CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

213436Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 130133

MEETING MINUTES

Impel NeuroPharma
Attention: Lynn Gold, PhD
Senior Vice President, Regulatory Affairs
201 Elliot Avenue West Suite 260
Seattle, WA 98119

Dear Dr. Gold:[1]

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for INP104 (dihydroergotamine mesylate nasal spray).

We also refer to the telecon between representatives of your firm and the FDA on June 16, 2020. The purpose of the meeting was to discuss the development plan for INP104.

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

If you have any questions, contact E. Andrew Papanastasiou, Regulatory Project Manager, by email at emilios.papanastasiou@fda.hhs.gov or by phone at (301) 796-1930.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Acting Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

[1] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: June 16, 2020 from 1:00 PM to 2:00 PM
Meeting Location: Teleconference

Application Number: IND 130133
Product Name INP104 (dihydroergotamine mesylate nasal spray)
Sponsor Name: Impel NeuroPharma
Regulatory Pathway: 505(b)(2) of the Food, Drug, and Cosmetics Act

FDA ATTENDEES

Billy Dunn, MD	Director, Office of Neuroscience (ON)
Nick Kozauer, MD	Acting Director, Division of Neurology 2 (DN2)
Paul Lee, MD	Acting Deputy Director, DN2
Heather Fitter, MD	Clinical Team Leader, DN2
Ryan Kau, MD	Clinical Reviewer, DN2
Laura Jawidzik, MD	Clinical Reviewer, DN2
Edmund Nesti, PhD	Nonclinical Reviewer, DN2
Lois Freed, PhD	Supervisory Toxicologist, DN2
Kun Jin, PhD	Statistical Team Leader, Biostatistics
Jinnan Liu, PhD	Statistical Reviewer, Biostatistics
Andrei Ponta, PhD	Product Quality Reviewer, OPQ
Angela Men, MD, PhD	Clinical Pharmacology Team Leader, OCP
Muzeeb Syed, PhD	Clinical Pharmacology Reviewer, OCP
Rumi Young, MS	Team Leader, Drug Devices, OPEQ
Briana Rider, PharmD	Safety Evaluator, DMEPA
Ebony Whaley, PharmD	Safety Evaluator, DMEPA
Daniel Ngembus, PharmD	Regulatory Project Manager, DRON
E. Andrew Papanastasiou, PharmD, MS	Senior Regulatory Project Manager, DRON

SPONSOR ATTENDEES

Lynn Gold, PhD	Senior Vice President, Regulatory Affairs	Impel NeuroPharma
John Hoekman, PhD	Founder & Chief Scientific Officer	Impel NeuroPharma
Adrian Adams	Chairman & Chief Executive Officer	Impel NeuroPharma
Stephen Shrewsbury, MD	Chief Medical Officer	Impel NeuroPharma
Sheena Aurora, MD	Vice President, Medical Affairs	Impel NeuroPharma
(b) (4)	Clinical Consultant	(b) (4)
Beatrix Taylor, MS	Director, Regulatory Affairs	Impel NeuroPharma
Kelsey Satterly, PhD	Senior Director, Analytical and Translational Sciences	Impel NeuroPharma
Vien Lai, PhD	Principal Medical Writer, Regulatory Scientist	Impel NeuroPharma
Karen Craig, PhD	Medical Writer II, Regulatory Scientist	Impel NeuroPharma
(b) (4)	Statistical Consultant	(b) (4)
(b) (4)	Director, Regulatory Strategy	(b) (4)

1.0 BACKGROUND

INP104 is a drug-device combination nasal spray product comprised of 1 mL of a 4 mg/mL dihydroergotamine mesylate solution and the I123 Precision Olfactory Delivery (POD) device under development by Impel NeuroPharma Inc. for the proposed treatment of migraine with or with aura. The sponsor submitted a Type B Pre-NDA meeting request on April 7, 2020. The sponsor's intent for the meeting is to discuss the following:

1. Whether the 505(b)(2) regulatory pathway, with the proposed listed drugs (LDs), Migranal® Nasal Spray (NDA 20148) and intravenous (IV) D.H.E 45® Injection (NDA 05929), and the bridging strategy are appropriate for the INP104 NDA submission.

2. The adequacy of the sponsor's proposed plan to submit the combined 6-month and 12-month safety data from the Phase 3 Study INP104-301 in

fulfillment of the Agency's safety requirements for NDA review acceptance.

3. The adequacy of the referenced clinical pharmacology, clinical, nonclinical, and device information along with the outlined drug development program, to support the NDA.

4. Any concerns that the Agency may have regarding the application and/or any filing issues for the INP104 product.

FDA sent Preliminary Comments to Impel NeuroPharma on June 12, 2020.

2.0 DISCUSSION

Question 1: Does the Agency agree that the 505(b)(2) regulatory drug development program, as previously confirmed, consisting of Sponsor-conducted studies, INP104-101 and INP104-301, and reliance on the systemic safety and efficacy findings in the labeling for the LDs, D.H.E. 45 Injection and Migranal Nasal Spray, respectively, is still sufficient for acceptance for review of the INP104 NDA?

FDA Response to Question 1:
On face, your proposed package appears acceptable, but a final determination will be made at the time of filing.

Discussion:
None

Question 2: Does the Agency agree that the indication "acute treatment of migraine headaches with or without aura" is appropriate for INP104?

FDA Response to Question 2:
Your proposed indication appears acceptable.

Discussion:
None

Question 3: Does the Agency agree that the proposed dosing regimen of 1 dose (a total of 1.45 mg DHE in a divided dose as 1 spray to each nostril) for a maximum of 2 doses (total 2.90 mg) in a 24-hour period, and a maximum of 3 doses (total 4.35 mg) in a 7-day period is appropriate for INP104 for the acute treatment of migraine headaches with or without aura?

FDA Response to Question 3:

The proposed initial dosing regimen appears acceptable based on the comparative bioavailability study results in which the systemic exposure to DHE for a single dose of INP104 falls between that of the LDs D.H.E. 45 Injection (IV) product and Migranal Nasal Spray. You should provide additional justification or safety information (from Study INP104-301) to support administration of a second or third dose of NP104 in your proposed NDA.

Discussion:
None

Question 4: For INP104, does the Agency agree that the scientific bridge to D.H.E. 45 Injection for systemic safety and Migranal Nasal Spray for efficacy has been established in Study INP104-101?

FDA Response to Question 4:
Yes, although a final determination will be made at the time of the NDA review.

For the device constituent, the NDA should include long term stability data from (3) GMP lots which support the defined Essential Performance Requirements [Pump Delivery (Spray Weight)], Spray Pattern and Plume Geometry Shape, Spray Content Uniformity (SCU), Droplet / Particle Size Distribution, and Actuation Force for the finished combination product up to the proposed shelf life ((b) (4) months).

Discussion:
None

Question 5: For the major metabolite, 8'-OH-DHE, does the Agency agree that no further data is required to address clinical impact since the concentration-time data and PK parameters fell between that of D.H.E. 45 Injection and Migranal Nasal Spray and did not present at substantial concentrations relative to DHE from INP104?

FDA Response to Question 5:
The pharmacokinetic (PK) parameters of 8'-OH-DHE after INP104 administration appear to fall between that of D.H.E. 45 Injection and Migranal Nasal Spray when each was administered per labeled instructions. Therefore, on face, it appears that no further data are required, pending a detailed review following your NDA submission.

Discussion:
None

Question 6: Does the Agency agree that reliance upon clinical pharmacology information from the approved labeling for Migranal Nasal Spray and D.H.E. 45

Injection, in conjunction with the pharmacokinetic data from Study INP104 101, and supplemented with supportive information in the published literature will satisfy the clinical pharmacology requirements for the review of the INP104 NDA, and that no additional clinical pharmacology studies are needed for the acceptance of NDA review?

FDA Response to Question 6:
It is acceptable to reference the clinical pharmacology information from the approved labelling from Migranal Nasal Spray and D.H.E 45 injection and the supportive clinical pharmacology information from the published literature. For the published literature you plan to rely on, please submit detailed information, including the study design, raw datasets, assay validation etc., in the NDA submission for review.

Discussion:
None

Question 7: Does the Agency agree with the plan for the clinical safety database that includes the Sponsor conducted Phase 3 long-term safety study (Study INP104-301; consisting of at least 150 patients who were exposed to 24 weeks and 50 patients who were exposed to 52 weeks of INP104 treatment), the Sponsor-conducted Phase 1 PK study (Study INP104-101), and safety information in the approved labeling for D.H.E 45, in conjunction with supportive safety information from the approved labeling for Migranal Nasal Spray and the published literature are sufficient for the acceptance of NDA review and that no additional clinical safety studies are needed?

FDA Response to Question 7:
On face, your proposed safety package appears acceptable, although a final determination will be made at the time of filing. Providing safety data from the literature is not needed.

To support evaluation of the device constituent, the specifications provided in the NDA must include the Essential Performance Requirements for the combination product.

In addition, to support the proposed change in color of the finger grip components, include the following:

1. The new chemical composition (e.g., resins, additives, colorants, adhesives, inks) of the components.

2. Documentation to support the biocompatibility of your device constituent including test reports and protocols to ensure that the system components are biocompatible commensurate with the level and duration of patient contact. Refer to the FDA Guidance titled Use

of International Standard ISO 10993-1, "Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" – Guidance for Industry and Food and Drug Administration Staff issued in June 2016 (https://www.fda.gov/downloads/medicaldevices/deviceregulationandguidance/guidancedocuments/ucm348890.pdf) for more details.

3. Any change to extraction data for the affected components.

4. Toxicological evaluation of any new extractables related to the affected components.

Additionally, the change should be governed by proper design controls. See additional comment section below under the heading "**Device content for marketing application"** for additional feedback for device information to provide in a future marketing application.

Discussion:
None

Question 8: Does the Agency agree that for supportive data in the published literature, the plan for presenting supportive clinical safety data for DHE in patients with migraine headaches published within approximately 10 years prior to the submission date is sufficient to support the acceptance of NDA review?

FDA Response to Question 8:
Please see the response to Question 7.

Discussion:
None

Question 9: Does the Agency agree that the Sponsor has adequately addressed the stock recovery issue during the study INP104-301 such that there is no impact on the integrity of the study data and safety outcome?

FDA Response to Question 9:
Please refer to the Division's response to Question 1 in your Chemistry, Manufacturing, and Controls (CMC) Pre-NDA meeting from May 18, 2020.

Discussion:
None

Question 10: Does the Agency agree that the assessment of adverse events (AEs) of DHE that includes narratives, descriptive statistics for the nasal related AEs, QSS-NM scores, and UPSIT scores is sufficient for the assessment of local safety and

tolerability of INP104, and no other analyses are needed to determine the local safety of INP104?

FDA Response to Question 10:

We do not agree. We have the following comments regarding your planned presentation of nasal related AEs:

1. We note that you plan to present data from the QSS-NM and UPSIT scales in tabular form, based on prespecified point change cut-offs or shift criteria. It is not clear to us how you have determined what degree of change on these scales represents a clinically meaningful change. We suggest that you provide detailed information in your application on the scales, including copies of the actual scales provided, the method of instruction given to investigators who are conducting these scales, and any qualitative or quantitative data you may have supporting the use of these scales.

2. We suggest that you conduct a standardized safety analysis based on nasal-related TEAEs. For example, while you may wish to present data from the QSS-NM scale as you describe in the briefing package, we suggest that you also do an analysis identifying the percentage of patients that developed the nasal-related TEAEs that contribute to the overall score of this scale, such as, epistaxis, nasal mucosal erosion, nasal mucosal ulcer, nasal septal perforation, and nasal septal ulceration.

3. Regarding the evaluation of olfactory dysfunction with your product, while you may present these data regarding UPSIT scale changes as you described, we would also like this data presented in a way that allows for an evaluation of the percentage of patients that have normal smell, mild microsmia, moderate microsmia, severe microsmia, and anosmia at baseline and at the end of the study.

   In addition, in your analysis of TEAEs related to olfactory dysfunction, we suggest you describe the olfactory related PTs by SAEs, or AEs that are mild, moderate, or severe.

4. We note that you plan to provide safety analyses of pooled investigational product (IP)-related TEAEs, in addition to all TEAEs for your proposed safety pools. Use of IP-related TEAEs is subjective and of limited interpretability. Therefore, it is not necessary to provide IP-related TEAEs for these safety pools.

5. In addition to the patient narratives for SAEs, we would like narratives provided for all nasal-related or olfactory-related AEs categorized as severe, that led to study drug discontinuation, or that are not reported to

have resolved by the end of the study. Please refer to our response to Question 18 for the format and content of these narratives.

Discussion:

The sponsor confirmed that comprehensive data of TEAEs and olfactory-related AEs would be provided and analyzed in a standardized fashion. The number and percentages of each TEAE will be presented in the safety analyses. FDA recommended that the sponsor incorporate data used for the QSS-NM score into the list of TEAEs and categorize them as mild, moderate, or severe, or as SAEs. In addition, the method of identification of each TEAE should be noted (e.g., nasal endoscopy, UPSIT score, spontaneous report, etc.).

The sponsor clarified that all AEs would be recorded. AEs that were part of the QSS-NM scale would be recorded irrespective of reaching certain thresholds on the scale. The sponsor also confirmed that a table of all TEAEs, and not just those thought to be treatment related, will be provided. FDA recommended that the tables with AEs include a breakdown by month or number of exposures.

FDA indicated that it would need to review the QSS-NM scale to determine whether it could be used for regulatory purposes. FDA did not think the provided mock table (listing 16.2.x.x) would be useful.

FDA found that the submitted mock table (listing 14.3.x.x) related to the UPSIT was potentially useful; however, it noted that there are potential problems with usage of the "probably malingering" category. The sponsor stated no subjects were placed in this category; therefore, the category would not be listed. The sponsor confirmed that all olfactory worsening events were recorded as AEs, not just those that met a minimum prespecified criteria based on a change from baseline in the UPSIT scale score. The sponsor also stated that asymptomatic patients who had UPSIT score changes of at least 5 would be recorded as an AE. FDA stated that interpretation of this type of information may be unclear. The sponsor clarified that these asymptomatic patients would be categorized in a similar fashion to the symptomatic patients and that the sponsor would attempt to present this data in such a way to maximize interpretability.

Question 11: Does the Agency agree that the plan for presenting supportive clinical efficacy data for nasal DHE in patients with migraine headaches published within approximately 10 years prior to the submission date is sufficient to support the acceptance of NDA review?

FDA Response to Question 11:

If you are able to establish an adequate scientific bridge of your product to the LDs, then additional efficacy data will not be needed.

Discussion:
None

Question 12: For DHE-related postmarketing safety data provided in the NDA, does the Agency agree that the summary of safety information for DHE in the FAERS Public Dashboard during 5 years prior to the submission date of this application will be sufficient to support the acceptance of NDA review, and that no other postmarketing safety databases need to be summarized?

FDA Response to Question 12:
Although you may provide such a summary, this is not necessary.

Discussion:
None

Question 13: Because no formal efficacy studies in patients with migraines were conducted, does the Agency agree that an ISE is not needed, and that all clinical efficacy information from various sources can be summarized in Module 2.7.3?

FDA Response to Question 13:
Yes, we agree.

Discussion:
None

Question 14: Because only 1 clinical safety study in patients with migraines was conducted, does the Agency agree that an ISS is not needed, and that all clinical safety information from various sources can be summarized in Module 2.7.4?

FDA Response to Question 14:
We agree that an ISS is not needed. In addition to your planned presentation of safety findings from Study IND104-301, we request that you to provide a safety summary of the Phase 1 study (INP104-101) in the SCS (Module 2.7.4). Patient narratives from the Phase 1 study should also be provided when criteria for submitting patient narratives are met.

Discussion:
None

Question 15: Clinical safety of DHE has been established for over 74 years of use (since 1946) and in recent published QT safety data, there is no risk of QT prolongation at the supratherapeutic DHE dose; does the Agency agree that no thorough QT studies are needed with INP104 for the acceptance of the NDA for review?

FDA Response to Question 15:
Yes, we agree.

Discussion:
None

Question 16: Based on the available data for stability and leachables, does the Agency agree that once the scientific bridging to the LDs (D.H.E. 45 Injection and Migranal Nasal Spray) is established, relying on nonclinical information from the approved labeling for the LDs, with the plan for presenting supportive data in the published literature, is sufficient, and no additional nonclinical studies will be needed for the acceptance of the NDA review?

FDA Response to Question 16:
To the extent that you are able to provide an adequate scientific bridge to the proposed LDs, additional nonclinical studies will not be needed.

Discussion:
None

Question 17: Does the Agency agree that in the labeling for INP104, because concomitant use of potent CYP3A4 inhibitors is contraindicated, (b) (4)

FDA Response to Question 17:
(b) (4)

Discussion:
None

Question 18: For the Phase 3 safety Study INP104-301, the Sponsor plans to submit [redacted] (b) (4) for patients who reported qualifying AEs. Is the format of the [redacted] (b) (4) acceptable and does the agency agree that given their format, [redacted] (b) (4) are not necessary for the NDA review?

FDA Response to Question 18:
We do not agree with your plan to submit [redacted] (b) (4) as presented in section 1.18.3 of your briefing package.

Narrative summaries should provide a complete synthesis of all available clinical data and an informed discussion of the case. The narrative should be comprehensive enough for the reader to come to a reasonable conclusion regarding the subject and adverse event. The following items should be included (but not limited to):

- Patient age and gender
- Adverse event onset and stop dates (presented as relative Study Day number)
- Signs and symptoms related to the adverse event being discussed
- An assessment of the relationship of exposure duration to the development of the adverse event
- Pertinent medical history
- Concomitant medications with start dates relative to the adverse event
- Pertinent physical exam findings
- Any abnormal vital sign measurements
- Pertinent test results (e.g., lab data, ECG data, biopsy data, autopsy results)
- Discussion of the diagnosis as supported by available clinical data
- For events without a definitive diagnosis, a list of the differential diagnoses
- Treatment provided
- Re-challenge results (if performed)
- Outcomes and follow-up information

Discussion:
The sponsor explained that the content of the [redacted] (b) (4) has evolved since submission of the meeting package and that the event paragraph section may include the narrative summary information requested by FDA. It was agreed to have a mock narrative submitted for review and feedback.

Post-Meeting Comment:
The sponsor provided additional samples of patient narratives by email on 6/16/2020. FDA reviewed these sample narratives and agreed that the format of the sample narratives was acceptable, and encouraged the sponsor to include as much detail as possible in Section 3 and 4 to facilitate review of the event.

Question 19: The Sponsor plans to submit the SDTM and ADaM datasets for both the Phase 1 comparative BA Study INP104-101 and the Phase 3 safety Study INP104-301. The sponsor does not plan to provide the ADaM or TLF programs as there is no primary or secondary efficacy as part of these studies. Does the Agency agree with this plan for the NDA review?

FDA Response to Question 19:
Your plan is acceptable.

Discussion:
None

Question 20: Does the Agency agree that the plan for the BIMO package is acceptable for the NDA review?

FDA Response to Question 20:
Based on the clinsite dataset sample you submitted, it appears that you are planning to submit the BIMO package for the bioavailability study INP104-101. For this submission, BIMO datasets are not required.

Discussion:
None

Question 21: Does the Agency agree that a waiver for the 2020 IND Annual Report be granted, so long as no clinical studies are initiated and the NDA for INP104 is submitted in 2020?

FDA Response to Question 21:
As a general matter, waiver requests for annual reporting requirements are not granted. Please refer to the "Study May Proceed Letter" sent on May 11, 2018, referencing 21 CFR 312.33. Annual reports are required to be submitted to your respective IND application within 60 days of the anniversary date the application went into effect. All active IND applications are subject to this requirement. If no clinical studies are initiated or ongoing during the year for which the annual report applies, the annual report should reflect this with a statement.

Discussion:
None

Additional Comments:
During the CMC pre-NDA meeting held May 18, 2020, OPQ responded to Question 8 below and suggested that the sponsor get additional information from CDER for this response, as stated below. DMEPA has provided additional feedback which is

listed below the original Question and FDA response given at the CMC pre-NDA meeting.

Question 8 (CMC Pre-NDA meeting):
Does the Agency agree that the proposed change in color will have a minor impact on the INP104 product and can be implemented based on the plan outlined in the meeting package?

FDA Response to Question 8 (CMC Pre-NDA meeting):
We agree that the change would have a minimal impact from a product quality perspective (pending any CDRH input on biocompatibility). We recommend that you consult the CDER Office of Safety Evaluation with respect to any impact of the results of the summative human factors study.

FDA Follow-up Response to Question 8 above from the Division of Medication Errors Prevention and Analysis (DMEPA):
The change in the color of the left and right finger grip from (b) (4) appears reasonable provided that it does not impact critical tasks or introduce new risk to the user interface. We suggest you include rationale in your NDA submission to support that the change does not require additional human factors validation study data to be submitted.

Discussion:
None

Device content for marketing application

Device information should be located in the appropriate eCTD module, as recommended in the FDA's eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" (https://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf).

When submitting a marketing application for the final finished combination product, provide the following information related to your device:

1) Device Description Documentation
   a) Provide a description of your device constituent design, including any novel features and/or functionalities. This should include drawings / diagrams of the device, descriptions of device components, or any other available information to explain the device design.

b) Describe the principles of operation of your device.
c) Describe any accessories or other devices labeled for use with your device.

2) Design Control (21 CFR 820.30) – The application should include design documentation. The use of recognized standards and FDA guidance to inform design and testing is recommended, as applicable. For questions about design control documentation, we recommend that you reference the FDA Design Control Guidance for Medical Device Manufacturers, https://www.fda.gov/ucm/groups/fdagov-public/@fdagov-meddev-gen/documents/document/ucm070642.pdf. We recommend that the design control information provided in your application include the following:

a) Design Input Requirements (e.g., safety, performance, and reliability requirements of a device that are used as a basis for device design)
b) Design Output Specifications (e.g., device description, drawings, specifications, bill of materials, etc.)
c) Design Verification Plan/Summary Report, supporting data and traceability
d) Design Validation Plan/Summary Report, supporting data and traceability
e) Risk Management File

3) Essential Performance – Identify essential performance requirements (EPR) for the device.

For each identified essential performance requirement, your marketing application should include verification and validation information of EPR specifications. While the final set of essential performance requirements should be based on your design control process, we are providing the following example EPRs for your device type. This is not an exhaustive list and product specific factors should influence your EPR selection.

Example nasal spray EPRs:

- Pump Delivery (Spray Weight)
- Spray Pattern and Plume Geometry Shape
- Spray Content Uniformity (SCU)
- Droplet / Particle Size Distribution
- Actuation Force

Please refer to the FDA Guidance titled Guidance for Industry Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation issued in July 2002 (https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm070575.pdf) for more details.

4) Stability (ICH Q1) – Your stability program should include endpoints to verify that device essential performance is maintained at expiry. You may exclude certain

EPRs from the stability study if you can provide scientific rationale that the excluded EPR is unlikely to change over time.

5) Shipping - Provide documentation for the final finished product to demonstrate that the device EPRs are met after shipping.

6) Control Strategy – Provide a control strategy that ensures that the final finished combination product maintains its essential performance requirements. The control strategy may consist of, but is not limited to, lot release, in-process, control of incoming materials, purchasing controls, etc.

Quality System- The marketing application should contain a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf).

3.0 ADDITIONAL INFORMATION

DISCUSSION OF THE CONTENT OF A COMPLETE APPLICATION

As stated in our April 22, 2020, 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 Plan. 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 FDA.gov.[2]

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*.[3] In addition, you may contact the Division of Pediatric and Maternal Health at 301-796-2200 or email Pedsdrugs@fda.hhs.gov. For further guidance on pediatric product development, please refer to FDA.gov.[4]

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

[2] https://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/default.htm
[3] 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.
[4] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development

Information[5] and Pregnancy and Lactation Labeling Final Rule[6] 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 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.

[5] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[6] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information please visit FDA.gov.[7]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[8]

ABUSE POTENTIAL ASSESSMENT

Drugs that affect the central nervous system, are chemically or pharmacologically similar to other drugs with known abuse potential, or produce psychoactive effects such as mood or cognitive changes (e.g., euphoria, hallucinations) need to be evaluated for their abuse potential and a proposal for scheduling will be required at the time of the NDA submission [21 CFR 314.50(d)(5)(vii)]. For information on the abuse potential evaluation and information required at the time of your NDA submission, see the guidance for industry *Assessment of Abuse Potential of Drugs*.[9]

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

[7] http://www.fda.gov/ectd
[8] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway
[9] 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.

information is provided in the attachment titled, "Product name, NDA/BLA 012345, Establishment Information for Form 356h."

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

Corresponding names and titles of onsite contact:

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

To facilitate our facility assessment and inspectional process for your marketing application, we refer you to the instructional supplement for filling out Form FDA 356h[10] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[11]. Submit all related manufacturing and testing facilities in eCTD Module 3, including those proposed for commercial production and those used for product and manufacturing process development.

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[12] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[13]

[10] https://www.fda.gov/media/84223/download
[11] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[12] 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.
[13] http://www.regulations.gov

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g. by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we

encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	**Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)**
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a "duplicate" of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA's policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

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*.[14]

4.0 ATTACHMENTS AND HANDOUTS

Attached are the documents provided by Impel NeuroPharma in advance of the June 16, 2020, teleconference.

[14] https://www.fda.gov/media/85061/download
U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

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

/s/

NICHOLAS A KOZAUER
07/16/2020 10:23:31 AM