CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

217470Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 136851

MEETING MINUTES

Opiant Pharmaceuticals, Inc.
c/o Pacific-Link Consulting
8195 Run of the Knolls Court
San Diego, CA 92127

Attention: Richard E. Lowenthal, MSc, MBA
U.S. Agent

Dear Mr. Lowenthal:

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

We also refer to the teleconference between representatives of your firm and the FDA on March 30, 2022. The purpose of the meeting was to obtain agreement on the suitability of the available clinical data for filing as an NDA application, to confirm certain aspects of the data package and regulatory filing strategy, and to request submission of portions of the NDA for rolling review.

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

If you have any questions, call me at 301-796-5719.

Sincerely,

{See appended electronic signature page}

Sandy Truong, PharmD
Senior Regulatory Project Manager
Anesthesiology, Addiction Medicine,
and Pain Medicine
Division of Regulatory Operations for Neuroscience
Office of Regulatory Operations
Center for Drug Evaluation and Research

Enclosure:
- Meeting Minutes

U.S. FOOD & DRUG ADMINISTRATION

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: March 30, 2022; 4:00 p.m. – 5:00 p.m. ET
Meeting Location: Teleconference

Application Number: IND 136851
Product Name: Nalmefene nasal spray

Indication: Emergency treatment of known or suspected opioid overdose as manifested by respiratory and/or central nervous system depression
Sponsor Name: Opiant Pharmaceuticals, Inc.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Silvana Borges, MD, Acting Deputy Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Meeting Recorder: Sandy Truong, PharmD, Senior Regulatory Project Manager, Division of Regulatory Operations for Neuroscience (DRO-N)

FDA ATTENDEES

Silvana Borges, MD	Acting Deputy Director, DAAP
Tanya Brescia-Oddo, MD	Medical Officer, DAAP
Srikanth C. Nallani, PhD	Clinical Pharmacology Reviewer, Division of Neuropsychiatric Pharmacology (DNP)
Yun Xu, PhD	Clinical Pharmacology Supervisor, DNP
Nikunj Patel, PhD	Nonclinical Team Lead, Division of Pharmacology/Toxicology for Neuroscience (DPT-N)
Newton Woo, PhD	Nonclinical Supervisor, DPT-N
Dan Mellon, PhD	Deputy Director, DPT-N
Renishkumar Delvadia, PhD	CMC Reviewer, Office of New Drug Products (ONDP), Office of Pharmaceutical Quality (OPQ)
Valerie Amspacher, PharmD	CMC Quality Assessment Lead, ONDP, OPQ
Jeffry Florian, PhD	General Health Scientist, Division of Applied Regulatory Science (DARS)

Katherine Meaker, PhD	Biostatistics Team Lead, Office of Biostatistics (OB)
Cameron Clark, PharmD	Safety Evaluator, Division of Medication Error and Prevention Analysis (DMEPA)
Valerie Vaughan, PharmD	Team Lead, DMEPA
Amy Seitz, PhD, MPH, BS	Team Lead, Division of Epidemiology II (DEPI-II)
Carolyn Tieu, PharmD, MPH	Team Lead, Division of Risk Management (DRM)
Sandy Truong, PharmD	Senior Regulatory Project Manager, DRO-N
Namrata Thakkar, PharmD, BCPS	Regulatory Project Manager, DRO-N

SPONSOR ATTENDEES

Roger Crystal, MD	CEO, Opiant Pharmaceuticals, Inc.
Phil Skolnick, PhD	CSO, Opiant Pharmaceuticals, Inc.
Mark Ellison, PhD	CDO, Opiant Pharmaceuticals, Inc.
Tania Thomas	VP Global Regulatory and Medical Affairs, Opiant Pharmaceuticals, Inc.
David McCann, PhD	Associate Director, DTMC, National Institute on Drug Abuse
Robert Walsh	Chief, Regulatory Affairs Branch, National Institute on Drug Abuse
Kristen Herring, PhD	Health Scientist, Biomedical Advanced Research and Development Authority
Anna O'Rourke, MD	Senior Clinical Studies Analyst, Biomedical Advanced Research and Development Authority
Nellie Byun, PhD	Health Scientist, Biomedical Advanced Research and Development Authority
Paul Roney	Regulatory Affairs Specialist, Biomedical Advanced Research and Development Authority
Judith Laney	Chem MCM Branch Chief, Biomedical Advanced Research and Development Authority
Richard Lowenthal, MSc, MBA	Regulatory Consultant, Pacific-Link Consulting

Tracy Ross-Teichert, MSc	Regulatory Consultant, Pacific-Link Consulting

BACKGROUND

Opiant Pharmaceuticals, Inc. is developing nalmefene nasal spray for the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression. The Sponsor submitted a pre-NDA meeting request on January 3, 2022, to obtain agreement on the suitability of the available clinical data for filing as an NDA application, to confirm certain aspects of the data package and regulatory filing strategy, and to request submission of portions of the NDA for rolling review.

The questions from the February 9, 2022, meeting package are shown in *italic font*, the Division's preliminary comments are shown in **bold font**, the Sponsor's pre-meeting comments are in calibri font and the meeting discussion is in normal font.

FDA sent Preliminary Comments to Opiant Pharmaceuticals, Inc. on March 25, 2022.

DISCUSSION

Clinical

Question 1: Does the Agency agree that there is sufficient clinical data from the OPNT003-PK-001, OPNT003-PK-002 and OPNT003-OOD-001 clinical studies to support submission of an NDA?

FDA Response:
The listed clinical studies address questions regarding intranasal nalmefene bioavailability with single or repeat administration and effects of the proposed nalmefene on ventilation compared to an approved naloxone product. The available clinical studies may be sufficient to support submission of an NDA. Since you appear to be relying on a single adequate and well-controlled clinical investigation plus confirmatory evidence, your results must be persuasive. For additional detail regarding the quantity of clinical evidence needed to establish effectiveness, refer to Guidance for Industry *Demonstrating Substantial Evidence of Effectiveness for Human Drug and Biological Products.*[1]

Opiant's Pre-meeting comments:
Opiant would like to clarify that the planned 505(b)(2) NDA is not relying on a single, well controlled efficacy study as the basis for approval.

[1] https://www.fda.gov/media/133660/download

The development program for nasal (IN) nalmefene is based on referencing REVEX (NDA 020459) as a 505(b)(2) NDA (as referenced in Pre-IND meeting minutes March 7, 2018). Thus, the basis for the efficacy of nasal (IN) nalmefene for the indication of the treatment of opioid overdose has already been established.

Based on data obtained in OPNT003-PK-001, plasma concentrations of nalmefene following a 3mg IN dose are more rapidly absorbed (t_{max}) and early partial AUCs are meaningfully higher at critical early time points (2.5-20 min) compared to the approved 1 mg IM dose of REVEX.

The Agency's advice/information request (November 7, 2019) raised a concern about the onset of action of nalmefene used in a community setting and how nalmefene compares to intranasal naloxone (Narcan Nasal Spray), which has been successful in treating opioid overdose in the community. In order to address this concern, the primary objective of OPNT003-OOD-001 study is to establish non-inferiority in the onset of action of IN nalmefene (5 min. was agreed to as the primary endpoint) compared to an FDA approved dose of naloxone (4 mg IN naloxone was selected as the comparator).

The basis for approval is thus considered as PK comparison to Revex injection (RLD) to create a scientific bridge to that approved product in the same indication. The pharmacodynamic (PD) study to compare the onset of action of nasal (IN) nalmefene to nasal (IN) naloxone is considered as a supportive study to ensure that nalmefene would not be inferior to the current standard of care in the community setting. Opiant would like to confirm this previously agreed assumption with the Agency.

Discussion:
The Sponsor clarified their primary scientific bridge is a PK study between nalmefene nasal spray and Revex and that the PD study, OPNT003-OOD-001, is a supportive study to ensure nalmefene nasal spray would not be inferior to the current standard of care in the community setting. Refer to Sponsor's pre-meeting comments for further details. The Sponsor asked whether the Agency had any comments or concerns. The Division agreed that the PD study is not the only study that will be relied upon in the NDA submission and that the Division will be reviewing the totality of the data from the development program including any references to Revex. The Division emphasized the PD study is an important study that will address the onset of action and duration of action to ensure the proposed product is not inferior to naloxone. The Division further noted the results should be maintained after performing sensitivity analyses and that the results are not driven by a few subjects. This will demonstrate that the results are persuasive. The Sponsor stated that they understood.

With regard to *OPNT003-OOD-001* we have the following comments:

a. **A statistical analysis plan was submitted to the Agency, but there was no discussion around the selected non-inferiority margin or proposed**

approaches before initiating Part 2 of the study. As such, the appropriateness of the non-inferiority margin will be determined during review of the NDA.

Opiant's Pre-meeting comments:
Opiant acknowledges the Agency's comment and will provide the relevant information for the Agency's review in the NDA. No further discussion is needed.

Discussion: No further discussion

b. The non-inferiority analysis in the statistical analysis plan includes a bullet that "no individual subject has a change in minute ventilation on nalmefene that is less than 50% of the change in minute ventilation on naloxone." Please provide additional details on how this criterion is being assessed (e.g., comparing subject-level changes in minute ventilation between treatments at 5 minutes).

Opiant's Pre-meeting comments:
(b) (4) The primary objective of OPNT003-OOD-001 is to establish non-inferiority in the onset of action of IN nalmefene compared to a previously approved dose of IN naloxone. The assessment of mean change in minute ventilation following the administration of the opioid antagonists, in accordance with the Guidance on Non-Inferiority Clinical Trials to Establish Effectiveness, will address this point.

Due to the complex study methodology, the inclusion of an individual subject's response may not be representative of non-inferiority. We believe the FDA recommendation to focus on population PK and a PK/PD analysis is more appropriate to demonstrate the robustness of the response to nasal (IN) nalmefene as compared to IN naloxone.

Discussion:
(b) (4) The Sponsor further stated they will instead conduct population PK analysis and PK/PD analysis. The Sponsor asked whether the Division agreed with their plan. The Division stated they agreed with the Sponsor's plan but suggested that the assessment of an individual subject's response be conducted as an exploratory analysis. The Sponsor stated that they understood.

c. We suggest that you conduct population pharmacokinetic (PK) analysis of nalmefene to characterize a nalmefene concentration-time profile, and PK/PD analysis of nalmefene to characterize the reversal of remifentanil-induced respiratory depression. This information could be useful to inform labeling (Section 12.2 and 12.3) and to support efficacy of nalmefene. The

PK/PD model should relate pharmacokinetic data from your product and opioids of interest to effects of interest such as mu-opioid receptor occupancy and effects on ventilation. References to two such examples are included[2,3]. If you are planning to conduct any such pharmacometrics analysis, refer to the following link[4] for information on the expectation for submitting data and model codes.

Refer to the guidance for industry *Clinical Pharmacology Section of Labeling for Human Prescription Drug and Biological Products — Content and Format*[5] for additional information on labeling of the clinical pharmacology information in your product label.

Opiant's Pre-meeting comments:
Opiant agrees to conduct the proposed population PK and PK/PD analysis as recommended by the Agency. Opiant will include the relevant findings in the label.

Discussion: No further discussion

Moreover, we noticed that the Indication and Usage mentioned in the meeting package submitted on February 9, 2022, is not the same as the Indication and Usage in the annotated label submitted by email on March 16, 2022. As with many sections, the final language in the Indication and Usage section of the product label will be considered after review of your NDA.

Opiant's Pre-meeting comments:
Opiant clarifies that the indication used will be as follows, per the REVEX label.

Nalmefene hydrochloride nasal spray is indicated for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids.

Nalmefene hydrochloride nasal spray is indicated in the emergency treatment of known or suspected opioid overdose.

Nalmefene hydrochloride nasal spray is not a substitute for emergency medical care.

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[2] Yassen, A., et al., Mechanism-based PK/PD modeling of the respiratory depressant effect of buprenorphine and fentanyl in healthy volunteers. Clin Pharmacol Ther, 2007. 81(1): p. 50-8
[3] Yassen, A., et al., Mechanism-based pharmacokinetic-pharmacodynamic modelling of the reversal of buprenorphine-induced respiratory depression by naloxone: a study in healthy volunteers. Clin Pharmacokinet, 2007. 46(11): p. 965-80.
[4] https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format.
[5] https://www.fda.gov/media/74346/download

Discussion:
The Sponsor asked whether the Division agreed with their proposed indication. Refer to Sponsor's pre-meeting comments for further details on the proposed indication. The Division advised the Sponsor to submit all the data that supports their proposed indication and stated the final determination of the indication will be made during review of the NDA submission in its entirety.

Regulatory

Question 2: Does the Agency agree with the proposal for a rolling review and the proposed timelines?

FDA Response:
As a feature of the Fast Track designation, your NDA qualifies for a rolling review. You may refer to Guidance for Industry *Expedited Programs for Serious Conditions – Drugs and Biologics*[6] for additional information on portions of the application eligible for early submission. However, as the guidance notes, "If FDA accepts a portion of an application, this does not necessarily mean that review will commence or proceed before the complete application is submitted. Actual commencement and scheduling of review depends on many factors, including staffing, workload, competing priorities, timeline for completing the application, and the perceived efficiency of commencing review before receipt of the complete submission. The review clock will not begin until the applicant informs the Agency that a complete BLA or NDA was submitted. After the Agency is notified of the complete application, we will make a filing determination within the usual time."

Moreover, we agree with the proposed timelines for your rolling review. The timeline of your submissions may be modified to align with the pace of your drug development program.

Discussion: No further discussion.

Question 3: Does the Agency agree that Opiant may express the product name and strength as a salt throughout NDA documentation and product labelling?

FDA Response:
No, we do not agree. Your product does not appear to meet any of the USP salt policy exemptions outlined in guidance for industry *Naming of Drug Products Containing Salt Drug Substances*.[7] Therefore, the strength of the proposed drug product should be expressed based on the amount of nalmefene base.

[6] https://www.fda.gov/media/86377/download
[7] https://www.fda.gov/media/87247/download

Discussion: No further discussion.

Question 4: Can the Agency comment as to whether or not an Advisory Committee will be consulted?

FDA Response:
Determination of whether an Advisory Committee Meeting will be necessary will be made upon preliminary review of your NDA. However, an Advisory Committee may be necessary to discuss your drug development program and the totality of the data.

Discussion: No further discussion.

ADDITIONAL COMMENTS

Center for Devices and Radiological Health (CDRH)

1. **We remind you of the agreement between the Division and Opiant to conduct (b) (4) prior to submission of your NDA.**

   As noted in the Full Clinical Hold Letter issued on January 27, 2020, (b) (4) "

   For additional details, refer to both the Full Clinical Hold Letter as well as the Type A Meeting Minutes issued on April 17, 2020.

Opiant's Pre-meeting comments:
The agreement to conduct (b) (4) prior to submission of the NDA was in relation to the (b) (4) ® device which is no longer being used. Opiant is now using the Aptar Unidose device which is currently used in several approved pharmaceutical products, including Narcan Nasal Spray. Opiant will have right of reference to the Aptar device DMF which contains the relative biocompatibility studies, and which will be included in the NDA.
No further discussion is needed.

Discussion: No further discussion

Nonclinical

2. **It appears that the systemic exposures associated with your proposed clinical doses may exceed those associated with the referenced drug product. Your repeat-dose nonclinical toxicology studies should include an evaluation of a full battery of all systemic toxicity endpoints, including histopathological evaluation of a full battery of tissues to support higher exposures at the maximum recommended human dose (MRHD), which exceed exposures from the referenced drug. It is acknowledged that you have conducted nonclinical PK studies in order to bridge to the reproductive and developmental data present in the Revex label. The exposure margins in your drug product label should be based upon the human exposures achieved at MRHD with your drug product.**

Opiant's Pre-meeting comments:
The 28 day repeat dose nonclinical toxicology studies in rat and dog have demonstrated a substantial safety margin in relation to the maximum recommended human dose. The studies were conducted using the proposed drug product formulation. An evaluation of a full battery of tissues has been conducted in both species to support higher exposures at the maximum recommended human dose. This will be included as part of the nonclinical section of the NDA. No further discussion is needed.

Discussion: No further discussion

3. **Your drug product contains Intravail A-3 (dodecyl maltoside), which is a novel excipient. We remind you that new excipients should be adequately qualified for safety as recommended in the guidance for industry, *Nonclinical Studies for the Safety Evaluation of Pharmaceutical Excipients*.[8] While we acknowledge that your repeat-dose general toxicity studies will provide local and systemic assessment of this excipient, your NDA, should also include an assessment of the genotoxicity potential as well as reproductive and developmental safety of this novel excipient.**

Opiant's Pre-meeting comments:
Intravail A-3 (dodecyl maltoside) is already approved in other previously CDER approved products. We acknowledge that it is not included in the FDA's Inactive Ingredient database. Opiant has full right of reference to the 2 DMF's associated with Intravail A-3 (dodecyl maltoside) which will be submitted in the NDA. No further discussion is needed.

[8] https://www.fda.gov/media/72260/download

Opiant acknowledges the Agency's Additional comments 4-14 and will address these in the NDA. No further discussion is needed.

Discussion: No further discussion

4. **The NDA submission should contain adequate information on potential leachables and extractables from the drug container closure system and/or drug product formulation, unless specifically waived by the Division. The evaluation of extractables and leachables from the drug container closure system or device should include specific assessments for residual monomers, solvents, polymerizers, etc. Provide justification for the choice of solvents and conditions for the extraction studies (e.g., time, temperature, agitation). The results of the extraction studies should be used to assure that you are adequately monitoring the drug product stability samples for potential leachables from the primary or secondary container closure systems and from your analysis of data from any upstream manufacturing processes that suggest the potential for additional leachable compounds in the final drug product formulation. Your analytical evaluation threshold (AET) should be established to be able to detect, identify, and quantitate levels of compounds based on these thresholds or you should provide adequate justification that these thresholds are not possible to be met by current analytical methodology. If you cannot meet these thresholds, safety evaluations will be based on the limits of quantitation (LOQ). Your submission should include a detailed discussion of how you established your AET as well as justification for the limits of detection (LOD) and LOQ for the analytical methods used.**

   Evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at each timepoint over the course of your stability studies in order to identify trends in leachable levels over time (including early, middle, and late time points). The materials tested should include any secondary container closure systems, if present, and be subjected to the same sterilization methods, as appropriate. These data are essential to determine the appropriate shelf life of your product.

   The AET should be set to evaluate both the potential for mutagenicity and general toxicity and sensitization. In general, for an acute drug product, the AET should be based on a Safety Concern Threshold (SCT) of 5 mcg/day and for a chronic drug product the AET should be based on a SCT of 1.5 mcg/day.

   For additional guidance on extractables and leachables testing, refer to the following documents:

- **USP <1663>: Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems**

- **USP <1664>: Assessment of Drug Product Leachables Associated with Pharmaceutical Packaging/Delivery Systems**

- **FDA guidance for industry: *Container Closure Systems for Packaging Human Drugs and Biologics*[9]**

In your assessment, include a table listing all compounds, including the concentration in ppm, the experimental conditions, and the maximum daily exposure to these compounds based on the maximum daily dose of the product. The extractable/leachable data should be accompanied by an adequate toxicological risk assessment. Although a toxicological risk assessment based on the results of the extraction studies may be adequate to support the safety assessment during development, for your NDA, the final safety assessment should be based on your evaluation of leachables from at least three batches of your drug product tested at multiple timepoints over the course of your stability studies, as discussed above. The approach for toxicological evaluation of the safety of leachables should be based on good scientific principles and take into account the specific container closure system or patch, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based. In addition, consider the following points as you prepare your toxicological risk assessment:

a. **If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.**

b. **Published literature submitted to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews, [e.g., BIBRA Toxicology Advice & Consulting (BIBRA), Cosmetic Ingredient Review (CIR), Human and Environmental Risk Assessment on ingredients of household cleaning products (HERA)], although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be**

[9] https://www.fda.gov/media/70788/download

independently verified. Submission of any published study reports should be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study should be discussed and justification should be provided to support your assertion that these data are adequate to support the safety of your container closure system.

c. Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the extractable/leachable compound.

5. Any impurity or degradation product that exceeds ICH thresholds should be adequately qualified for safety as recommended in ICH Q3A(R2) and ICH Q3B(R2). In order to provide adequate qualification:

a. You should complete a minimal genetic toxicology screen (two *in vitro* genetic toxicology studies, e.g., one point mutation assay and one chromosome aberration assay) with the isolated impurity, tested up to the limit dose for the assay.

b. In addition, you should conduct a repeat-dose toxicology study of appropriate duration to support the proposed indication. In this case, a study of 14 days should be completed.

Refer to
Guidance for industry: *Q3A(R2) Impurities in New Drug Substances*[10]

and

Guidance for industry: *Q3B(R2) Impurities in New Drug Products*[11]

6. If the drug substance batch(es) proposed for use in your clinical study are not the same batches as those used in your nonclinical toxicology studies, provide a table in your IND submission that compares the impurity profile across batches. Include justification for why the levels of impurities in the pivotal nonclinical toxicology studies provide adequate coverage for the proposed levels in the clinical batches or do not otherwise represent a safety concern.

[10] https://www.fda.gov/media/71727/download
[11] https://www.fda.gov/media/71733/download

7. **Your NDA should adequately address the safety of residual solvents as recommended in the ICH guidance document, Q3C(R6): *Residual Solvents*.[12]**

8. **Your NDA should adequately address the safety of elemental impurities as recommended in the ICH guidance document: *Q3D Elemental Impurities*.[13] In addition, refer to the FDA guidance, *Elemental Impurities in Drug Products*.[14]**

9. **In Module 2 of your NDA (2.6.6.8 Toxicology Written Summary/Other Toxicity), include a table listing the drug substance and drug product impurity specifications, the maximum daily exposure to these impurities based on the maximum daily dose of the product and how these levels compare to ICH Q3A(R2) and ICH Q3B(R2) qualification thresholds and determination if the impurity contains a structural alert for mutagenicity. Any proposed specification that exceeds the qualification thresholds should be adequately justified for safety from a toxicological perspective.**

10. **Genotoxic impurities, carcinogenic impurities, or impurities that contain a structural alert for genotoxicity should be adequately controlled during drug development. Drug substance manufacturing often creates the potential for introduction of compounds with structural alerts for genotoxicity through use of reagents, catalysts and other processing aids or the interaction of these with starting materials or intermediates during the stages of chemical synthesis. Refer to the ICH guidance document titled: *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*[15] for the appropriate framework for identifying, categorizing, qualifying, or controlling these impurities. As noted in the guidance, actual and potential impurities likely to arise during synthesis and storage of a new drug substance and manufacture and storage of a new drug product should be identified for assessment. A hazard assessment should be undertaken to categorize these impurities with respect to mutagenic and carcinogenic potential and risk characterization applied to derive acceptable intakes during clinical development. Finally, a control strategy should be proposed and enacted where this is determined to be necessary to ensure levels are within the accepted limits established for the stage of drug development to mitigate risk.**

[12] https://www.fda.gov/media/71736/download
[13] https://www.fda.gov/media/135956/download
[14] https://www.fda.gov/media/98847/download
[15] https://www.fda.gov/media/85885/download

11. **Your drug product should be evaluated for the potential presence of nitrosamine impurities and, if present, controlled at acceptable levels. Refer to the guidance for industry, *Control of Nitrosamine Impurities in Human Drugs*.[16]**

12. **Include a detailed discussion of the nonclinical information in the published literature and specifically address how the information within the published domain impacts the safety assessment of your drug product in Module 2 of the NDA submission. Include copies of all referenced citations in the NDA submission in Module 4. Translate all journal articles that are not in English into English.**

13. **All NDA applications filed after June 30, 2015, must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). In order to prepare for this new labeling format, conduct a thorough review and integrated analysis of the existing clinical and nonclinical literature for each drug substance in your drug product and propose a risk summary statement and text for Section 8 of the labeling. Information on the final rule and links to the FDA draft guidance document are available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm.**

14. **We may refuse to file your application if your NDA submission does not contain safety qualification data for any identified impurity, degradant, or residual solvent that exceeds the recommended qualification thresholds or novel excipients that are not justified for safety or if the application lacks extractable leachable safety justification to permit substantive review.**

Clinical Pharmacology

15. **In your NDA submission, submit the rationale for PK study (b) (4) supporting the proposed repeat dosing 2-5 minutes after first dose. While reviewing protocol OPNT003-PK-002, the time after which the second nasal spray was administered is not readily described. Provide sufficient details of second dose administration in the clinical study report and clinical pharmacology summary.**

Opiant's Pre-meeting comments:
The development program for nasal (IN) nalmefene is based on referencing REVEX (NDA 020459) as a 505(b)(2) NDA. Thus, the basis of efficacy of nalmefene for the indication of the treatment of opioid overdose has already been established.

[16] https://www.fda.gov/media/141720/download

Based on data obtained in OPNT003-PK-001, plasma concentrations of nalmefene following a 3mg IN dose are meaningfully higher at critical early time points (2.5-20 min) compared to the approved 1 mg IM dose of REVEX. The wording for the proposed repeat dosing is from the REVEX label. For PK study OPNT003-PK-002, the second dose was administered immediately after the first dose. This represents the most robust assessment of safety and absorption based on the maximum possible exposure. Opiant will include these details in the clinical study report and clinical pharmacology summary. No further discussion is needed.

Discussion: No further discussion

ISSUES REQUIRING FURTHER DISCUSSION
No issues requiring further question

ACTION ITEMS
There are no action items.

ATTACHMENTS AND HANDOUTS
No attachments and handouts.

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.

In addition, your iPSP should specifically provide your justification why you believe that nonclinical juvenile animal studies are or are not needed to support your pediatric drug development taking into consideration the specific age ranges to be studied. The justification should be based on a comprehensive literature search focusing on the specific toxicological concerns related to the drug substance and each individual

excipient in your drug product and any data you have generated suggesting a unique vulnerability to toxicological insult for the proposed age range to be tested. This risk assessment should take into consideration the expected maximum daily dose of the drug product for the intended patient population and include rationale for your proposed maximum daily dose. In addition, your risk assessment should address how the drug substance and excipients are absorbed, distributed, metabolized, and excreted by the ages of the children you will be studying. Include copies of all referenced citations. If you conclude that a juvenile animal study is necessary, provide a detailed outline of the specific study you propose to conduct, including what toxicological endpoints you will include in the study design to address any specific questions, and justification for your selection of species and the age of the animal to be tested. We recommend that you refer to the FDA guidance to industry, *Nonclinical Safety Evaluation of Pediatric Drug Products*.[17]

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*.[18] 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.[19]

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[20] and Pregnancy and Lactation Labeling Final Rule[21] 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.

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[17] https://www.fda.gov/media/119658/download
[18] 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.
[19] https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development
[20] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[21] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

- 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.

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.[22]

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*

[22] http://www.fda.gov/ectd

Specifications. For additional information, see FDA.gov.[23]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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)				

[23] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

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[24] and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*[25]. 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).[26] 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.[27]

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)).

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[24] https://www.fda.gov/media/84223/download
[25] https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and
[26] 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.
[27] http://www.regulations.gov

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.

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/

SANDY TRUONG
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