission.

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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.

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

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

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

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

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

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

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

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

- Bacterial filter retention study for the sterilizing filter. Include a comparison of validation test parameters with routine sterile filtration parameters.
- Sterilization and depyrogenation of equipment and components that contact the sterile drug product. Provide summary data for the three validation studies and describe the equipment and component revalidation program.
- In-process microbial controls and hold times. Three successful product intermediate hold time validation runs should be performed at manufacturing scale, unless an alternative approach can be scientifically justified. Bioburden and endotoxin levels before and after the maximum allowed hold time should be monitored and bioburden and endotoxin limits provided.
- 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.
- Low endotoxin recovery studies. Certain product formulations have been reported to mask the detectability of endotoxin in the USP <85> *Bacterial Endotoxin Test* (BET). The effect of hold time on endotoxin detection should be assessed by spiking a known amount of standard endotoxin (RSE or purified CSE) into undiluted drug product and then testing for recoverable endotoxin over time. Low endotoxin recovery studies may not be necessary for products that do not contain polysorbate.
- Microbiological studies in support of the post-reconstitution 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 reconstitution and/or transfer to the syringe. 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 reconstitution solution. 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 storage period is not more than 4 hours.

Product Quality - Additional Comments:

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1. Immunogenicity:

For the BLA file we recommend that you provide an Integrated Summary of Immunogenicity in eCTD section 2.7.2.4 Special Studies or Section 5.3.5.3 Reports of Analysis of Data from More than One Study. This Integrated Summary of Immunogenicity should provide:

- a) Immunogenicity Risk Assessment- this section should provide a concise immunogenicity risk assessment specific to the therapeutic product, in accordance to the principles discussed in the FDA Guidance (2014) *Immunogenicity Assessment for Therapeutic Protein Product*. This section should include discussions on product quality -related factors and how these may impact the immunogenic potential of the product; patient-related factors including a discussion on how likely is the patient population and clinical indication to result in immunogenic responses to the product, and a section on trial design-related factors, with a discussion of how the clinical study conditions may facilitate an immunogenic response to the product.
- b) Tiered strategy and Stage-Appropriate Bioanalytical Assays- This section should provide details on the tiered immunogenicity strategy that the applicant followed in the clinical program, and validation summaries for the various immunogenicity assay methods that were developed throughout the program. In addition this section should provide links to method development and validation reports for all the immunogenicity assays used in the various clinical studies supporting the application, particularly those used to test immunogenicity samples from the pivotal clinical study(ies). The method validation report should include validation of tests for anti-drug antibodies to both daxibotulinumtoxin A and the peptide RTP004.
- c) Clinical Study Design and Sampling Strategy: this section should provide the immunogenicity sampling plan(s) for all clinical studies that had immunogenicity assessment performed. This section should include as justification for pre-treatment, in-treatment, and post-treatment sampling time points for immunogenicity and pharmacokinetics, where applicable. This section should discuss how the immunogenicity program aims to reveal the incidence, persistence and clinical significance of anti-drug antibodies.
- d) Clinical Immunogenicity Data Analysis- This section should provide summary results of immunogenicity analysis for all clinical studies having immunogenicity component, including the results of linear and/or non-linear correlation analysis between anti-drug antibody status and titers with PK/PD/efficacy/safety (adverse-events) data. This section should

include drug levels measured in the samples tested for anti-drug antibodies, and trace drug product lots used in the individual clinical studies. Discussion should examine the impact of any pre-existing antibodies on pharmacokinetics, safety and efficacy, the impact of treatment-emergent anti-drug antibodies on pharmacokinetics, pharmacodynamics, efficacy and safety

- e) Conclusions and Risk Evaluation and Mitigation Strategies, if applicable. This section should discuss how product immunogenicity impacts the benefit/risk ratio of the therapeutic biologic for the patient population. In addition, consideration should be given to how product immunogenicity will be monitored in post-marketing stage, and how this will be incorporated into the planned REMS. Lastly, a discussion should be provided regarding life-cycle management of approved immunogenicity assays including assay requalification schedule, and assay transfer plans to any contract testing laboratories for post-marketing surveillance.

2. Extractables/Leachables Comments:

A risk assessment of extractables and leachables, for both drug substance and drug product, are required to support BLA approval.

A separate evaluation is required for the potential generation of in-process leachables from the product contact to equipment including disposables such as filters, containers, and bags. Data from a risk assessment should be provided to assure patient safety if in-process leachables are identified. However, testing might not be required (or necessary) if you provide scientific justification that the downstream purification/ process steps are expected to clear any potential in-process leachables.

The evaluation of leachables in the final drug product may provide information about the cumulative leachables including those introduced during manufacture and those introduced during storage from the container closure systems. This information may inform a scientific justification regarding in-process leachables testing.

3. Control Strategy:

- a) To facilitate the Agency's review of your drug substance and drug product manufacturing process control strategies, provide the following information for each process parameter and in-process control in a tabular format:
- Process parameter and in-process control name
 - Criticality classification (e.g., critical, key, non-critical)
 - Justification for parameter classification
 - Acceptable range determined from process development studies (if applicable)
 - Range evaluated during commercial-scale process validation

- Proposed acceptable range for the commercial manufacturing process
 - Justification of the proposed acceptable range.
- b) To facilitate the Agency's review of product quality attribute control strategies, provide the following information for each quality attribute in a tabular format:
- Quality attribute name
 - Analytical methods used during characterization, in-process, release, and stability testing
 - Classification (e.g., critical, non-critical)
 - Justification for quality attribute classification
 - Proposed control strategy for the quality attribute, including in-process testing, specifications, and specifics of pertinent process controls
 - Justification of the proposed control strategy and control limits.

3.0 Administrative Comments

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our October 17, 2018 communication granting this meeting, if, at the time of submission, the application that is the subject of this meeting is for a new molecular entity or an original biologic, the application will be subject to "the Program" under PDUFA VI. Therefore, at this meeting be prepared to discuss and reach agreement with FDA on the content of a complete application, including preliminary discussions on the need for risk evaluation and mitigation strategies (REMS) or other risk management actions and, where applicable, the development of a Formal Communication. You and FDA may also reach agreement on submission of a limited number of minor application components to be submitted not later than 30 days after the submission of the original application. These submissions must be of a type that would not be expected to materially impact the ability of the review team to begin its review. All major components of the application are expected to be included in the original application and are not subject to agreement for late submission.

Discussions and agreements will be summarized at the conclusion of the meeting and reflected in FDA's meeting minutes. If you decide to cancel this meeting and do not have agreement with FDA on the content of a complete application or late submission of any minor application components, your application is expected to be complete at the time of original submission.

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

Information on the Program is available at
<https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm>.

PREA REQUIREMENTS

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

Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

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

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final

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report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry – *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format* (<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM425398.pdf>).

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

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1.				
2.				

Office of Scientific Investigations (OSI) Requests

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

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

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

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

4.0 ATTACHMENT

- Sponsor's Comment to FDA Responses

61 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/

JILL A LINDSTROM
08/09/2019 07:52:21 AM