

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

218590Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS



IND 137597

MEETING MINUTES

Purdue Pharma, L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Rashmi Upasani, PhD
Director, Regulatory Strategy

Dear Dr. Upasani:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for nalmefene hydrochloride auto-injector.

We also refer to the teleconference between representatives of your firm and the FDA on November 2, 2023. The purpose of the meeting was to seek advice and obtain concurrence from the Agency regarding the format and content of the 505(b)(2) nalmefene hydrochloride auto-injector NDA submission.

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, contact me at 301-796-5719 or sandy.truong@fda.hhs.gov.

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



MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B
Meeting Category: Pre-NDA

Meeting Date and Time: November 2, 2023; 4:00 p.m. to 5:00 p.m. ET
Meeting Location: Teleconference

Application Number: IND 137597
Product Name: Nalmefene hydrochloride autoinjector
Indication: For the emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression induced by either natural or synthetic opioids

Sponsor Name: Purdue Pharma, L.P.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Rigoberto Roca, MD, 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

Rigoberto Roca, MD	Director, DAAP
Celia Winchell, MD	Associate Director for Therapeutic Review, Addiction Medicine and Acting Clinical Team Lead, DAAP
Zachary Dezman, MD	Medical Officer, DAAP
Srikanth C. Nallani, PhD	Clinical Pharmacology Reviewer, Division of Neuropsychiatric Pharmacology (DNP)
Deep Kwatra, PhD	Clinical Pharmacology Team Lead, DNP
Yun Xu, PhD	Master Scientist, DNP
Min Zhang, PhD	Nonclinical Reviewer, Division of Pharmacology/Toxicology for Neuroscience (DPT-N)
Newton Woo, PhD	Nonclinical Supervisor, DPT-N
Jing Han, PhD	Biostatistics Reviewer, Division of Biometrics I (DBI), Office of Biostatistics (OB)

Xinyu Tang, PhD	Biostatistics Team Lead, DBI, OB
Zhihua Li, PhD	Biologist, Division of Applied Regulatory Science (DARS)
Jeffry Florian, PhD	Associate Director, DARS
Vishnu Sharma, PhD	Pharmacometrics Reviewer, Division of Pharmacometrics (DPM)
Sonaly McClymont, MD	Clinical Reviewer, Division of Pediatric and Maternal Health (DPMH)
Shetarra Walker, MD	Clinical Team Lead, DPMH
Jacqueline Yancy, PhD	Senior Regulatory Project Manager, Division of Regulatory Operations for Rare Diseases, Pediatrics, Urologic and Reproductive Medicine (DRORDPURM)
Jagjit Grewal, MPH	Team Lead, Division of Regulatory Policy (DRP)
Damon Birkemeier, PharmD	Safety Evaluator, Division of Medication Error Prevention and Analysis (DMEPA)
Sandy Truong, PharmD	Regulatory Project Manager, DRO-N

SPONSOR ATTENDEES

Stacy Baldrige, PhD, RN	Executive Director, Public Health Initiatives
Sailaja Bhaskar BPharm, PhD, MBA	VP, Clinical R&D
Alessandra Cipriano, MS	Sr. Director, Clinical Operations
Sara Draper, PhD	Director, Analytical Research and Development
Evangeline Priya Eddy, PhD, DABT	Associate Director, Toxicology
Stephen Harris, MD	Head of Clinical Pharmacology
David Igo, PhD	Executive Director, Pharmaceutical and Analytical Development
Ronnie Ortiz, PhD	Director, Pharmaceuticals
Anita Rajmane, PhD	Sr. Manager, Regulatory Strategy
Greg Sparta, Rph	Executive Director, Regulatory Affairs

BACKGROUND

Purdue Pharma, L.P. is developing nalmefene hydrochloride auto-injector as a single-dose device containing 1.5 mg of nalmefene designed to be delivered intramuscularly (IM) or subcutaneously (SC) for the emergency treatment of known or suspected opioid

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overdose, as manifested by respiratory and/or central nervous system depression induced by either natural or synthetic opioids. The Sponsor plans to utilize Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act as the planned regulatory pathway, relying on the Agency's findings of safety and efficacy for Revex (nalmeferene hydrochloride injection), NDA 020459 as the listed drug (LD). The Sponsor has completed a bioavailability study in healthy subjects to create a scientific bridge to Revex. Additionally, a pharmacokinetic (PK) and pharmacodynamic (PD) study has been completed to elucidate the PK profile and to demonstrate early onset and long duration-of-action using the Opioid (Fentanyl) Induced Respiratory Depression (OIRD) Model.

Past interactions between the Sponsor and the Agency on this application include a pre-IND (PIND) meeting on June 19, 2018, with submission of the initial IND on December 17, 2018. That submission also included a request for Fast Track designation which was granted on February 15, 2019. Written Responses were provided to address combination production agreement meeting (CPAM) issues on April 20, 2021, and an End-of-Phase 1 (EOP1) meeting was held on October 4, 2021. Subsequently a CMC-only EOP1 meeting was held on March 31, 2022. An EOP2 meeting was then held on May 25, 2023.

The Sponsor then submitted a Type B pre-NDA meeting request on August 15, 2023, to seek advice and obtain concurrence from the Agency regarding the format and content of the 505(b)(2) nalmeferene hydrochloride auto-injector NDA submission. The questions from the September 28, 2023, meeting package are shown in *italic font*, the Division's preliminary responses are shown in **bond font**, and the meeting discussion is in normal font.

FDA sent Preliminary Comments to Purdue Pharma LP on October 30, 2023.

DISCUSSION

Clinical

Question 1: Does the Agency agree that the clinical studies conducted are adequate to support the NDA submission and approval for the Nalmeferene Auto-Injector?

FDA Response:

The listed clinical studies address questions regarding intramuscular nalmeferene bioavailability with single or repeat administration and effects of the proposed nalmeferene on ventilation compared to an approved naloxone product. The available clinical studies may be sufficient to support submission of an NDA. The review will be based on the totality of the data from your development program including any references to Revex. This includes evaluations to confirm whether

the clinical data address questions about the onset of action and duration of action and that the results are maintained after performing sensitivity analyses.

Discussion:

The Sponsor stated they are planning to perform sensitivity analyses to evaluate the robustness of their findings regarding onset and duration of reversal of fentanyl induced respiratory depression. The primary sensitivity analysis will examine the primary endpoint (change in minute ventilation from nadir at 5 minutes) after excluding extreme high and low values. In addition, sensitivity analyses will be performed on secondary endpoints (change in minute ventilation from nadir at 2.5, 10, 15, 20, 30 and 90 minutes). The Sponsor asked whether the Division recommended additional sensitivity analyses. The Division stated the Sponsor's approach appears reasonable but recommended that the Sponsor include a scientific rationale for excluding any data points in the sensitivity analyses. The Sponsor acknowledged the Division's feedback.

Question 2a: Does the Agency agree that pooling the efficacy data for studies conducted by Sponsor is not required?

FDA Response:

The efficacy data generated by Studies 1004 and 1005 should not be pooled because they have different populations, controls, and endpoints.

Discussion: No further discussion.

Question 2b: Does the Agency agree with the proposed ISE strategy split between Section 2.7.3 and Section 5.3.5.3?

FDA Response:

This appears to be acceptable. As discussed during the EOP2 meeting (5/2/2023, Q #8), we agreed that for this planned NDA, you can present the narrative text of the ISE and ISS in Module 2 and present the tables, appendices, and datasets in Module 5. In each module, we advise you to appropriately refer the reader to Section 5 for the tables, appendices, and datasets and to Section 2 for the text portion of the ISE and ISS.

Discussion: No further discussion.

Question 3: Does the Agency agree that pooling the safety data for studies conducted by Sponsor is not required?

FDA Response:

Present safety and tolerability data from Studies 1004 and 1005 both pooled and separately. For example, we would expect injection site reactions to be similar between studies and we would generally expect systemic reactions to nalmeferene to be independent of the method of administration.

Discussion: No further discussion.

Question 4: Does the Agency agree with the proposal for provision of the clinical datasets as described?

FDA Response:

If you are planning to conduct any pharmacometrics analyses, refer to the following website¹ regarding the expectation for submitting data and model codes.

Discussion: No further discussion.

Question 5: In the Written Response to Initial Pediatric Study Plan (iPSP) dated May 23, 2023, the Agency stated that a deferral of the pediatric studies could be requested and asked the Sponsor to provide a timeline for completion of pediatric studies as deferred studies. Consistent with the Agency's advice, on July 28, 2023, Sponsor submitted an Agreed iPSP incorporating the PK, PD and safety studies in children birth to less than 12 years of age and requested a deferral of pediatric studies as postmarketing studies and proposed a study timeline (sequence # 0050). On September 08, 2023, Agency sent a nonagreement letter declining the request for deferral as postmarketing studies.

Because NAI 1.5 mg NDA will be ready for filing for use in adults and children ≥ 12 years of age well in advance of the completion of the pediatric studies in children birth to less than 12 years of age, does the Agency agree with (a) the proposal to defer the pediatric studies (in children birth to less than 12 years of age) to be conducted as postmarketing requirements and (b) submission of the proposed Agreed iPSP to the IND/NDA?

FDA Response:

As discussed in our responses during the EOP2 meeting held on May 25, 2023, marketing applications for opioid reversal products for community use should include data supporting efficacy and safety in all ages.

¹ <https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/model-data-format>

Discussion:

The Sponsor stated they are ready to submit the NDA by December 2023 and the only item missing may be an agreed iPSP. To demonstrate their commitment of conducting pediatric studies in ages 2 to <17 years, (b) (4)

(b) (4) The Division stated it would be ideal to have the pediatric studies submitted at the time of the NDA submission, but acknowledge the adult studies are completed and ready for submission. The Division recommended that the Sponsor provide documentation to demonstrate they are working on expediting the pediatric development plan. The Sponsor inquired what type of documentation should be submitted. The Division stated the Sponsor can revise the agreed iPSP to provide a brief outline of each pediatric study planned with an overview and justification for the various elements of the study design to the best of their abilities. The Sponsor can also list various options that are under consideration and describe the process they are undergoing to obtain input from subject matter experts. The Sponsor stated that they understood. The Sponsor then inquired on the next steps. The Division stated the Sponsor would need to resubmit the agreed iPSP and then the Division would review, and if applicable, issue an agreement letter. The Sponsor inquired on the timeline of review and whether the submission should be labeled as an agreed iPSP. The Division stated the timeline could be around 30 to 45 days, depending on the Pediatric Review Committee (PeRC) availability, and confirmed the submission should be labeled as an agreed iPSP. The Sponsor expressed understanding.

Nonclinical

Question 6: Does the Agency agree that the nonclinical studies conducted are sufficient to support the NDA submission and approval for the Nalmefene Auto-Injector?

FDA Response:

Based upon the information provided in the meeting package, the nonclinical studies conducted appear supportive of the filing of your NDA submission. However, the adequacy of the nonclinical studies to support the approval can only be determined during the review of the submitted final study reports and NDA submission in its entirety.

Discussion: No further discussion.

Regulatory

Question 7: Does the Agency agree with the Sponsor's request to submit portions of the NDA application separately to support rolling review?

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FDA Response:

Fast Track designation was made in 2019 and so your application is eligible for Rolling Review. A request for submission of portions of an application, along with proposed schedule for submission of those portions, should be submitted as an amendment to the IND. Refer to guidance for industry *Expedited Programs for Serious Conditions – Drugs and Biologics*² for additional information.

Discussion:

The Sponsor stated they are planning to submit a request for rolling review along with the proposed schedule as an IND amendment. The Sponsor then inquired on the timeline of review for a rolling review request. The Division stated they will respond to the rolling review request within 60 days. The Sponsor stated all portions of the NDA are ready for submission but they would like to submit a rolling review request in case an item is missing (i.e., agreed iPSP). Upon further discussion with the Division, the Sponsor will instead resubmit their agreed iPSP to the IND. Refer to discussion under Question 5.

Question 8: Does the Agency agree that Nalmefene Hydrochloride Injection, Auto-Injector NDA may be considered for priority review?

FDA Response:

You may request Priority Review. The Priority Review request should elucidate why the current product provides advantages over the current therapies. Note that seven products for opioid reversal for community use have been approved since this product was granted Fast Track designation, including two that are non-prescription and one using nalmefene.

Determination of priority review status will be made at the time of filing.

Discussion: No further discussion.

Question 9: Does the Agency agree with the 505(b)(2) pathway filing approach?

FDA Response:

You intend to rely, in part, on information required for approval that comes from studies not conducted by you or for which you have not obtained a right of reference (i.e., reliance on the FDA’s finding of safety and effectiveness for NDA 020459 Revex). Therefore, submission of a marketing application pursuant to the 505(b)(2) regulatory pathway is appropriate. See the “505(b)(2) REGULATORY PATHWAY” section below for additional information.

² <https://www.fda.gov/media/86377/download>

Based on the preliminary information submitted, it appears that your product will have higher systemic exposure compared to the listed drug Revex. Therefore, you may not rely solely on previous Agency findings regarding the systemic safety of Revex and should provide additional information to support the systemic safety of your product.

Discussion: No further discussion.

Question 10: Does Agency agree with the format of the proposed label as outlined in the pre-NDA briefing book?

FDA Response:

From a nonclinical pharmacology toxicology perspective, we agree that the format of nonclinical sections in the proposed drug label appear consistent with the PLLR format.

Discussion: No further discussion.

Miscellaneous

Question 11: Based on the data presented and Agency's experience of approved nalmefene and other opioid antagonists for the proposed indication, does the Agency have any additional feedback regarding the NDA application?

FDA Response:

Based on the meeting package, it is not clear whether you will conduct toxicological risk assessments based on the leachables data. In general, results from adequate extraction studies are important in informing the targeting strategy for leachable studies. It is noted that many instances that unexpected compounds are identified and quantitated from the leachables assessment that are not in correlation with the extraction data and therefore the risk assessment on extraction data may not cover all the leachable compounds.

Another issue with conducting toxicological risk assessment on data from an extraction study is that generally extraction studies do not utilize validated methodologies with adequate sensitivity to report the identity and level of a compound to a reasonable degree of scientific certainty. Safety assessments on structures that are not clearly elucidated are not considered adequate to inform definitive toxicological risk assessments. For your NDA, the final toxicological 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) taking into consideration the maximum daily dose of your product.

The following is an updated version of recommendations, which have been previously provided in the PIND meeting, for your NDA submission.

1. 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 use 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*³**

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:

- If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.
- 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 independently verified. Submission of any published study reports

³ <https://www.fda.gov/media/70788/download>

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.

- 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.
2. 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*⁴

and

Guidance for industry: *Q3B(R2) Impurities in New Drug Products*⁵

3. Your NDA should adequately address the safety of residual solvents as recommended in the ICH guidance document, Q3C(R6): *Residual Solvents*.⁶

⁴ <https://www.fda.gov/media/71727/download>

⁵ <https://www.fda.gov/media/71733/download>

⁶ <https://www.fda.gov/media/71736/download>

4. Your NDA should adequately address the safety of elemental impurities as recommended in the ICH guidance document: *Q3D(R2) Elemental Impurities*.⁷ In addition, refer to the FDA guidance, *Elemental Impurities in Drug Products*.⁸
5. Your drug product should be evaluated for the potential presence of (b) (4) impurities and, if present, controlled at acceptable levels. Refer to the FDA guidances for industry: (b) (4)
(b) (4)
6. 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.
7. The nonclinical information in your proposed drug product labeling should include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label should be updated to reflect exposures from your product. If the referenced studies employ a different route of administration or lack adequate information to allow scientifically justified extrapolation to your product, you may need to conduct additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.
8. All NDA applications filed after June 30, 2015, must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). To comply with this 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>.

⁷ <https://www.fda.gov/media/148474/download>

⁸ <https://www.fda.gov/media/98847/download>

(b) (4)

- 9. 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.**

Discussion: No further discussion.

ISSUES REQUIRING FURTHER DISCUSSION

No issues requiring further discussion.

ACTION ITEMS

1. The Sponsor will provide a scientific justification for excluding any data points in the sensitivity analyses.
2. The Sponsor will resubmit their agreed iPSP and provide a brief outline of each pediatric study planned with an overview and justification for the various elements of the study design to the best of their abilities. The Sponsor can also list various options that are under consideration and describe the process they are undergoing to obtain input from subject matter experts.

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*.¹¹

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*.¹² 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.¹³

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 Information¹⁴ and Pregnancy and Lactation Labeling Final Rule¹⁵ websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for

¹¹ <https://www.fda.gov/media/119658/download>

¹² 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>.

¹³ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

¹⁴ <https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information>

¹⁵ <https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule>

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.

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](http://www.fda.gov).¹⁶

¹⁶ <http://www.fda.gov/ectd>

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.¹⁷

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."

¹⁷ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>
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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 356h¹⁸ and the guidance for industry, *Identification of Manufacturing Establishments in Applications Submitted to CBER and CDER Questions and Answers*¹⁹. 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).²⁰ 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.²¹

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

¹⁸ <https://www.fda.gov/media/84223/download>

¹⁹ <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/identification-manufacturing-establishments-applications-submitted-cber-and-cder-questions-and>

²⁰ 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>.

²¹ <http://www.regulations.gov>

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)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX “TRADENAME”</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYY “TRADENAME”</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>(4)</i>	

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

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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*.²²

²² <https://www.fda.gov/media/85061/download>

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

/s/

SANDY TRUONG
12/01/2023 04:22:22 PM



IND 137597

MEETING MINUTES

Purdue Pharma, L.P.
One Stamford Forum
Stamford, CT 06901-3431

Attention: Rashmi Upasani
Director Regulatory Strategy

Dear Ms. Upasani:

Please refer to your investigational new drug application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for nalmefene hydrochloride auto-injector.

We also refer to the teleconference between representatives of your firm and the FDA on May 25, 2023. The purpose of this meeting was to discuss preparations for Phase 3 development of your product (i.e., an EOP2 meeting.)

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 301-796-1191.

Sincerely,

{See appended electronic signature page}

Kimberly Compton, RPh, RAC-US

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



MEMORANDUM OF MEETING MINUTES

Meeting Type/Category: Type B, End-of-Phase 2 (EOP2)
Meeting Date and Time: May 25, 2023, at 2:00 P.M. (Eastern)
Meeting Location: Teleconference
Application Number: IND 137597
Product Name: Nalmefene hydrochloride auto-injector.
Indication: Emergency treatment of known or suspected opioid overdose, as manifested by respiratory and/or central nervous system depression induced by either natural or synthetic opioids, for immediate administration as emergency therapy in settings where opioids may be present but not as a substitute for emergency medical care
Sponsor Name: Purdue Pharma L.P.
Planned Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

FDA ATTENDEES

- Rigoberto Roca, MD, Director, Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP), Office of New Drugs (OND)
- Silvana Borges, MD, Deputy Director and Clinical Team Leader, DAAP, OND
- Celia Winchell, MD, Associate Director for Therapeutic Review for Addiction, DAAP, OND
- Izabella Khachikyan, MD, Medical Officer, DAAP, OND
- Zachary Dezman, MD, Medical Officer, DAAP, OND
- Lisa Wiltrout, MD, Medical Officer, DAAP, OND
- Daniel Mellon, PhD, Deputy Director, Division of Pharmacology/Toxicology for Neuroscience (DPT-N), OND
- Newton Woo, PhD, Supervisory Pharmacologist, DPT-N, OND
- Min Zhang, PhD, Nonclinical Reviewer, DPT-N, OND
- Srikanth Nallani, PhD, Clinical Pharmacology Reviewer, Division of Neuropsychiatric Pharmacology (DNP), Office of Clinical Pharmacology (OCP)
- Jing Han, PhD, Primary Statistical Reviewer, Division of Biometrics I (DBI), Office of Biostatistics (OB), Office of Translational Science (OTS)
- Jeffry Florian, PhD, Associate Director, Division of Applied Regulatory Science (DARS), Office of Clinical Pharmacology (OCP)
- Zhihua Li, PhD, Pharmacokineticist, DARS, OCP
- Kim Compton, RPh, RAC, Senior Regulatory Project Manager, DAAP Group, Division of Regulatory Operations-Neuroscience (DRO-N), OND

SPONSOR ATTENDEES

- Sailaja Bhaskar, BPharm, PhD, MBA VP, Clinical R&D
- Alessandra Cipriano, MS, Sr. Director, Clinical Operations
- Evangeline (Priya) Eddy, PhD, DABT, Associate Director, Toxicology
- Stephen Harris, MD, Head of Clinical Pharmacology
- Ronnie Ortiz, PhD, Director, Pharmaceuticals
- Anita Rajmane, PhD, Sr. Manager, Regulatory Strategy
- Greg Sparta, RPh, Executive Director, Regulatory Affairs
- Rashmi Upasani, PhD, RAC, Director, Regulatory Strategy

BACKGROUND

The Sponsor's states that their combination drug-device product is intended to administer 1.5 mg of nalmeferne hydrochloride via either intramuscular (IM) or subcutaneous (SC) injection via a pre-filled autoinjector. They intend the product to be indicated for the emergency treatment of known or suspected opioid overdose, to provide another treatment option for opioid overdose reversal in the community setting by non-medically trained responders such as caregivers, relatives, friends, and bystanders, as well as by medically trained personnel either in a community or healthcare setting. The Sponsor states that the product will be supplied as a single-dose, (b) (4), disposable autoinjector which houses a prefilled syringe that contains a sterile, nonpyrogenic solution containing 1.5 mg of nalmeferne per 0.5 mL.

Nalmeferne is an opioid antagonist which is a 6-methylene analogue of naltrexone. It acts to prevent or reverse the effects of opioids, including respiratory depression, sedation, and hypotension and has no opioid agonist activity. It is marketed in a 2 mg/2mL (1 mg/1 mL) concentration in a single-dose 2 mL vial as a solution for injection to be titrated to effect and is approved for the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids and in the management of known or suspected opioid overdose. The Sponsor states that their product utilizes the (b) (4) used in the FDA-approved product (b) (4). The Sponsor states that they conducted a formative human factors (HF) study (b) (4), and note that they have submitted an HF Study Validation Protocol for their planned HF study (b) (4)-S1. The Agency provided feedback on that protocol on March 22, 2022, and the Sponsor subsequently submitted an amended protocol in response. The Sponsor notes that the device is designed to enable injection through clothing if needed and includes a number of features designed to avoid accidental triggering and prevention of accidental needle sticks.

The Sponsor plans to utilize Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act as the planned regulatory path for their eventual NDA, relying on the Agency's findings of safety and efficacy for Revex (nalmeferne hydrochloride injection), NDA 020459 as the listed drug (LD). The Sponsor states that they plan to conduct a relative bioavailability study in healthy subject to create a scientific bridge to Revex.

To support a planned NDA for their product, the Sponsor has completed or is in the process of conducting a series of Phase 1 pharmacokinetic (PK)/pharmacodynamic (PD)/bioavailability (BA) studies with their product in addition to the HF studies noted above. The Sponsor states that they have completed a 14-day repeat-dose toxicity study in the rat and dog via the IM route; a single-dose, local tolerance study in the rat and rabbit via the IM and SC route; and a 14-day metabolite toxicity study in the rat via the IV route. The Sponsor submitted a proposed initial pediatric study plan (iPSP) on February 21, 2023, which is currently under review. No Phase 3 studies with the product are currently planned.

Past interactions between the Sponsor and the Agency on this application include a pre-IND (PIND) meeting on June 19, 2018, with submission of the initial IND on December 17, 2018. That submission also included a request for Fast Track designation which was granted on February 15, 2019. Written Responses were provided to address combination production agreement meeting (CPAM) issues on April 20, 2021, and an end-of-Phase 1 (EOP1) meeting was held on October 4, 2021. Subsequently a CMC-only EOP1 meeting was held on March 31, 2022.

The Sponsor states that their primary purpose for this meeting is to obtain advice regarding the ongoing development program for their drug-device product, noting that they would specifically like to obtain guidance from the Agency regarding clinical and nonclinical studies to support the use of their auto-injector in the community setting as well as by medically trained personnel.

The Agency's Preliminary Comments were issued on May 23, 2023. The Sponsor replied on May 23, 2023, that they would like to focus discussion at the meeting on Questions 6, 2, 4, 10, and 1 (in that order). The Agency's comments and responses and to the Applicant's questions are shown in **bold** type with the Applicant's questions in shown in *italics*. The Sponsor's May 23, 2023, replies, are captured in *italics* below the Agency's initial preliminary comments and discussion which took place at the meeting is shown in normal type following the question to which it pertains.

DISCUSSION

Clinical Questions

Question 1

Purdue has conducted pharmacokinetic modeling to inform the administration of an additional dose of Nalmefene Autoinjector following an initial single dose administration of nalmefene autoinjector in an emergency setting. Does the Agency agree with the approach to support the proposed additional dosing in the label using pharmacokinetic modeling?

FDA Response

We have reviewed the methodology (software, non-parametric superposition) and scenarios (repeat dosing every 2 – 5 minutes) you employed in the simulations, as submitted in the meeting package. We have also noted your arguments using the FDA review of Revex (NDA 020459) to support the safety of higher doses of nalmefene.

The simulation approach seems reasonable to support repeat dosing of your product. However, you should account for additional considerations such as your plan for [REDACTED] ^{(b) (4)}, or availability of multiple units of your product with personnel (lay persons or trained medical personnel) while supporting repeat dosing with your product.

It is best that you conduct simulations using data from Study NAL1005, where you would have data following single-dose administration of your product and reference treatment of IM 1 mg nalmefene injection. When using simulation to inform the systemic drug exposure between your product and Revex (your intended listed drug (LD)), the simulation should use the dosing regimen recommended in the product labeling of the listed drug, since the Agency's previous findings were established under the described labeling recommendations. For your own product, utilize the dosing regimen for which you are seeking approval.

In terms of your plan to support efficacy (in part) and safety with the PK program, we have the following advice: While use of IM 1 mg nalmefene injection would provide context to your product as it relates to the lowest effective dose, it is also important to show that repeat dosing would not result in plasma nalmefene concentrations beyond the highest safe and effective dose of nalmefene following IV injection. In this regard, you may rely on the information in the NDA label of the LD or conduct your own evaluation by adding an arm of IV bolus injection of nalmefene approved in the US in study NAL1005. For reference, the Revex label indicates the following dosing for management of known or suspected opioid overdose: "The recommended initial dose of Revex for non-opioid dependent patients is 0.5 mg/70 kg. If needed, this may be followed by a second dose of 1.0 mg/70 kg, 2-5 minutes later."

Additionally, you may utilize published information on single or repeated doses of IV bolus nalmefene in patients with opioid dependence to support safety. We note that you refer to the use of doses up to 24 mg IV bolus of Revex to support its safety. However, the use of such a high dose was in healthy volunteers and not in patients with opioid dependence, thus such data may not support the safety of your product for community use where a

significant portion of the patients receiving treatment with your product is likely to be opioid dependent.

If you have PK data with single dose administration of IV nalmefene, you may conduct simulations for repeated IV doses evaluated in supporting publications. Thus, you may use the simulation results to understand the PK exposure of repeat doses of your product and how it relates to the PK exposure with the lowest effective dose and the highest safe and effective dose of nalmefene.

In the meeting package, you made reference to information included in the Agency's review for Revex (NDA 020459). For a 505(b)(2) NDA, you may only rely on the Agency's previous findings for the LD as described in the product label. You may not rely on the information or data described in the NDA submission of the listed drug, or the Agency's review of the NDA. Please refer to the comments on 505(b)(2) regulatory pathway at the end of this document. If you have acquired right of reference to some or all the data in NDA 20459, indicate the specific rights you have acquired.

Sponsor's emailed reply of May 23, 2023

Sponsor is assuming that the 1.5 mg total dose (initial dose of 0.5 mg followed by a second dose of 1.0 mg, 2-5 minutes later) is the highest safe and effective dose. Does the FDA agree?

Should the simulation regimen for the nalmefene IV bolus be a single dose nalmefene 1.5 mg IV bolus or should it be an initial nalmefene 0.5 mg IV bolus followed by a nalmefene 1.0 mg IV bolus 2 minutes later.

If the repeat dosing simulations of Nalmefene Auto-Injector result in peak plasma nalmefene concentrations (C_{max}) that are less than the highest safe and effective dose of nalmefene following IV injection simulations, will this represent sufficient pharmacokinetic data to support the proposed repeat dosing regimen?

In addition to simulations, can sponsor reference and compare the repeat dose PK data presented in the recently approved Opvee (nalmefene nasal spray) label?

The sponsor is not planning for multi-pack presentation of our product.

Meeting Discussion

The Division stated that the Sponsor should ensure that the C_{max} and AUC/exposure for the proposed dosing regimen is within a known exposure. The Division noted that Study NAL1005 set the lowest effective dose at 1 mg IM. The Revex label also specifies an initial IV dose of 0.5 mg, followed by an IV 1-mg dose 2 to 5 minutes later. Therefore, that would be another logical comparison. The Sponsor stated that,

according to the Revex label, Revex administered by the IM and SC routes shows 100% bioavailability. Therefore, the Sponsor expects the bioavailability to be 100% for their product as well. The Division concurred that the AUC of nalmeferene administered by the IM/SC routes might eventually show 100% bioavailability; however, the Division also noted that a bioavailability study with an IV arm might allow further understanding of how a single dose of the test product compares with the reference product in terms of C_{max} . The modeling plan will help put into context the peak plasma levels (C_{max}) and systemic exposure (AUC) seen in the Sponsor's study. Then, supplemental information from the literature describing the clinical use of higher doses or exposures, not necessarily PK, will aid in the understanding of which nalmeferene doses/exposure are safe. If the Sponsor plans to use old literature, they'll need to justify why it's applicable to the evaluation of their product.

The Division noted that the Sponsor's proposal to conduct Study NAL1005 with their product and the reference product they choose with IM/IV nalmeferene dosing, and to rely on dosing previously published (Kaplan et al.) and general PK simulation data to address the additional dosing proposed in order to put into context where their product falls seemed reasonable at this time.

The Division referred the Sponsor to the FDA presentation at the Regan Udall Foundation Workshop on fatal overdoses, "*Understanding Fatal Overdoses to Inform Product Development and Public Health Interventions to Manage Overdose*"¹ to understand requirements for repeat dose systemic exposure.

The Division suggested that if the Sponsor chose to include an additional arm in Study NAL1005, a 0.5 mg IV bolus followed by a 1 mg IV bolus as described in the Revex label would be appropriate. In light of the above discussion, the Sponsor inquired if they could use either 0.5 mg or 1 mg IV bolus for the additional arm and the Division responded that either one would be acceptable.

Given that the proposed product is intended for use by lay people with the understanding that additional dose/s may be necessary if there is no response after administration of the initial dose, the Division noted that the proposed product's label should describe repeat dosing. The Sponsor noted that they do plan to label the product for repeat dosing as they understand the need to offer the intended population the option to administer more than one dose of an opioid reversal product. However, the Sponsor also stated that they only plan to package the product as a single unit.

¹ <https://reaganudall.org/news-and-events/events/understanding-fatal-overdoses-inform-product-development-and-public-health>

Question 2

(b) (4)
(b) (4) Does the Agency agree with the proposed indication for nalmefene autoinjector (b) (4)?

FDA Response

No, we don't agree. We note that Revex is not intended to be used in the community setting. As we have conveyed to you in previous communications, we are concerned that a delayed and/or variable time to onset of action with your nalmefene product may result in irreversible hypoxia or other serious adverse effects, including death, when used in the community setting by untrained lay persons to reverse an opioid overdose.

Whether your proposed nalmefene product could be used for the emergency treatment of opioid overdose in the community will depend on the results of your proposed study, particularly as related to the time to onset of action.

Sponsor's emailed reply of May 23, 2023

Upon review of Opvee's label, it is noted that the indication includes pediatric patients aged 12 years. This indication was established and supported by Population PK simulations.

Based on the Agency's response to question 4, if our analyses support the extrapolation of the safety and efficacy of our product in adults to adolescents, will we be able to include 12 years and older to our indication?

Meeting Discussion

The Division stated that we would entertain allowing the indication to include children 12 years of age and older. However, a final determination on the proposed product's indication could only be made upon review of the NDA.

Question 3

Based on the Agency's feedback in the PIND meeting minutes dated July 19, 2018, CPAM WRO letter dated April 21, 2021, and EOP1 meeting minutes dated November 03, 2021, Purdue is conducting clinical studies that include relative bioavailability and pharmacodynamic evaluations. Does the Agency agree that no further clinical studies are required to support submission and approval of the nalmefene autoinjector?

FDA Response

It is premature at this stage to comment on the need for additional clinical data since important data relevant to the evaluation of the safety and efficacy of

your product have yet to be produced. Once you obtain data to address the pending concerns with your product, we recommend that you request a pre-NDA meeting to discuss the status of your development program with us.

Sponsor's emailed reply of May 23, 2023

(As the Sponsor did not wish to further discuss this question a response was not included in their emailed reply.)

Meeting Discussion

There was no discussion of this question at the meeting.

Question 4

An initial Pediatric Study Plan (iPSP) for the nalmefene autoInjector as required under PREA Requirements is proposed. (b) (4)

Does the Agency agree with Purdue's approach to fulfill PREA requirements?

FDA Response

It appears reasonable to assume that the PK of IM injections with your product will be similar, if not the same, in adults and adolescents. To support this assumption, we recommend that you evaluate the effect of bodyweight on clearance and volume of distribution of nalmefene from all the adult PK studies conducted so far, preferably using the population PK methodology. This should be followed by simulation of nalmefene PK in a population representative of adolescents with respect to bodyweight.² These analyses could then potentially support the extrapolation of the safety and efficacy of your product in adults to adolescents.

At this time, there is no evidence to support (b) (4)

Therefore, you will need to provide PK and PD data to support the efficacy and safety of your nalmefene product in subjects between 0 and 12 years of age.

We remind you that an agreed initial pediatric study plan (iPSP) must be in place for inclusion in your NDA submission.

² https://www.cdc.gov/growthcharts/clinical_charts.htm

Sponsor's emailed reply of May 23, 2023

Can FDA provide clarification regarding the PK and PD data required to support the efficacy and safety of the nalmefene product in subjects between 0 and 12 years of age?

Meeting Discussion

The Division stated that we would entertain extrapolating safety and efficacy data from adults to patients down to 12 years of age, but noted that there are no data available for nalmefene in patients less than 12 years of age. Therefore, the Sponsor would need to provide such data to support the indication in patients younger than 12 years of age. The Division acknowledged that gathering such data in the pediatric population could be challenging, encouraged the Sponsor to explore research options with subject matter experts, and advised the Sponsor to seek agreement with the Division on the proposed study/es before conducting the studies. The Division suggested pediatric patients who are at a high risk of accidental opioid overdose or those who are in the PICU on fentanyl for sedation as possible populations to be studied. The Sponsor proposed pediatric patients in the post-operative setting where opioids were used and opioid reversal is desired as another population to be studied to generate the necessary nalmefene data in patients under 12 years of age. The Division agreed that such a patient population should also be considered. The Sponsor inquired about conducting such studies as post-marketing requirements (PMRs). The Division noted that the need to provide data to support the indication in patients under 12 years of age with the NDA, or instead as PMRs, would have to be discussed as development of the proposed product progresses.

Nonclinical Questions

Question 5

Based on the Agency's feedback in the CPAM WRO letter dated April 21, 2021, Purdue has conducted two local tolerance studies (rat and rabbit) and two 14-day repeat dose toxicity studies (rat and dog) to support the nalmefene autoinjector formulation. Does the Agency agree that no further nonclinical studies are required to support submission and approval of the Nalmefene Auto-injector NDA?

FDA Response

The local tolerance studies in rats and rabbits and the 14-day repeat-dose studies appear supportive of an NDA submission. However, the adequacy of the nonclinical studies will be determined during the NDA review in the context of your maximum recommended human dose. Note that an additional nonclinical study may be needed for the safety qualification of (b) (4) (see our response to Question 6a).

Sponsor's emailed reply of May 23, 2023

(As the Sponsor did not wish to further discuss this question a response was not included in their emailed reply.)

Meeting Discussion

There was no discussion of this question at the meeting.

Question 6

The degradant, (b) (4), has been studied in a 14-day repeat dose toxicity study in rats and an in silico computational analysis for mutagenicity. In the IR dated September 19, 2022, the Agency communicated that the study evaluations were not sufficient to qualify (b) (4) for a NDA submission. Does the Agency agree:

(a) that adding the histopathological evaluation of tissues collected in the study according to GLP regulations, AND

FDA Response

We agree that the addition of the histopathological evaluation of tissues to the 14-day repeat-dose toxicity study in rats addresses the systemic safety of (b) (4) impurity. However, the repeat-dose study was conducted with IV administration, and therefore does not address the local safety of this impurity with respect to the IM/SC route of administration that is proposed for your drug product. Provide justification for the local safety of your proposed specification of (b) (4) taking into consideration the concentration and the tissues exposed at the injection sites. Otherwise conduct a local tolerance study evaluating a concentration of (b) (4) that is higher than the proposed specification using the proposed routes of administration for your product.

(b) the lack of any mutagenic alerts in a previously performed in silico computational analysis will be sufficient to qualify the safety of (b) (4) ?

FDA Response

Yes, we agree with your proposal. The adequacy of the in silico computational report will be determined upon review of your NDA submission.

Sponsor's emailed reply of May 23, 2023

Reply to item 6a:

Purdue is seeking the following clarifications regarding the conduct of a local tolerance study recommended by the Agency.

According to the ICH M3 Guidance document, a single dose local tolerance study in a single species is considered appropriate to support human administration by parenteral routes. It is also determined that the rabbit is an appropriate nonclinical model to conduct local tolerance studies³. Purdue is proposing to study groups of male and female rabbits dosed via a single intramuscular (IM) injection of the degradant, (b) (4) at 2 doses higher than the degradant specification (note Revex (b) (4) specification is NMT (b) (4) %) as well as the placebo (0.9% NaCl).

In this study, rabbits will be observed for 14 days following a single IM injection. Clinical observations, body weight changes and histopathology of the injection site will be conducted at 2 days post dose to determine acute effects and delayed local effects at 14 days post dose.

Does the Agency agree that:

- a) A single dose, in a single species is sufficient to qualify the local tolerance of the degradant, (b) (4) ?
- b) That the rabbit will be the appropriate species to study local tolerance of the degradant, (b) (4) ?
- c) Administration of the degradant via the IM route of administration alone be sufficient to complete the qualification of the degradant (b) (4) ?

Meeting Discussion

Addressing points a and b in the Sponsor's emailed reply, the Division stated that a single dose study in rabbits is acceptable for local tolerance evaluation of the degradant; however, for point c, the Division noted that extrapolation from the IM route to the SC route (which is a planned route of administration for the product) is not the preferred approach. If the Sponsor wants to utilize the approach described in point c, they should provide a justification supporting how SC information may be extrapolated from IM administration. The Division noted that an alternative approach would be to consider both IM and SC dosing on the same animals used to assess local effects such that additional animals would not need to be utilized.

The Division requested that the Sponsor provide justification supporting why a Day 2 timepoint was appropriate to capture the peak effects for acute local toxicology effects.

³ Karin Jochims, Joerg Kemkowski, Thomas Nolte, Thomas Bartels, and Alexander Heusenere (2003). Local tolerance testing of parenteral drugs: how to put into practice. Regulatory Toxicology and Pharmacology 38: 166–182.

The Division recommended that the Sponsor consider including an additional concentration of the degradant at (b) (4) % in addition to the two proposed concentrations as the (b) (4) % is the expected maximum concentration for human use and data at the maximum concentration would be helpful in assessing clinically relevant local safety if adverse findings are observed at the higher concentrations.

505(b)(2) Regulatory Pathway Questions

Question 7

Does the Agency agree that since no Phase 3 efficacy studies are proposed in this development program, the Integrated Summary of Effectiveness (ISE) can reference the Agency's previous findings of efficacy for Revex (NDA 020459)?

FDA Response

No, we do not agree. The Integrated Summary of Effectiveness (ISE) should be an integrated analysis of all the relevant data you have submitted in your NDA that demonstrates comparable BA between your product and Revex and supports your reliance on the Agency's previous findings of efficacy for Revex.

Sponsor's emailed reply of May 23, 2023

(As the Sponsor did not wish to further discuss this question a response was not included in their emailed reply.)

Meeting Discussion

There was no discussion of this question at the meeting.

Question 8

Does the Agency agree that for this NDA, since the ISS and ISE will be small, the narrative text of the ISS and ISE can be presented in Module 2, and the tables, appendices, and datasets can be contained in Module 5, as described in Example 4 (page 7) of the guidance "Integrated Summaries of Effectiveness and Safety: Location Within the Common Technical Document" (April 2009)?

FDA Response

Yes, we agree that it is acceptable for your planned NDA to present the narrative text of the ISE and ISS in Module 2 and present the tables, appendices, and datasets in Module 5. In each module, we advise you to appropriately refer the reader to Section 5 for the tables, appendices, and datasets and to Section 2 for the text portion of the ISE and ISS.

Sponsor's emailed reply of May 23, 2023

(As the Sponsor did not wish to further discuss this question a response was not included in their emailed reply.)

Meeting Discussion

There was no discussion of this question at the meeting.

Question 9

Does the Agency agree that it will not be necessary to integrate the safety data from the relative bioavailability and pharmacodynamic studies for the Integrated Summary of Safety (ISS)?

FDA Response

No, we don't agree. We understand that the safety data from some of the conducted/future studies with your product may not be pooled for safety analysis because of differences in study design and study population. However, all available clinical data with your product should be analyzed and integrated in the ISS section of your NDA submission.

Sponsor's emailed reply of May 23, 2023

(As the Sponsor did not wish to further discuss this question a response was not included in their emailed reply.)

Meeting Discussion

There was no discussion of this question at the meeting.

General Question

Question 10

Based on the data presented and Agency's experience of approved nalmefene and other opioid antagonists for the proposed indication, does the Agency have any additional feedback on the proposed development program?

FDA Response

We remind you of our previous advice related to the device aspects of your product included in our July 19, 2018, April 20, 2021, and April 18, 2022, communications which included advice on submitting a plan for the device testing and reliability data for the autoinjector for our review prior to NDA submission. Ensure that the information provided contains all the device design and performance data needed to complete the review, including a

complete and detailed description of your device constituent design and delivery system, including any features and functionalities unique to your device, detailed descriptions of the principles of operation of your device, from beginning to end of the activation process, a complete and detailed device constituent design requirements and specifications document, including design inputs and outputs in accordance with 21 CFR 820.30 design controls.

We have concerns that the long half-life of nalmefene may lead to prolonged precipitated withdrawal in opioid-dependent subjects. Provide safety information to support the use of your product in the opioid-dependent population.

We recommend you request a pre-NDA meeting with the Division before NDA submission to discuss the development program for your product and the plans for submission of your NDA.

Sponsor's emailed reply of May 23, 2023

Can FDA provide clarification regarding the type of safety information needed to support the use of our product in the opioid-dependent population. Sponsor will conduct a comprehensive literature search to provide the requested safety information. In addition, sponsor plans to rely on sections 5.3 and 5.4 in the recently approved Opvee's label. Is this sufficient?

(b) (4)

Sponsor proposes to conduct a 505(b)(2) comparative bioavailability bridging study with Revex (Study Protocol NAL1005).

An amended reliability protocol following Agency's advice (reference to EOP1 CMC meeting minutes dated 18 April 2022, General Advice letter dated 27 April 2022) was submitted to IND on 27 July 2022; please refer to sequence #0033.

Meeting Discussion

The Sponsor stated that they are planning to provide comparable bioavailability data to Revex and refer to it as their listed drug (LD).

(b) (4)

(b) (4)

(b) (4)

The Division stated that literature could be sufficient to support the safe use of the proposed product in the opioid-dependent population. (b) (4)

The Division added that the Sponsor could also choose to conduct a study to generate these data and in such case, the Division would be willing to discuss study designs with the Sponsor.

ADDITIONAL COMMENTS

Nonclinical

- 1. We remind you that the nonclinical information in your proposed drug product labeling should include relevant exposure margins with adequate justification for how these margins were obtained. As you intend to rely upon the Agency's previous finding of safety for an approved product, the exposure margins provided in the referenced label should be updated to reflect exposures from your product, which may entail conducting additional pharmacokinetic studies in animals in order to adequately bridge your product to the referenced product labeling.**
- 2. 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 use 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*⁴**

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).

⁴ <https://www.fda.gov/media/70788/download>

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:

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

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 *M7(R1) Assessment and Control of DNA Reactive (Mutagenic) Impurities in Pharmaceuticals to Limit Potential Carcinogenic Risk*³ 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.

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*.⁴

4. 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.
5. Your NDA should adequately address the safety of residual solvents as recommended in the ICH guidance document Q3C(R6): *Residual Solvents*.⁷
6. Your NDA should adequately address the safety of elemental impurities as recommended in the ICH guidance document: *Q3D(R2) Elemental Impurities*.⁸ In addition, refer to the FDA guidance *Elemental Impurities in Drug Products*.⁹
7. All NDA applications filed after June 30, 2015, must submit labeling consistent with the Final Pregnancy Labeling and Lactation Rule (PLLR). To comply with this 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 online.¹⁰

- 8. 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.**

SPONSOR SUMMARY OF THE MEETING and ACTION ITEMS

1. Regarding Question 6, the Division agreed the Sponsor may conduct the local tolerance study via a single-dose study in the rabbit, but recommends the Sponsor consider both IM and SC routes to assess local tolerance. These may be conducted in the same animals.
2. The Sponsor should provide a justification for their selection of Day 2 timepoint to assess the acute effects of the degradant.
3. The Division recommends adding dosing at the maximum specification concentration of the degradant of (b) (4) % in addition to the doses already planned.
4. Regarding pediatric dosing, at this time the Division believes it's reasonable to consider extrapolation of safety and efficacy from adults to patients 12 years of age and older, but final determination cannot be made until the NDA is reviewed.

The Division is requesting safety and efficacy data in patients under 12 years of age, but understands the challenge of obtaining such data. The Division encouraged the Sponsor to engage subject matter experts to help identify appropriate populations and study designs for this purpose and agreed to continue the dialogue with the Sponsor on this issue.

5. The Division will consider allowing studies in patients less than 12 years of age to be conducted as PMRs.
6. To address safety in opioid-tolerant patients, the Sponsor may choose to utilize literature to support safe use in that population, (b) (4) or to conduct a study to assess the safety of their product in opioid-tolerant patients.
7. Regarding Question 1 on repeat dose exposure, the Division agreed that a simulation to demonstrate systematic exposure of the auto-injector compared to Revex in study NAL1005 and also 0.5 mg IV bolus followed by a 1 mg IV bolus of Revex could support labeling of repeat dosing.

OTHER IMPORTANT INFORMATION

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. You should 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*.⁵

⁵ <https://www.fda.gov/media/119658/download>

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*.⁶ 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.⁷

DATA STANDARDS FOR STUDIES

Under section 745A(a) of the FD&C Act, electronic submissions “shall be submitted in such electronic format as specified by [FDA].” FDA has determined that study data contained in electronic submissions (i.e., NDAs, BLAs, ANDAs and INDs) must be in a format that the Agency can process, review, and archive. Currently, the Agency can process, review, and archive electronic submissions of clinical and nonclinical study data that use the standards specified in the Data Standards Catalog.⁸

On December 17, 2014, FDA issued the guidance for industry *Providing Electronic Submissions in Electronic Format - Standardized Study Data*. This guidance describes the submission types, the standardized study data requirements, and when standardized study data are required. Further, it describes the availability of implementation support in the form of a technical specifications document, *Study Data Technical Conformance Guide*, as well as email access to the eData Team (cdereadata@fda.hhs.gov) for specific questions related to study data standards. Standardized study data are required in marketing application submissions for clinical and nonclinical studies that started after December 17, 2016. Standardized study data are required in commercial IND application submissions for clinical and nonclinical studies that started after December 17, 2017. CDER has produced a Study Data Standards Resources web page⁹ that provides specifications for sponsors regarding implementation and submission of clinical and nonclinical study data in a standardized format. This web page will be updated regularly to reflect CDER's growing experience in order to meet the needs of its reviewers.

For commercial INDs and NDAs, Standard for Exchange of Nonclinical Data (SEND) datasets are required to be submitted along with nonclinical study reports for study types that are modeled in an FDA-supported SEND Implementation Guide version. The FDA Data Standards Catalog, which can be found on the Study Data Standards Resources web page noted above, lists the supported SEND Implementation Guide versions and associated implementation dates.

⁶ <https://www.fda.gov/media/86340/download>

⁷ <https://www.fda.gov/drugs/development-resources/pediatric-and-maternal-health-product-development>

⁸ <http://www.fda.gov/forindustry/datastandards/studydatastandards/default.htm>

⁹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

Although the submission of study data in conformance to the standards listed in the FDA Data Standards Catalog will not be required in studies that started on or before December 17, 2016, CDER strongly encourages IND sponsors to use the FDA supported data standards for the submission of IND applications and marketing applications. The implementation of data standards should occur as early as possible in the product development lifecycle, so that data standards are accounted for in the design, conduct, and analysis of clinical and nonclinical studies. For clinical and nonclinical studies, IND sponsors should include a plan (e.g., in the IND) describing the submission of standardized study data to FDA. This study data standardization plan (see the FDA Study Data Technical Conformance Guide) will assist FDA in identifying potential data standardization issues early in the development program.

If you have not previously submitted an eCTD submission or standardized study data, we encourage you to send us samples for validation following the instructions at FDA.gov. For general toxicology, supporting nonclinical toxicokinetic, and carcinogenicity studies, submit data in the Standards for the Exchange of Nonclinical Data (SEND) format. The validation of sample submissions tests conformance to FDA supported electronic submission and data standards; there is no scientific review of content.

The Agency encourages submission of sample data for review before submission of the marketing application. These datasets will be reviewed only for conformance to standards, structure, and format. They will not be reviewed as a part of an application review. These datasets should represent datasets used for the Phase 3 trials. The FDA Study Data Technical Conformance Guide (Section 7.3 eCTD Sample Submission pg. 44) includes the link to the instructions for submitting eCTD and sample data to the Agency. The Agency strongly encourages Sponsors to submit standardized sample data using the standards listed in the Data Standards Catalog referenced on the FDA Study Data Standards Resources web site. When submitting sample data sets, clearly identify them as such with **SAMPLE STANDARDIZED DATASETS** on the cover letter of your submission.

Additional information can be found at FDA.gov.¹⁰

DISCUSSION OF SAFETY ANALYSIS STRATEGY FOR THE ISS

After initiation of all trials planned for the Phase 3 program, you should consider requesting a Type C meeting to gain agreement on the safety analysis strategy for the Integrated Summary of Safety (ISS) and related data requirements. Topics of discussion at this meeting would include pooling strategy (i.e., specific studies to be pooled and analytic methodology intended to manage between-study design

¹⁰ <https://www.fda.gov/industry/study-data-standards-resources/study-data-submission-cder-and-cber>

differences, if applicable), specific queries including use of specific standardized MedDRA queries (SMQs), and other important analyses intended to support safety. The meeting should be held after you have drafted an analytic plan for the ISS, and prior to programming work for pooled or other safety analyses planned for inclusion in the ISS. This meeting, if held, would precede the Pre-NDA meeting. Note that this meeting is optional; the issues can instead be addressed at the pre-NDA meeting.

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

- Description of all trials to be included in the ISS. Please provide a tabular listing of clinical trials including appropriate details.
- ISS statistical analysis plan, including proposed pooling strategy, rationale for inclusion or exclusion of trials from the pooled population(s), and planned analytic strategies to manage differences in trial designs (e.g., in length, randomization ratio imbalances, study populations, etc.).
- For a Phase 3 program that includes trial(s) with multiple periods (e.g., double-blind randomized period, long-term extension period, etc.), submit planned criteria for analyses across the program for determination of start / end of trial period (i.e., method of assignment of study events to a specific study period).
- Prioritized list of previously observed and anticipated safety issues to be evaluated, and planned analytic strategy including any SMQs, modifications to specific SMQs, or sponsor-created groupings of Preferred Terms. A rationale supporting any proposed modifications to an SMQ or sponsor-created groupings should be provided.

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

LABORATORY TEST UNITS FOR CLINICAL TRIALS

CDER strongly encourages IND sponsors to identify the laboratory test units that will be reported in clinical trials that support applications for investigational new drugs and product registration. Although Système International (SI) units may be the standard reporting mechanism globally, dual reporting of a reasonable subset of laboratory tests in U.S. conventional units and SI units might be necessary to minimize conversion needs during review. Identification of units to be used for laboratory tests in clinical trials and solicitation of input from the review divisions should occur as early as possible in the development process. For more information, please see the FDA website entitled Study Data Standards Resources¹¹.

¹¹ <http://www.fda.gov/ForIndustry/DataStandards/StudyDataStandards/default.htm>

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.¹²

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.¹³

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*.¹⁴

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)*.¹⁵ 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).¹⁶

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of

¹² <http://www.fda.gov/ectd>

¹³ <http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway>

¹⁴ 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>.

¹⁵ <https://www.fda.gov/media/72419/download>

¹⁶ <http://www.regulations.gov>

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)
<i>(1) Example: Published literature</i>	<i>Nonclinical toxicology</i>
<i>(2) Example: NDA XXXXXX "TRADENAME"</i>	<i>Previous finding of effectiveness for indication A</i>
<i>(3) Example: NDA YYYYYY "TRADENAME"</i>	<i>Previous finding of safety for Carcinogenicity, labeling section B</i>
<i>(4)</i>	

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*.¹⁷

NEW PROTOCOLS AND CHANGES TO PROTOCOLS

To ensure that the Division is aware of your continued drug development plans and to facilitate successful interactions with the Division, including provision of advice and timely responses to your questions, we request that the cover letter for all new Phase 2 or Phase 3 protocol submissions to your IND or changes to these protocols include the following information:

- (1) Study phase
- (2) Statement of whether the study is intended to support marketing and/or labeling changes
- (3) Study objectives (e.g., dose finding)
- (4) Population
- (5) A brief description of the study design (e.g., placebo or active controlled)
- (6) Specific concerns for which you anticipate the Division will have comments
- (7) For changes to protocols only, also include the following information:
 - A brief summary of the substantive change(s) to the protocol (e.g., changes to endpoint measures, dose, and/or population)
 - Other significant changes
 - Proposed implementation date

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

¹⁷ <https://www.fda.gov/media/85061/download>

UNITED STATES PATIENT POPULATION

FDA expects sponsors to enroll participants who are relevant to the planned use of the drug in the US population. Describe the steps you are taking to ensure that the clinical trial population will be relevant to the US patient population that will receive the drug. Include a discussion of participation of US vs. non-US sites and discuss whether the subjects likely to be enrolled will adequately represent the US patient population in terms of disease characteristics, sex, race/ethnicity, age, and standards of care. See 21 CFR 312.33(a)(2) and 21 CFR 314.50(d)(5)(v) and the guidance for industry *Collection of Race and Ethnicity Data in Clinical Trials* for more information.

We recommend you consider requesting a meeting to facilitate discussion of multiple and/or complex issues.

ISSUES REQUIRING FURTHER DISCUSSION

There were no issues requiring further discussion.

ATTACHMENTS AND HANDOUTS

There are no attachments or handouts for this meeting.

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/

KIMBERLY A COMPTON
08/02/2023 10:48:59 PM