

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761225Orig1s000

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**



IND 123178

MEETING MINUTES

CROMA-PHARMA GmbH
c/o ICON Clinical Research LLC
Attention: Mehri Hezari-Adam, PhD
Director Regulatory Affairs
P.O. Box 14353
Durham, NC 27709

Dear Dr. Hezari-Adam:

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

We also refer to the telecon between representatives of your firm and the FDA on September 21, 2020. The purpose of the meeting was to discuss the planned contents and format of the BLA.

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 Jennifer Harmon, Regulatory Project Manager at 240-402-4880.

Sincerely,

{See appended electronic signature page}

Kendall A. Marcus, MD
Director
Division of Dermatology and Dentistry
Office of Immunology and Inflammation
Office of New Drugs
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes
- Sponsor's Agenda



MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-BLA

Meeting Date and Time: September 21, 2020, 1:30p.m. – 2:30p.m. EDT
Meeting Location: Teleconference

Application Number: IND 123178
Product Name: letibotulinumtoxinA

Proposed Indication: For the temporary improvement in the appearance of moderate to severe glabellar lines associated with procerus and corrugator muscle activity in adults.

Sponsor Name: CROMA-PHARMA GmbH
Regulatory Pathway: 351(a) of the Public Health Service Act

Meeting Chair: Kendall A. Marcus, MD
Meeting Recorder: Jennifer Harmon, PharmD

FDA ATTENDEES

Kendall A. Marcus, MD, Director, Division of Dermatology and Dentistry (DDD)
Snezana Trajkovic, MD, Clinical Team Leader, DDD
Tong Li-Masters, MD, Clinical Reviewer, DDD
Mohamed Alesh, PhD, Biometrics Team Leader, Division of Biometrics III
Marilena Flouri, PhD, Biometrics Reviewer, DB III
Parima Ghafoori, PhD, Clinical Outcomes Assessment Reviewer
Barbara Gould, MBAHCM, Chief, Project Management Staff, Division of Regulatory Operations for Dermatology and Dentistry (DRO – DD)
Jennifer Harmon, PharmD, Regulatory Health Project Manager, DRO – DD

SPONSOR ATTENDEES

David Kuroki-Hasenöhr, PhD, Director Development
Paolo Picker, PhD, Team leader CMC & Lifecycle Management, Development
Michael Cecerle, DVM, Global Director Clinical Development
Marion Pucher, PhD, Clinical Development
Yun Jeong Kim, Manager, Global Regulatory Affairs, Hugel, Inc.
Changjin Lee, PhD, Head of R&D, Hugel, Inc.
Taekseung Kim, Director of RA team, Hugel, Inc.

(b) (4)

1.0 BACKGROUND

The purpose of this teleconference is to discuss the planned contents and format of the BLA. FDA sent Preliminary Comments to CROMA-PHARMA GmbH on September 16, 2020.

Regulatory History:

We have had the following meetings/teleconferences with you:

- October 23, 2019 – Final Written Responses
- October 3, 2016 – Final Written Responses
- September 10, 2014 – Pre-IND

We have sent the following correspondences:

- July 29, 2020 – Advice
- June 14, 2019 – Advice
- June 16, 2016 – Advice
- April 18, 2016 – Advice
- March 16, 2016 – Pediatric Study Plan Initial Agreement
- January 8, 2016 – Advice
- December 29, 2015 – Pediatric Study Plan – Written Response
- December 21, 2015 – Remove Full Clinical Hold
- November 24, 2015 – Full Clinical Hold

Coronavirus 19 (COVID-19) Clinical Trial Guidance

During the COVID-19 pandemic, ensuring the safety of trial participants is paramount. Sponsors should consider each circumstance, focus on the potential impact on the safety of trial participants, and modify study conduct accordingly. It is critical that trial participants are kept informed of changes to the study and monitoring plans that could impact them, and that the Agency is appropriately informed of these changes. Refer to the FDA Guidance on *Conduct of Clinical Trials of Medical Products during COVID-19 Public Health Emergency*. 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>.

2.0 DISCUSSION

2.1 Regulatory

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No regulatory questions were provided for this meeting.

2.2. Chemistry, Manufacturing and Controls (CMC)

Question 1:

Does FDA agree that the drug substance is adequately controlled?

FDA Response to Question 1:

This question is pending internal review and will be addressed at a forthcoming CMC-specific teleconference.

Question 2:



Does FDA agree?

FDA Response to Question 2:

This question is pending internal review and will be addressed at a forthcoming CMC-specific teleconference.

Question 3:

Does FDA agree that neither a general safety test, an abnormal toxicity test, or a rabbit pyrogen test would be required for commercial product release purposes?

FDA Response to Question 3:

This question is pending internal review and will be addressed at a forthcoming CMC-specific teleconference.

Question 4:

Does FDA agree that the comparability data between Sinbuk and Geodu batches provide sufficient supportive data to bridge between the supportive and pivotal data to be included in the BLA?

FDA Response to Question 4:

This question is pending internal review and will be addressed at a forthcoming CMC-specific teleconference.

Question 5:

Does FDA agree that the CMC information as summarized in this meeting information package for BoNT/A drug substance and drug product is adequate and appropriate to support the marketing application for the target indication?

FDA Response to Question 5:

This question is pending internal review and will be addressed at a forthcoming CMC-specific teleconference.

Question 6:

Does FDA agree that the comparability data presented in this MIP supports the proposed approach to include both the 50 U and 100 U data in the BLA to support commercial use?

FDA Response to Question 6:

This question is pending internal review and will be addressed at a forthcoming CMC-specific teleconference.

2.3. Nonclinical

Question 7:

Does the FDA agree that the BoNT/A-DP nonclinical program supports the ability of FDA to determine the risk-benefit profile of BoNT/A-DP in the planned marketing application?

FDA Response to Question 7:

We agree that the BoNT/A-DP nonclinical program, which includes a 6-month repeat-dose toxicity study conducted in rats, is adequate to support a BLA submission for BoNT/A-DP.

2.4. Clinical Pharmacology

There were no clinical pharmacology questions submitted for this meeting.

2.5. Clinical/Biostatistics

Question 8

The phase 3 program for BoNT/A-DP consists of 3 identical randomized, double blind, placebo-controlled, multi-national (including US) studies to assess the efficacy and safety of BoNT/A-DP in the treatment of glabellar lines in comparison with placebo, followed by an open label extension period (short titles: Botulinum Toxin Treatment of Glabellar Lines: Efficacy and Safety Study I, II, and III [BLESS I, II, and III]). The results of these 3 studies, enrolling a total of approximately 1,162 subjects, will form the core basis of the clinical portion of the planned marketing application as detailed in additional questions below.

As previously discussed with FDA in the pre-IND meeting (September 2014), an additional phase 3 study (Study HG-11-01) was previously conducted to support South Korean registration of BoNT/A-DP for the treatment of glabellar lines. FDA considered this study as only supportive. As requested by the FDA, the sponsor included the clinical study report as part of the initial IND submission. Because this Korean study is only considered supportive, it will not be included as part of the ISE or ISS and will only be summarized in the planned BLA with inclusion of the clinical study report, but without additional electronic supporting dataset and analysis files. Moreover, additional clinical studies conducted in Korea to support other BoNT/A-DP Korean-specific indications will not be included in the ISS or BLA safety summaries given the difference in the patient populations and dose/dosing regimens compared to the target indication for the planned US BLA.

Does FDA agree with the above approach for BLA clinical study content?

FDA Response to Question 8:

Taking into account that the study was conducted with different dosing and in a different population, your proposal not to submit the data from studies conducted in Korea appears reasonable.

For the pivotal Phase 3 trials, you should submit both Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets. For the analysis datasets, we have the following general comments:

1. Each analysis dataset should include treatment assignments, baseline assessments, and key demographic variables. The analysis datasets should include all variables, including the center variables (i.e., original and analysis), needed for conducting all primary, secondary, and sensitivity analyses included in the study report. For endpoints that include imputations, both observed and imputed variables should be included and clearly identified. If any subjects were enrolled in more than one study, include a unique subject ID that permits subjects to be tracked across multiple studies. Further, assign a unique ID to the original site (center) to permit analysis across the Phase 3 trials.
2. The analysis dataset documentation (Define.xml) should include sufficient detail, such as definitions or descriptions of each variable in the dataset, algorithms for derived variables (including source variable used), and descriptions for the code used in factor variables. For ease of viewing by the reviewer and printing, submit corresponding Define.pdf files in addition to the Define.xml files.

In addition to the electronic datasets, you should submit study protocols including the statistical analysis plan (SAP), all protocol and SAP amendments (with dates), generated treatment assignment lists, and the actual treatment allocations (along with

the date of enrollment). In addition, you should submit the study reports and SAPs (with dates) for the ISS and the ISE.

Question 9:

The sponsor believes that the design and analysis of the BLESS phase 3 study program addresses previous FDA meeting comments regarding endpoints (per FDA 2014 draft guidance on Upper Facial Lines: Developing Botulinum Toxin Drug Products), number of patients evaluated for safety, randomization, potential bias and analyses issues, antigenicity potential, age, race, and skin type representation.

Does FDA agree?

FDA Response to Question 9:

Endpoint:

Your primary efficacy endpoint, “the proportion of subjects among BoNT/A-DP and placebo groups with a Facial Wrinkle Scale (FWS) score of 0 or 1 and an improvement ≥ 2 points in FWS score (at maximum frown) at the Week 4 visit (of the first treatment cycle) relative to baseline (responders), based on both the investigator’s and the subject’s in-clinic assessments” is acceptable.

Number of subjects evaluated for safety:

Your development program’s safety database includes 1162 subjects on active treatment from the BLESS studies and 134 from supportive Phase 3 study. The size of the safety database is acceptable.

Safety assessments:

Your safety assessments include:

1. Adverse Events (AEs), including AEs of Special Interest that could be suggestive of distant spread of toxin at each visit.
2. ECG and laboratory evaluations (hematology and clinical chemistry): screening, Week 4, and end of cycle (EOC).
3. Pregnancy tests: screening, baseline, and EOC.
4. Vital Signs: screening, baseline, Weeks 1 and 4, and EOC
5. Physical exam (PE): baseline, Week 1, 2, 4 and EOC (although it is unclear if PEs were conducted at EOC in BLESS I and II studies).
6. Immunogenicity of BoNT/A-DP was assessed by the measurement of antibody formation at screening, Week 4 following each treatment, EOC and End of Study visits.

Overall, your safety assessments appear acceptable.

Age, race, and skin type representation:

You state that all 3 studies allowed 18 – 75 years of age; actual:

BLESS I: 12% $\geq$ 65 years of age

BLESS II: 13% $\geq$ 65 years of age

BLESS III: 12% $\geq$ 65 years of age

Fitzpatrick skin type I, II, III, IV, V and VI was reported for 36 (3.1%), 470 (40.4%), 434 (37.3%), 131 (11.3%), 58 (5.0%) and 33 (2.8%) subjects, respectively, in the 3 BLESS studies.

Race: Black = 6.7%, Asian 1.5%, Hispanic 11.9%

The age, race, and skin type representations in your Phase 3 studies appear acceptable.

Randomization in a 3:1 ratio stratified by center is acceptable. However, it is not clear what the intention of your question about potential bias and analyses issue is taking into account your trials are already completed.

Antigenicity potential: We acknowledge the immunogenicity samples collected in your Phase 3 program, specifically at Screening, 4 weeks after each treatment and at the end of treatment cycle/study visit. The sample collecting scheme in your Phase 3 program appears reasonable to address the antigenicity potential of your product.

Additional Comments:

We reiterate the following comments conveyed in the advice letter dated 6/14/2019 regarding secondary endpoints:

1. After establishing treatment effect against placebo at the primary time point, comparison against placebo would not be meaningful for assessing the duration of treatment effect. However, we note that efficacy results for clinically meaningful endpoints at time points after the designated primary time point (Week 4) may be described in the labeling via plots or other descriptive statistics without the need for formal testing against placebo.
2. You specified several secondary endpoints relying on $\geq$ 1 point/grade reduction in FWS score. We do not consider one grade improvement to represent clinically meaningful change in the treatment of GL. Therefore, these endpoints will not be eligible for labeling.

Meeting Discussion:

The Agency clarified that while high-level comments were provided regarding secondary endpoints for BLESS I and BLESS II trials, for BLESS III trial, the Agency had previously provided detailed comments that testing after the primary time-point would not be useful (advice letter dated 6/14/2019). As for the rationale, the Agency noted that after establishing treatment effect against placebo at the designated primary time-point, for testing for significant results at later time-points, all that is needed is to have a small

proportion of subjects who maintain success, as the placebo response would be very small, if any. The Agency recognized that efficacy results for later time-points than the designated primary time-point can be important; therefore, such efficacy results are usually represented in plots for response over time.

The Sponsor inquired whether they could submit efficacy results over time using the pooled data from all three pivotal trials jointly (ISE). In response, the Agency noted that presenting efficacy results for individual studies will provide stronger evidence as it enables examining replication of signals across the trials. The Sponsor noted that they will submit results for the individual trials, as well as for the pooled data.

Question 10:

In the FDA Type C WRO meeting of October 2019, FDA agreed to the sponsor's proposal to present data for initial and repeat cycles for BLESS I and II trials and initial cycle for the BLESS III trial at the time of filing. These data will be presented in clinical study reports and the ISE and ISS. Additional safety-related data from the open label extension period of BLESS III will be available and included in the 120-day safety update. The sponsor proposes to include the safety data from the repeat cycles of BLESS III study (extension period) in the form of an update to the ISS in the 120-day safety update to the BLA and subsequently submit the complete clinical study report for additional documentation later in the FDA review.

Does FDA agree with this approach?

FDA Response to Question 10:

All safety data for BLESS III study should be submitted by the 120-day safety update timepoint. Clarify if you are proposing to include safety data from all additional cycles after the 120-day safety update timepoint.

Meeting Discussion:

The Sponsor clarified that all treatment cycles of BLESS III trial will be completed prior to BLA submission but the data from the open-label portion of the trial will be submitted with the 120-day safety update report. They will also submit pooled safety analysis including all three BLESS trials in the 120-day safety report update. The Agency stated that this is acceptable.

Question 11:

The sponsor has performed a preliminary analysis

(b) (4)

In addition, the sponsor has conducted a preliminary analysis comparing the GLS-I rating performed

(b) (4)

(b) (4)

Does FDA agree?

FDA Response to Question 11:

There is insufficient information regarding (b) (4).
Therefore, we cannot conclude that the difference in the BLESS studies (b) (4) for the GLS-I are not clinically meaningful. We will further review the completed quantitative data to evaluate the reliability and validity of the GLS-I at the time of BLA submission.

Question 12:

(b) (4)

Does FDA agree?

FDA Response to Question 12:

We acknowledge that (b) (4).
we recommend that you also use this data to confirm the reliability and validity of these instruments. Without this data, (b) (4) will be a review issue.

Meeting Discussion:

*The Sponsor inquired about the acceptability of the (b) (4).
The Agency stated that this will be a review issue.*

Question 13:

The BLA will include a systematic literature search for safety for both nonclinical and clinical publications. The sponsor's search strategy and filtering approach will be

described and the resultant citation reprints included. If publications are not in English, the original and a certified translated version will be included. Although there are 4 different botulinum toxin products approved in the US, the sponsor is proposing a literature search only for BoNT/A-DP (letibotulinumtoxin A). The sponsor believes this is appropriate given the size of the BoNT/ADP phase 3 program to support safety.

Does FDA agree with the proposed approach?

FDA Response to Question 13:

We agree with literature search for publications on use of your product. Safety information on other letibotulinumtoxin A products from the published literatures may be informative. However, it is not clear how the information obtained from botulinumtoxin products that are different with respect to structure, function, animal toxicity, human pharmacokinetics (PK) and pharmacodynamics (PD), formulations, dosing and dosing regimens, relate to your product.

Question 14:

The BLA will contain a summary of the post-marketing safety data for the BoNT/A-DP product marketed in South Korea and other countries. This will be provided outside of the ISS in Module 5.

Does FDA agree with this approach?

FDA Response to Question 14:

Yes, we agree.

Additional Comments:

1. The Integrated Summary of Efficacy (ISE) and Integrated Summary of Safety (ISS) are required in applications submitted to the FDA in accordance with the regulations for NDA submissions (21 CFR 314.50(d)(5)(v) and 21 CFR 314.50(d)(5)(vi)(a), respectively).

You are referred to the guidance for industry, Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document.

2. You did not discuss strategy for data pooling across trials for safety analysis. The primary basis for safety evaluation should be pooled data from the three placebo-controlled Phase 3 trials (BLESS I, II and III).
3. Provide the following in your ISS:
 - a. 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.

- b. Adverse event tables with incidence rate of $\geq 1\%$ regardless of causality.
- c. Adverse reaction tables (adverse reactions are defined as those AEs with possible or probable causality) with incidence rate of $\geq 1\%$.
- d. In addition to providing overall incidence rates of adverse reactions, conduct an analysis of the safety data from BLESS trials by treatment cycle to evaluate whether the number of treatment sessions was associated with increased risk of adverse reactions.
- e. Conduct an issue-based safety review of your product, provide a list of discussion on 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.
- f. Electronic links to Case report forms (CRFs) and narratives
- g. Line listings for all abnormal safety findings (e.g. adverse events, vital signs etc.)
- h. Shift tables for all laboratory values and vital signs for both outside the normal range and outside the range that is considered clinically significant. Provide the normal range of values for all parameters, the threshold for concern for a clinically significant change and your justification for why this threshold is appropriate.
- i. An analysis of ECG data. 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.).
- j. A worldwide safety update in addition to safety update report, if the product is approved in any other jurisdiction.
- k. 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.

- I. Evaluation of uncommon, rare or unexpected events that may be possibly related to the study drug.
 - m. Provide separate analyses for local and distant spread of toxin AEs, and injection site reactions.
4. Provide safety analyses for the following subgroups:
 - a. Race categories include Caucasian, African American, Asian and Other
 - b. Age categories (18 to 45, >45 to 75), age group (<65 and >65)
 - c. Ethnicity (Hispanic/Latino or not Hispanic/Latino)
 - d. Sex
 - e. Baseline severity
 - f. Any prior exposure to botulinum toxin products
 5. Provide Case Report Forms (CRF) for all deaths, serious adverse events, anaphylaxis/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.
 6. 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
 7. In the 120-day safety update report (SUR), per section 505(i) of the act, you should update the BLA application with new safety information learned about the product that may reasonably affect the statement of contraindications, warnings, precautions, and adverse reactions in the draft labeling. Provide narratives in the SUR for all subjects who died, experienced SAEs, pregnancies and AEs of special interest.
 8. 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.

9. Include the full text version of any referenced articles.
10. 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>							

3.0 ADMINISTRATIVE COMMENTS

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

- The content of a complete application was discussed.
- All applications are expected to include a comprehensive and readily located list of all clinical sites and manufacturing facilities included or referenced in the application.
- Major components of the application are expected to be submitted with the original application and are not subject to agreement for late submission. You stated you intend to submit a complete application and therefore, there are no agreements for late submission of application components.

In addition, we note that a Chemistry, Manufacturing and Controls pre-submission

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meeting was held on October 13, 2020. We refer you to the minutes of that meeting for any additional agreements that may have been reached.

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.

Please be advised that under the Food and Drug Administration Safety and Innovation Act (FDASIA), you must submit an Initial Pediatric Study Plan (iPSP) within 60 days of an End-of-Phase-2 (EOP2) meeting. In the absence of an EOP2 meeting, refer to the draft guidance below. The iPSP must contain an outline of the pediatric study or studies that you plan to conduct (including, to the extent practicable study objectives and design, age groups, relevant endpoints, and statistical approach); any request for a deferral, partial waiver, or waiver, if applicable, along with any supporting documentation, and any previously negotiated pediatric plans with other regulatory authorities. The iPSP should be submitted in PDF and Word format. Failure to include an Agreed iPSP with a marketing application could result in a refuse to file action.

For additional guidance on the timing, content, and submission of the iPSP, including an iPSP Template, please refer to the draft guidance for industry *Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans*.¹ In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Ped drugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.²

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 Information³ and Pregnancy and Lactation Labeling Final Rule⁴ websites, which include:

¹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at

<https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>.

² <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

³ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

⁴ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug’s use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to the draft guidance for industry *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format*.

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

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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.

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*, 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*.⁵

4.0 ATTACHMENTS AND HANDOUTS

⁵ <https://www.fda.gov/media/85061/download>

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

/s/

KENDALL A MARCUS
10/22/2020 01:54:09 PM