CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

218590Orig1s000

OTHER REVIEW(S)

MEMORANDUM

HUMAN FACTORS STUDY RESULTS REVIEW MEMO

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

Date of This Memorandum:	August 5, 2024
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 218590
Product Name, Dosage Form, and Strength:	Zurnai[a] (nalmefene hydrochloride) injection, 1.5 mg
Applicant/Sponsor Name:	Purdue Pharma L.P. (Purdue Pharma)
TTT ID #:	2024-8303-1
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised instructions for use (IFU), container label and carton labeling received on July 25, 2024, and August 2, 2024 for Zurnai. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised IFU, container label and carton labeling for Zurnai (Appendix A) to determine if it is acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous human factors study results review.[b]

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

[a] The proposed proprietary name, Zurnai was found conditionally acceptable on April 15, 2024.

[b] Bhalodia, A. Human Factors Study Results Review for Zurnai (NDA 218590). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUL 23. TTT ID No.: 2024-8303.

APPENDIX A. IMAGES OF LABEL AND LABELING RECEIVED ON JULY 25, 2024, AND AUGUST 2, 2024

Instructions for Use (Image not shown) available from:
\\CDSESUB1\EVSPROD\nda218590\0019\m1\us\nda-218590-nalmefene-ifu-8-1-2024.pdf

Container label

Carton labeling

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/

AVANI BHALODIA
08/05/2024 11:24:09 AM

OLUWAMUREWA OGUNTIMEIN
08/05/2024 12:16:23 PM

HUMAN FACTORS STUDY REPORT REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 23, 2024
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 218590
Product Type:	Combination Product (Drug-Device)
Product Name, Dosage Form and Strength:	Zurnai[a] (nalmefene hydrochloride) Injection, 1.5 mg
Device Constituent:	Autoinjector
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Purdue Pharma L.P. (Purdue Pharma)
FDA Received Date:	February 7, 2024
TTT #:	2024-8303
DMEPA 1 Safety Evaluator:	Avani Bhalodia, PharmD, BCPS
DMEPA 1 Team Leader:	Murewa Oguntimein, PhD, MHS, CPH, MCHES
DMEPA 1 Deputy Director	Jason Flint, MBA, PMP

[a] The proposed proprietary name, Zurnai was found conditionally acceptable on April 15, 2024.

1 REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report submitted under NDA 218590 for Zurnai (nalmefene hydrochloride) Injection for the indication listed in table 2 below.

We considered the materials listed in Table 1 for this review.

Table 1. Materials Considered for this Review	
Material Reviewed	**Section/Appendix**
Product Information	Section 1.1
Background Information Previous DMEPA HF Reviews	Section 1.2
Human Factors (HF) Validation Study Report and HF-Related Supporting Documents	Appendix A
Information Requests Issued During the Review	Appendix B – N/A
Labels, Labeling, and Packaging	Appendix C
Detailed list of use errors, use difficulties, and close calls from section 3.1	Appendix D

N/A=not applicable for this review

1.1 PRODUCT INFORMATION

Table 2 presents relevant product information for Zurnai that Purdue Pharma L.P. submitted on February 7, 2024.

Table 2. Relevant Product Information for Zurnai	
Initial Approval Date	N/A
Active Ingredient	nalmefene hydrochloride
Indication	indicated for the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, (b) (4) (b) (4)
Route of Administration	intramuscular and subcutaneous
Dosage Form	injection
Strength	1.5 mg
Dose and Frequency	Initial Dosing: The recommended dose of Zurnai autoinjector (AI) in adults and pediatric patients aged 12 years and older is 1.5 mg delivered by

	intramuscular or subcutaneous injection into the anterolateral aspect of the thigh, through clothing if necessary. <u>Repeat Dosing:</u> Seek emergency medical assistance as soon as possible after administration of the first dose of Zurnai AI. The requirement for repeat doses of Zurnai AI depends upon the amount, type, and route of administration of the opioid being antagonized. If the patient responds to Zurnai AI and subsequently relapses back into respiratory depression before emergency assistance arrives, administer an additional dose of Zurnai AI using a new AI and continue surveillance of the patient. If the desired response is not obtained after 2 to 5 minutes, administer an additional dose of Zurnai AI using a new AI. If there is still no response and additional doses are available, administer additional doses of Zurnai AI every 2 to 5 minutes using a new Zurnai AI with each dose until emergency medical assistance arrives. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.
How Supplied	Each single-dose AI device delivers 1.5 mg of nalmefene in 0.5 mL. Each carton contains one single-dose Zurnai AI.
Storage	Store at controlled room temperature 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F). Do not freeze or refrigerate. Store in a clean dry place. Protect from light.
Container Closure/ Device Constituent (including figure)	Autoinjector  (b) (4)
Intended Users	Lay adults, lay adolescents, and first responders
Intended Use Environment	a variety of non-clinical environments, including public areas and home environments

1.2 RELEVANT REGULATORY HISTORY RELATED TO THE PROPOSED PRODUCT'S HUMAN FACTORS DEVELOPMENT PROGRAM

On March 1, 2024, we searched for previous DMEPA reviews and FDA/Applicant interactions relevant to this current review using the terms, "*IND 137597", "NDA 218590" and "nalmefene*". The identified reviews and FDA/Applicant interactions are provided below.

- On June 19, 2018, Purdue Pharma had a Type B Pre-IND meeting with the Agency to discuss the development plan of nalmefene hydrochloride auto-injector for a 505(b)(2) application. DMEPA provided general human factors (HF) comments recommending that Purdue Pharma conduct a comprehensive use-related risk analysis to determine if they need to perform a HF validation study. Additionally, we stated that the above information can be used to inform the design of a HF validation study protocol for their product. We recommended they submit their study protocol for feedback from the Agency before commencing their study.[b]
- On January 13, 2022, Purdue Pharma submitted a HF validation study protocol under IND 137597 for Nalmefene hydrochloride AI. We reviewed the protocol and provided recommendations.[c]
- On February 07, 2023 and March 20, 2023 respectively, Purdue Pharma submitted the following:
    - A revised HF validation study protocol under IND 137597 for Nalmefene hydrochloride AI.
    - Response to each recommendation provided in the March 14, 2022, Human Factors Validation Study Protocol Advice letter in tabular format.
    - A red-lined, annotated version of the revised HF protocol, Use-Failure Mode and Effect Analysis (uFMEA), and instructions for use (IFU), that identifies any changes made after the March 14, 2022, HF Advice letter.
    - An annotated version of container label, and carton labeling that identifies any changes made.
    - Purdue Pharma indicated that they started the study, after implementing our recommendations.
- Based on Purdue Pharma's aforementioned information, we determined that further review of the revised HF validation study protocol and responses to each recommendation is not necessary.[d]
- On September 22, 2023, Purdue Pharma submitted HF validation study results under IND 137597 for nalmefene hydrochloride AI, 1.5 mg. We informed Purdue Pharma that the submission of the HF validation report as part of the IND submission is not the

[b] Meyer A. Type B Meeting Minute for Nalmefene hydrochloride (IND 137597). Silver Spring (MD): FDA, CDER, OND, DAAP; 2018 JUL 19. Available at: https://darrts.fda.gov/darrts/faces/ViewDocument?documentId=090140af804a8aeb

[c] Oguntimein, M. Human Factors Protocol Review for Nalmefene hydrochloride (IND 137597). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2022 MAR 09. RCM No.: 2022-107.

[d] Oguntimein, M. Response to Human Factors Advice Letter Memorandum for Nalmefene hydrochloride (IND 137597). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 APR 19. TTT ID #: 2023-3748.

appropriate mechanism for Agency's review. Additionally, we informed Purdue Pharma to submit the HF validation report as part of the submission of the marketing application.[e]

- On February 7, 2024, Purdue Pharma submitted a new drug application (NDA) for Zurnai (nalmefene hydrochloride) injection under NDA 218590. This submission included an HF validation study results report, which is the subject of this review.

2 OVERALL ASSESSMENT OF HUMAN FACTORS STUDY DESIGN AND METHODOLOGY

This section provides a summary of the study design, and our evaluation of the study methodology to determine if the user interface has been appropriately designed to support the safe and effective use of the proposed product.

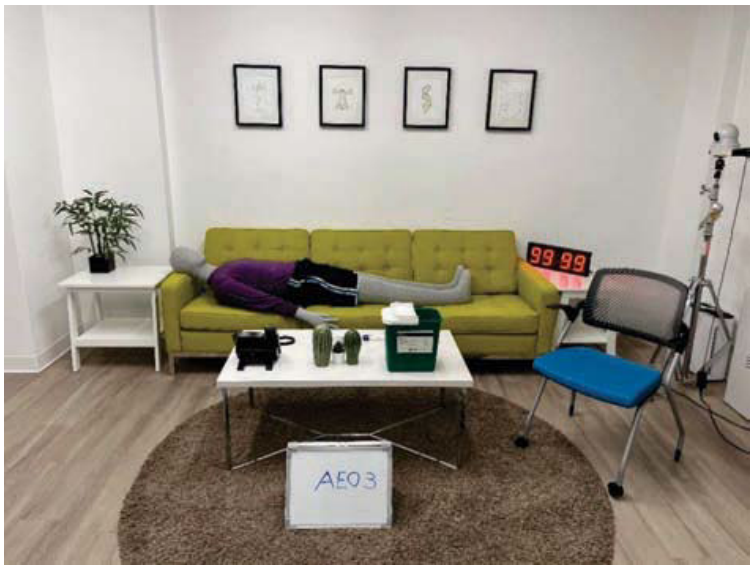
2.1 SUMMARY OF STUDY DESIGN

Table 3 presents a summary of the HF validation study (HFVS) design and our discussion of methodology concerns (as applicable). See Appendix A for more details on the study design.

Table 3. Study Methodology for Human Factors (HF) Validation Study

Study Design Elements Proposed	Sponsor Provided Methodology Deviation	DMEPA Discussion of Methodology Concerns
User Group(s) 15 First responders 15 Injection experience lay adults 15 Injection naive lay adults 15 Injection experience lay adolescents (ages 10–17) 15 Injection naive lay adolescents (ages 10–17)	N/A	N/A
Training No training was provided to the participants.	N/A	N/A
Test Environment & Materials The study environment simulated the intended home environment. All participants completed the simulated-use scenario in an emergency home environment in well-lit room containing a manikin experiencing a simulated drug overdose, the system user interface (i.e., the autoinjector, packaging, and IFU), large digital clock, and distractions. The overdosing patient was simulated with an injectable adult manikin. To create an emergency situation, the manikin was placed supine on the couch in the environment. An audio and visual distraction of a TV playing the in background was provided. To increase the stress and urgency of the situation, a large digital clock was placed in the room to provide feedback about the duration of the task.	N/A	N/A

[e] Huang, L. Human Factors Advice Letter Memorandum for Nalmefene hydrochloride (IND 137597). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 NOV 03. TTT ID #: 2023-6505.

The emergency environment testing room setup is shown in Figures below.  		
Sequence of Study 1. Simulated use testing 2. Subjective data and Root cause analysis 3. Knowledge tasks questions *4.* Subjective data and Root cause analysis	N/A	N/A

3 RESULTS AND ANALYSIS

In this section, we have carefully reviewed each reported issue (i.e., use error, close call, use difficulty), the Applicant's URRA, the participants' subjective feedback, the Applicant's RCA, and the Applicant's comments and proposed mitigations (if applicable) to determine if the results

indicate that the user interface has been appropriately designed to support the safe and effective use of the proposed product.

We provide a discussion of the identified use tasks and knowledge task assessment, where we agree with the Applicant's conclusions and have no further recommendation or comment, in Appendix D.

In Table 4 below, we provide a summary of the use-related events supplied by the Applicant along with our detailed analysis of use-related events that resulted in recommendations and document our points of dissent with the Applicant's findings.

Table 4. Detailed Analysis of Use Related Events and DMEPA's Recommendations	
Legend: **UE** = use error; **CC** = close call; **UD** = use difficulty; **URRA** = use-related risk analysis; **RCA** = root cause analysis; **HFVS** = Human Factors Validation Study **Participants ID: FR** = First responders; **PE** = Injection experience lay adults; **PN** = Injection naive lay adults; **AE** = Injection experience lay adolescents; **AN** = Injection naive lay adolescents	
Summary of Information Supplied by Applicant	**DMEPA's Identified Areas of Dissent and Recommendations**
Task: Check the Person Reported Issues: UE (n=40) Participant Type(s): AE = 11, AN = 12, FR = 1, PE = 7, PN = 9	
Observed event(s): • Participants did not check the person for signs of a suspected overdose.	
Risk associated with errors associated with this task: • Nalmefene injected in person other than patient.	The URRA is incomplete because the Applicant did not include the clinical impact of the individual with opioid overdose not receiving the product.
Relevant RCA/Subjective Feedback: • Participants assumed the injection was priority over inspections steps due to the emergency situation. • Test artifact - participants did not check the person for signs of a suspected overdose due to the simulated nature of the study.	
Applicant's Comments and Proposed Post- HFVS Mitigations: None	We note that the moderator's guide included statements that may have confused participants to give the injection without checking the person. For example, • "*If you have any questions during the session, I'd like you to try and do your best and complete the task as best as you can, as if you were actually at home or in a public place and had to use this product on someone who appears to be unconscious from an opioid overdose*." • "*The manikin is injectable, please give the injection as you would give it to the person who is unconscious*." • "*I would like you to imagine that you are at home or at the park, and you see a person (the manikin) exhibiting the symptoms of an opioid overdose. Please do whatever you would do in real life in this situation*." It appears that the abovementioned statements may have caused the participants to give the injection without checking the person and it does not seem reflective of actual use. However, it is reasonable to assume that as an initial step in determining whether nalmefene needs to be delivered, a user would make this assessment in actual use. Based on our review of the user interface, we note that the IFU states: Check Person for Signs of a Suspected Overdose: • Will not wake to voice or touch • Very sleepy • Not breathing well However, we note, that the carton labeling does not include instructions to check person for signs of a suspected overdose. We find that the carton labeling can be improved to include instructions to check person for signs of a suspected overdose. We provide recommendation in Table A to address this concern. We have determined that this change can be

<table>
<tr><td></td><td>implemented without submitting additional HF testing data for Agency review.</td></tr>
<tr><td>Task: Remove Cap<table><tr><th>Reported Issues:</th><th>Participant Type(s):</th></tr><tr><td>UD (n=15)</td><td>AE = 4, AN = 6, PE = 2, PN = 3</td></tr></table></td><td></td></tr>
<tr><td>Observed event(s):
• Participants had difficulty removing the cap initially.</td><td></td></tr>
<tr><td>Risk associated with errors associated with this task:
• No therapeutic dose delivered (failure to deliver drug)</td><td>The URRA is incomplete because the Applicant did not include the clinical impact of the individual with opioid overdose not receiving the product.</td></tr>
<tr><td>Relevant RCA/Subjective Feedback:
• Participants underestimated the force required to remove cap.
• Participants used their previous experience of previous cap removal from other devices that only required the cap to be pulled straight off.</td><td></td></tr>
<tr><td>Applicant's Comments and Proposed Post- HFVS Mitigations: None</td><td>The Applicant stated that, "All participants were able to successfully remove the cap in the end without abandoning the task or moderator assistance." We reached out to Center for Devices and Radiologic Health (CDRH) colleagues to discuss the cap removal force specifications. CDRH indicated concerns with the cap removal force for this autoinjector (i.e., cap removal torque was significantly different between devices produced from different injection (b) (4)) CDRH will request a postmarketing commitment (PMC) be issued recommending the Applicant provide test results for additional devices with the data separated by injection (b) (4).

We find that the term "Twist" on the cap on container label can be improved to be more prominent. We provide recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.</td></tr>
<tr><td>Task: Disposal<table><tr><th>Reported Issues:</th><th>Participant Type(s):</th></tr><tr><td>UE (n=36)</td><td>AE = 6, AN = 8, FR = 6, PE = 7, PN = 9</td></tr></table></td><td></td></tr>
<tr><td>Observed event(s):
• Participants did not dispose of the autoinjector after the injection was complete.</td><td></td></tr>
<tr><td>Risk associated with errors associated with this task:
• Needlestick (cut, scrape, laceration)
• Sharps injury resulting in blood-borne pathogen (from person-to-person sharps contamination)
• No therapeutic dose delivered (failure to deliver drug)</td><td>The URRA is incomplete because the Applicant did not include the clinical impact of the individual with opioid overdose not receiving the product.</td></tr>
<tr><td>Relevant RCA/Subjective Feedback:
• Participants held onto the autoinjector believing it can be reused.
• Participants prioritized the emergency situation, the person themselves, or calling 911.
• Test Artifact – participants did not dispose of the autoinjector because they thought they didn't need to complete the disposal step and they were not sure if the sharps container was part of the study.</td><td></td></tr>
</table>

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<tr><td>

- Participants held onto the autoinjector because they believed it was beneficial to show EMS.

</td><td></td></tr>
<tr><td>Applicant's Comments and Proposed Post- HFVS Mitigations: None</td><td>Based on the subjective feedback (participants thought the device could be reused), and our overall assessment, we find that the IFU disposal instructions can be improved to be more prominent. We provide recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.</td></tr>
<tr><td>Knowledge task: How should you store the device before use? [Answer: At room temperature between 59°F to 77°F (15°C to 25°C), do not freeze or refrigerate, protected from light, store in a clean dry place, out of the reach of children.]
<table>
<tr><td>Reported Issues:</td><td>Participant Type(s):</td></tr>
<tr><td>Incorrect (n=59)</td><td>AE = 14, AN = 11, FR = 12, PE = 13, PN = 9</td></tr>
</table>
</td><td></td></tr>
<tr><td>Observed event(s):

- Participants did not state all of the above answers.

</td><td></td></tr>
<tr><td>Risk associated with errors associated with this task:

- Reduced drug efficacy (intended drug potency not met)
- Drug degradation
- No therapeutic dose delivered (failure to deliver drug)

</td><td>The URRA is incomplete because the Applicant did not include the clinical impact of the individual with opioid overdose not receiving the product.</td></tr>
<tr><td>Relevant RCA/Subjective Feedback:

- Participants assumed that the full storage instructions would be located in another section of the instructions for use (IFU).
- Participant assumed storage instructions were common sense answers and did not need to be verbalized.
- Participants answered incorrectly due to their mindset thinking about their current storage process at home or work of medication.
- Participants expected to find all the storage instructions on the box.

</td><td></td></tr>
<tr><td>Applicant's Comments and Proposed Post- HFVS Mitigations:
The Applicant updated carton labeling to add the storage information "Store TRADENAME in a clean dry place".</td><td>Based on the subjective feedback (participants assumed that the full storage instructions would be located in another section of the IFU), and our overall assessment, we find that the IFU storage instructions can be improved to be more prominent. We provide recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.</td></tr>
<tr><td>Knowledge task: What should you periodically check on the Auto-Injector during storage prior to use? [Answer: If the solution is discolored, cloudy, contains particles, device is damaged, expired, safety seal is broken, cap is missing or not secure]
<table>
<tr><td>Reported Issues:</td><td>Participant Type(s):</td></tr>
<tr><td>Incorrect (n=54)</td><td>AE = 13, AN = 13, FR = 7, PE = 10, PN = 11</td></tr>
</table>
</td><td></td></tr>
<tr><td>Observed event(s):

- Participants did not state all of the above answers.

</td><td></td></tr>
<tr><td>Risk associated with errors associated with this task:

- Reduced drug efficacy (intended drug potency not met)
- No therapeutic dose delivered (failure to deliver drug)

</td><td>The URRA is incomplete because the Applicant did not include the clinical impact of the individual with opioid overdose not receiving the product.</td></tr>
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- Drug degradation
- Local infection

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Relevant RCA/Subjective Feedback:

- Participants assumed that the inspection steps would be located elsewhere in the IFU. Specifically, the participant expected steps to check safety seal is broken and cap is missing or not secure would be located in the "*Preparing to Inject TRADENAME*" section instead of (b) (4) section of the IFU. One participant thought the injection steps would have all the inspections there as well.
- Participants were only looking at the prescribing information (PI) side.
- Participants were thinking about their current inspection process at home or work.
- Participants assumed the autoinjector would not be damaged.

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Applicant's Comments and Proposed Post- HFVS Mitigations: None

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Based on the subjective feedback (participants expected to have all the inspection steps in the preparing to inject section and participants were only looking at the PI), and our overall assessment, we find that the IFU preparing to inject section can be improved to include all inspection steps. Additionally, we note that the IFU and the IFU title/header can be improved to be more prominent; currently the carton includes one document that has the PI on one side and the IFU and patient medication information on the other side. We provide recommendations in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.

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Knowledge task: How do you know when treatment with TRADENAME may be necessary? [Answer: For suspected overdose; person will not wake to voice or touch, is very sleepy, or not breathing well]

<table>
<tr><th>Reported Issues:</th><th>Participant Type(s):</th></tr>
<tr><td>Incorrect (n=9)</td><td>AE = 3, AN = 3, FR = 1, PN = 2</td></tr>
</table>

</td><td></td></tr>
<tr><td>

Observed event(s):

- Participants did not state for suspected overdose.

</td><td></td></tr>
<tr><td>

Risk associated with errors associated with this task:

- Nalmefene injected in person other than patient.
- No therapeutic dose delivered (failure to deliver drug).

</td><td>

The URRA is incomplete because the Applicant did not include the clinical impact of the individual with opioid overdose not receiving the product.

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Relevant RCA/Subjective Feedback:

- Participants assumed they would find/locate the information elsewhere. One participant focused on the PI side for answers. One participant expected to find the answer on the box.
- Negative transfer – participants applied knowledge from another injection device.

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<tr><td>

Applicant's Comments and Proposed Post- HFVS Mitigations: None

</td><td>

Based on the subjective feedback (one participant focused on the PI for answers and one participant expected to find the answer on the box), and our overall assessment, we note that the IFU and the IFU title/header can be improved to be more prominent; currently the carton includes one document that has the PI on one side and the IFU and patient medication information on the other side. Additionally, we find the carton labeling can

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<table>
<tr><td></td><td>be improved to refer users to the IFU. We provide recommendations in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.</td></tr>
<tr><td>Knowledge task: What should you do before using the autoinjector? [Answer: Check the medication label. Check that the expiration date has not passed, check for visible damage. Check the liquid through the viewing window.]<table><tr><td>Reported Issues:</td><td>Participant Type(s):</td></tr><tr><td>Incorrect (n=53)</td><td>AE = 10, AN = 13, FR = 10, PE = 10, PN = 10</td></tr></table></td><td></td></tr>
<tr><td>Observed event(s):
Participants did not state all of the above answers.</td><td></td></tr>
<tr><td>Risk associated with errors associated with this task:
Reduced drug efficacy (intended drug potency not met)
No therapeutic dose delivered (failure to deliver drug)
Drug degradation
Local infection</td><td>The URRA is incomplete because the Applicant did not include the clinical impact of the individual with opioid overdose not receiving the product.</td></tr>
<tr><td>Relevant RCA/Subjective Feedback:
Participants expected to find/locate information elsewhere. Further, some participants stated that they assumed that some of the instructions that were outside of the inspection step bubbles were unimportant and therefore they did not read them. One participant was focused on the box instructions because they thought the paper instructions would only have specific instructions.
Participants thought their answer was encompassing.
Participants misunderstood the question.</td><td></td></tr>
<tr><td>Applicant’s Comments and Proposed Post- HFVS Mitigations: None</td><td>Based on the subjective feedback (participants thought inspection steps outside the bubble were unimportant, and one participant was focused on the box instructions), and our overall assessment, we find that the IFU “Preparing to Inject TRADENAME” section can be improved to be more prominent. Additionally, we find the carton labeling can be improved to refer users to the IFU. We provide recommendations in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.</td></tr>
<tr><td>Knowledge task: What should you do following giving the injection? [Answer: Call 911 and stay with the person.]<table><tr><td>Reported Issues:</td><td>Participant Type(s):</td></tr><tr><td>Incorrect (n=14)</td><td>AE = 4, AN = 6, PE = 2, PN = 2</td></tr></table></td><td></td></tr>
<tr><td>Observed event(s):
Participants did not mention calling 911.
Participants did not mention to stay with the person.</td><td></td></tr>
<tr><td>Risk associated with errors associated with this task:
Partial dose delivery (inadequate reversal of symptoms)</td><td></td></tr>
<tr><td>Relevant RCA/Subjective Feedback:
Participant could not find the answer because they were focusing on the PI side and thought all the information would be there.</td><td></td></tr>
</table>

• Test Artifact - participant did not think this scenario was a real emergency. • Participants misunderstood the question.	
Applicant's Comments and Proposed Post- HFVS Mitigations: None	Based on the subjective feedback (one participant could not find the answer because they were focusing on the PI side), and our overall assessment, we note that the IFU and the IFU title/header can be improved to be more prominent; currently the carton includes one document that has the PI on one side and the IFU and patient medication information are on the other side. We provide recommendation in Table A to address this concern. We have determined that this change can be implemented without submitting additional HF testing data for Agency review.

3.1 ANALYSIS OF OTHER CRITICAL AND NON-CRITICAL TASK ERRORS

The HF validation study report showed issues with the tasks evaluated by simulated use and knowledge-based assessments listed in Appendix D. However, based on our review of the available assessment of these identified issues, the available participants' subjective feedback (including when participants' subjective feedback did not indicate any potential issue with the user interface), the Applicant's root cause analysis, the Applicant's post HF validation study mitigations and our evaluation of the residual risks, we have no additional recommendations to address the identified issues with the tasks in Appendix D.

4 LABELS AND LABELING

Tables A below include the identified medication error issues with the submitted label and labeling, our rationale for concern, and our proposed recommendations to minimize the risk for medication error.

We note that the DMEPA 1 nomenclature and labeling review team evaluated product specific label and labeling under separate cover.[f]

Table A. Identified Issues and Recommendations for Purdue Pharma L.P. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Instructions for use (IFU)			
1.	The IFU disposal instructions lacks prominence as presented.	Per the use-related risk analysis (URRA), if the user does not dispose the product, there is risk of needlestick (cut, scrape, laceration), harps injury resulting in blood-borne pathogen (from person-to-person sharps contamination), and no therapeutic dose delivered (failure to deliver drug). The human factors (HF) validation study results identified subjective feedback that indicated	Revise the IFU disposal instructions to increase prominence. For example, consider making it step 5.

[f] Getahun, S. Label and Labeling Review for Zurnai (nalmefene hydrochloride) injection (NDA 218590). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 07. TTT No.: 2024-8241.

Table A. Identified Issues and Recommendations for Purdue Pharma L.P. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		that the participants thought the device could be reused.	
2.	Storage instructions lacks prominence as presented.	Per the URRA, if the user does not store the device appropriately before use, there is risk of reduced drug efficacy (intended drug potency not met), drug degradation, and no therapeutic dose delivered (failure to deliver drug). The HF validation study identified subjective feedback that indicated that participants assumed that the full storage instructions would be located in another section of the IFU.	Revise IFU storage information to increase prominence by separating the information from disposal instructions section.
3.	Instruction to check for safety seal is missing under "*Preparing to Inject TRADENAME*" section.	Per the URRA, if the user does not periodically check on the Auto-Injector during storage prior to use, there is risk of reduced drug efficacy (intended drug potency not met), no therapeutic dose delivered (failure to deliver drug), drug degradation, and local infection. The HF validation study identified subjective feedback that indicated that participants expected to have all the inspection steps in the preparing to inject section.	Revise IFU to include instructions to check the safety seal to make sure it is not broken, cap is secure and not missing under "*Preparing to Inject TRADENAME*" section.

Table A. Identified Issues and Recommendations for Purdue Pharma L.P. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
4.	The IFU and the IFU title/header lacks prominence as presented.	Per the URRA, if the user does not periodically check on the Auto-Injector during storage prior to use, there is risk of reduced drug efficacy (intended drug potency not met), no therapeutic dose delivered (failure to deliver drug), drug degradation, and local infection. The HF validation study identified subjective feedback that indicated that participants were only looking at the prescribing information (PI) side for answers. We note currently the carton includes one document that has the PI on one side and the IFU and patient medication information on the other side.	Revise the IFU to increase prominence. For example, consider making the IFU a separate document. Additionally, revise the IFU title/header to increase prominence.
		Per the URRA, if the user does not know when treatment with TRADENAME may be necessary, there is risk of nalmefene injected in person other than patient and no therapeutic dose delivered (failure to deliver drug). The HF validation study identified subjective feedback that indicated that a participant focused	

Table A. Identified Issues and Recommendations for Purdue Pharma L.P. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		on the PI side for answers. We note currently the carton includes one document that has the PI on one side and the IFU and patient medication information on the other side.	
		Per the URRA, if the user does not call 911 or stay with the person following giving the injection, there is risk of partial dose delivery (inadequate reversal of symptoms). The HF validation study identified subjective feedback that indicated that one participant could not find the answer because they were focusing on the PI side. We note currently the carton includes one document that has the PI on one side and the IFU and patient medication information on the other side.	
5.	As currently presented, the layout for the instruction titled, "*Preparing to Inject TRADENAME*" appears cluttered.	Per the URRA, if the user does not know what to do before using the autoinjector, there is risk of reduced drug efficacy (intended drug potency not met), no therapeutic dose delivered (failure to deliver drug), drug degradation, and local infection.	We recommend revising the information under "*preparing to inject TRADENAME*" section to increase prominence. For example, add space between statements or utilize bullet points.

Table A. Identified Issues and Recommendations for Purdue Pharma L.P. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	**RATIONALE FOR CONCERN**	**RECOMMENDATION**
		The HF validation study identified subjective feedback that indicated that participants thought inspection steps outside the bubble were unimportant.	
Carton Labeling			
1.	The carton labeling does not include instructions to check person for signs of a suspected overdose.	In the HF validation study, we note that the participants did not check the person before giving the injection. Although we acknowledge that some of these errors were attributed to test artifact, we note that this is a critical step in the administration of nalmefene.	Revise carton labeling to include instructions to check person for signs of a suspected overdose (as the first step), which includes what signs to look for.
2.	The carton labeling does not instruct the user to refer to IFU. (b) (4)	Per the URRA, if the user does not know when treatment with TRADENAME may be necessary, there is risk of nalmefene injected in person other than patient and no therapeutic dose delivered (failure to deliver drug). Per the URRA, if the user does not know what to do before using the autoinjector, there is risk of reduced drug efficacy (intended drug potency not met), no therapeutic dose delivered (failure to deliver drug), drug degradation, and local infection.	Revise the carton labeling to include the statement, "*Refer to Instructions for Use for additional administration details*." above the phrase "*use instructions*" and the corresponding graphics. (b) (4)

Table A. Identified Issues and Recommendations for Purdue Pharma L.P. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		The HF validation study identified subjective feedback that indicated that one participant expected to find answer on box. Another participant was focused on the box instructions.	
Container Label			
1.	The term "Twist" on the cap lacks prominence.	We note that several participants had difficulty in removing the cap. Some of these participants used their previous experience with other devices and attempted to 'pull' the cap straight off, rather than twist the cap initially. Per the URRA, if the user does not remove the cap, there is risk of no therapeutic dose delivered (failure to deliver drug). In this instance, such an error could be clinically significant and life-threatening.	Revise the container label to increase prominence of the term "Twist" on the cap. For example, you may consider some or all of the below options • Highlight term "Twist" in a different color • Include term "twist" on the other three sides of the cap (without the seal) • Revise the phrase to (b) (4) "Twist then pull"

5 CONCLUSION AND RECOMMENDATIONS

The results of the HF validation study demonstrated several use errors, close calls, use difficulties with critical tasks that may result in harm. Based on our review of the available participants' subjective feedback, and root cause analysis, we identified additional risk mitigations to address the use errors. Above, we have provided recommendations in Table A for the Applicant. We ask that the Division convey Table A in its entirety to the Applicant so that recommendations are implemented for this NDA 218590. These changes can be implemented without submitting additional HF validation testing results for Agency review.

5.1 RECOMMENDATIONS FOR PURDUE PHARMA L.P.

Our evaluation of your human factors (HF) validation study for your proposed nalmefene hydrochloride 1.5 mg autoinjector user interface indicates that there are additional mitigations that can be implemented to address use errors that occurred with critical tasks. We provide recommendations in Table A, and we recommend that you implement these recommendations and submit the revised label and labeling for our review prior to the approval of this new drug application. We have determined that in this instance, you may implement these revisions without submitting additional human factors validation testing data for Agency review.

APPENDICES:

APPENDIX A. HUMAN FACTORS (HF) VALIDATION STUDY REPORT AND HF-RELATED SUPPORTING DOCUMENTS

- The HF study results report and background information can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda218590\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-opioid-overdose\5354-other-stud-rep\pd-rpt-0647\pd-rpt-0647-rev-001(b) (4)-sum-human-factors-valid-study-report.pdf
  \\CDSESUB1\EVSPROD\nda218590\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-opioid-overdose\5354-other-stud-rep\pd-rpt-0689\pd-rpt-0689-human-factors-summary-report-v2.pdf
  \\CDSESUB1\EVSPROD\nda218590\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-opioid-overdose\5354-other-stud-rep\pd-rpt-0689\justification-label-changes-post-human-factors.pdf
- The use failure modes and effects analysis can be accessed in EDR via: \\CDSESUB1\EVSPROD\nda218590\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\treatment-of-opioid-overdose\5354-other-stud-rep\qa-rsk-0042\qa-rsk-0042-rev-004-use-fmea-for(b) (4)-2.pdf

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

N/A

APPENDIX C. LABELS AND LABELING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[g] along with postmarket medication error experiences with similar products, we reviewed the following Zurnai labels and labeling submitted by Purdue Pharma L.P. received on February 7, 2024.

- Container label
- Carton labeling
- Prescribing Information and Instructions for Use (Image not shown), available from \\CDSESUB1\EVSPROD\nda218590\0001\m1\us\draft-label-text-pdf.pdf

[g] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX D. DETAILED LIST OF USE ERRORS, USE DIFFICULTIES, AND CLOSE CALLS FROM SECTION 3.1

- Inspect Device
- Position Device – there were 3 use errors observed for this task. The root cause analysis indicated that participants selected incorrect injection site due to the urgency of the situation causing them to focus more on delivering the medication and misreading outer thigh as upper thigh. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
- Inject Drug – there were 2 use errors observed for this task. The root cause analysis indicated that participants inserted the device due to their belief that the hard end of the device was the needle side. Upon moderator discussion due to safety concerns, the participant was able to correct due to realizing there was no needle on the hard end. Ultimately, the participant was able to self-correct without moderator assistance or guidance. We note the needle end is labeled on the device labeling. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
- Complete Injection Confirmation – there were 2 use errors observed for this task. The root cause analysis indicated that these use errors were due to participants not fully reading instructions and being confused about the meaning of the window. The Applicant indicated that despite not confirming the injection was complete, these participants held the device down long enough to deliver a full dose of medication. Based on our review of the user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.
- Remove Device (do not replace the cap after the injection)
- Call 911

Knowledge task questions

- Once removed, when can you recap the device? Answer: Never recap the device after the cap has been removed
- How can you tell if the liquid inside the auto-injector is okay to use? Answer: The medication should be clear to light yellow and free of particles
- What does it mean if drops of liquid appear on the needle end after removing the cap? Answer: This is normal
- What should you do if the viewing window is not fully blocked/orange after injecting? Answer: Use a new Auto-Injector. – there were 22 incorrect answers with this task. The root cause analysis indicated that these use errors were due to participants were thinking back to the emergency simulated use scenario that entailed a situation where only one autoinjector was available to use for injection, were expecting to find the information elsewhere and test artifact (unclear question). Based on our review of the

user interface, we did not identify any additional mitigations to address these use errors and have no recommendations at this time.

- Where should you dispose of the Auto-injector? Answer: In an FDA-cleared sharps disposal container. If you do not have an FDA-cleared sharps container you may use a household container that is made of a heavy-duty plastic, can be closed with a tight-fitting, puncture-resistant lid, without sharps being able to come out, upright and stable during use, leak resistant, and properly labeled to warn of hazardous waste inside the container.

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/

AVANI BHALODIA
07/23/2024 12:45:04 PM

OLUWAMUREWA OGUNTIMEIN
07/23/2024 12:50:25 PM

JASON A FLINT
07/23/2024 02:35:25 PM

OFFICE OF PRODUCT EVALUATION AND QUALITY
OFFICE OF HEALTH TECHNOLOGY 3

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS

INTERCENTER CONSULT MEMORANDUM

Date	7/17/2024		
To:	Sandy Truong		
Requesting Center/Office:	CDER/OPQ	**Clinical Review Division:**	Other
From	Michael Lancina OPEQ/OHT3/DHT3C		
Through (Division) ***Optional**	Shruti Mistry, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA 218590 , Nalmefene ICC2400130 ICCR00972667		
Recommendation	**Filing Recommendation Date: 3/14/2024** ☐ CDRH did not provide a Filing Recommendation ☑ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies		
	Mid-Cycle Recommendation Date: 5/8/2024 ☑ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☐ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A.		
	Final Recommendation Date: 7/17/2024 ☐ Device Constituent Parts of the Combination Product are Approvable. ☑ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (*Optional)
Michael G. Lancina -S Digitally signed by Michael G. Lancina -S Date: 2024.07.17 16:30:51 -04'00'	Shruti N. Mistry -S	2024.07.17 16:40:33 -04'00'

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA 218590
Sponsor	Purdue Pharma
Drug/Biologic	Nalmefene
Indications for Use	For the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older. (b) (4) (b) (4)
Device Constituent	Auto-Injector
Related Files	MAF (b) (4) -A003

Review Team		
Lead Device Reviewer	*Michael Lancina*	
Discipline Specific Consults	**Reviewer Name (Center/Office/Division/Branch)**	**CON #**

Important Dates	
Discipline-Specific Review Memos Due	
Final Lead Device Review Memo Due	
Interim Due Dates	**Meeting/Due Date**
Filing	3/14/2024
74-Day Letter	
Mid-Cycle	5/8/2024
Primary Review	7/17/2024
Internal Meeting(s)	
Sponsor Meeting(s)	

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

☐ Approvable – the device constituent of the combination product is approvable for the proposed indication.

☑ Approvable with PMC or PMR, See Section 2.3

☐ Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, see Section 2.2.

Section	Adequate			Reviewer Notes
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis	X			
Design Verification	X			Design verification is extensively documented. Cap removal torque reliability data indicates that the manufacturing process for this device component is poorly controlled, although all samples tested are well within the specification.
Consultant Discipline Reviews			X	No consults issued.
Clinical Validation			X	Deferred to CDER
Human Factors Validation			X	Deferred to CDER/DMEPA
Facilities & Quality Systems	X			

2.1. Comments to the Review Team

☐ CDRH does not have any further comments to convey to the review team.

☑ CDRH has the following comments to convey to the review team:

Comment #1: Reliability testing data indicates that cap removal torque is significantly different between [redacted] (b) (4) [redacted] (b) (4). Because pooling data from different [redacted] (b) (4) produces non-normal distributions, tolerance intervals cannot be computed using routine statistical analysis from pooled samples. The sponsor has segregated data by [redacted] (b) (4) for analysis to demonstrate reliability. For cap removal torque, the control strategy [redacted] (b) (4) [redacted]. This testing data should also be analyzed per [redacted] (b) (4) to ensure that the reliability specification for this EPR is maintained.

2.2. Complete Response Deficiencies

☑ There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.

☐ The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☑

CDRH does not have Post-Market Commitments or Requirements	☐

Post-Market Commitment or Requirement:

Stability testing documents indicate that the 24 month real-time aging study should have been completed on July 5, 2024. Provide completed test reports for device EPRs for review by October 5, 2024. Please analyze cap removal torque test results (b) (4).

TABLE OF CONTENTS

3. PURPOSE/BACKGROUND

3.1. Scope

Purdue Pharma is requesting approval of Nalmefene. The device constituent of the combination product is an Auto-Injector.

CDER/OPQ has requested the following consult for review of the device constituent of the combination product:

Please assign a reviewer to this NDA application. CDRH was involved in the IND 137597

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following review areas:

Device design, device design verification, device design control strategy.

This review will not cover the following review areas:

All other areas, including human factors validation.

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

The subject device, (b) (4) autoinjector, is already used with at least one other combination product, (b) (4) . It is not clear if CDRH was consulted on the original submission, but a supplement to the NDA involving a change in device control strategy was reviewed in (b) (4). CDRH recommended that this supplement was approvable on (b) (4). Device EPRs listed in the memo for (b) (4) are similar to device EPRs for this submission but slightly different. (b) (4) **is not an emergency lay user application.**

There have been multiple type C meeting requests related to the reliability testing plan for the subject NDA. CDRH feedback was provided to the sponsor in ICC2300789 (Jan 5th, 2024), ICC2200285 (May 23rd, 2023), and ICC2200094 (Mar 24th. 2022).

Apparent updates after most recent feedback (ICC2200094) Reviewer notes based on review of the documentation provided with this NDA are shown in red.

Your device is an autoinjector (AI) assembled around a prefilled syringe (PFS) to create the final finished combination product. The PFS Essential Performance Requirements (EPRs) such as Break Loose and Glide Force influence the delivery of Nalmefene and should be considered in your reliability and performance testing protocols.

• While the adequacy of the specifications for the identified EPRs is a review issue, it is noted that the Activation Force of the proposed AI is (b) (4). This appears to be high for activation of an autoinjector. You may consider narrowing the specification based on the data obtained from performance testing. This would ensure that the Activation Force is consistent between devices and can be activated easily by intended users.

(b) (4) remains the activation force specification. Devices evaluated in the reliability testing showed an average activation force of about (b) (4). A justification for the activation force is provided in 3.2.P.5.6. A study conducted by British equivalent of the CPSC is cited for both the activation force and cap removal torque specifications. (Government Consumer Safety Research. “Strength Data for Design Safety.” Department of Trade and Industry. Oct 2000.) The minimum values listed for a 6 year old child in that study exceed both of these specifications. This justification is acceptable and there are no indications that the activation force specification is too high for the product.

• You have provided a fault tree analysis that includes the EPRs for failure to deliver a successful injection. As previously mentioned, you should consider the EPRs for the PFS component for your device and include these within your fault tree analysis. You have included visual feedback as an Applicable Design Input; however, it does not appear to be included in the fault tree analysis or release/stability testing. Please include visual feedback in the fault tree analysis and in final release/stability testing.

Mean injection time is (b) (4) seconds. This is an extremely fast injection performed on an unconscious patient. Premature withdrawal due to insufficient audio visual feedback is not likely to occur. If the device is successfully triggered the injection will be completed before the user can withdraw the device. Evidence of this is provided in the HF validation study where no participants held the injection for less than 1 second, even if they did not check the viewing window.

• A rationale for the proposed samples sizes based on risks and statistical significance, unless determined by a standard for all combination product testing should be provided.

Detailed justification for sample size is provided and detailed in the fault tree section of the reliability report.

• Testing of the combination product should consider the following:
o Sample sizes and preconditioning should at a minimum be tested in accordance with ISO11608-1 based on your system designation and any deviations from a test standard (e.g., pre-conditioning temperatures) should be justified.

Minor deviations are listed in section 4.8 of the Reliability Summary Report with acceptable justifications.

o Environmental factors such as altitude and air particulates should be considered, per FDA's guidance, "Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA, or ANDA: Guidance for Industry and Food and Drug Administration Staff." Rationale should be provided for any in-use conditions that are inapplicable based on intended use and intended use environments.

Particulates and altitude were not tested, justifications are provided. Altitude was not tested (b) (4) . Particulates were not tested because the device is stored in a box prior to use. These justifications are acceptable.

o Rationale should be provided where data is non-norm

The results of several tests are non-normal. Alternative evaluation methods are used, **but rationale for why the data is non-normal is not provided.** This is discussed in detail in the reliability testing section.

3.2.1. Related Files

3.3. Indications for Use

Combination Product	Indications for Use
Nalmefene	For the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, (b) (4) (b) (4)
Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	**Module(s)**

1.2	Reviewer's Guide
2.3	Overall Quality Summary
3.2.P.3	Manufacture
3.2.P.7	Container Closure System
MAF (b) (4) -A003	Device Design Master Files
3.3	Literature References

4. DEVICE DESCRIPTION

4.1. Device Description

MAF (b) (4) includes the following device description:
The NAI (Nalmefene Auto Injector) is an automated drug delivery device for the subcutaneous administration of nalmefene (0.50 mL via a pre-filled syringe). It is a pre-assembled, pre-filled, single dose, (b) (4) disposable drug delivery device that may be used by nonmedically trained responders (such as caregivers, relatives, friends and bystanders) in the community setting as well as by medically trained personnel in a community or health care setting. It is designed to accommodate a (b) (4) syringe.

The NAI was designed to be capable of injecting 0.50 ml of fluid (b) (4) . The delivery volume is fixed (b) (4) and cannot be adjusted by the end user (fixed dose). The device has no fluid path and does not come in contact with the drug contained within the syringe.

The auto-injector was designed to enable injection through clothing, if required, and includes safety features to avoid accidental triggering of the device and the prevention of accidental sharps injury.

Injection is accomplished by pushing the device against the injection site. (b) (4) When the needle has penetrated the user's skin to the required depth, the device "triggers" and the drug is delivered simultaneously using (b) (4) injection force. The user must hold the device firmly against the injection site for a short period of time to allow drug delivery to occur. (b) (4)

(b) (4) Labeling and final packaging of the autoinjector is then completed. Images of the completed device and the device assembly are shown below.

Image (Not to scale)	Description	Skin Contact	Material
(b) (4)		No	(b) (4)
		Yes	
		No	
		Yes	

4.2. Steps for Using the Device

1. Remove syringe needle cap.
2. Twist the blue safety cap to remove. There is a safety seal on the device which must be ruptured.
3. Force the needle into the upper thigh. Injection will automatically start and is indicated by an audible click.
4. Hold the device in place for 3 seconds to complete injection.
5. When viewing window turns completely orange, remove needle from thigh. Injection is complete.

The device description states that the device is designed to be used by non-medically trained responders in the community as well as healthcare professionals in a healthcare setting.

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION

Filing Deficiencies:	Mid-Cycle Deficiencies:	Final Deficiencies:
☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A

Reviewer Comments

Device is adequately described. The container closure system is a pre-filled syringe placed into the auto-injector. Injector is activated by applying pressure (b) (4) The device is indicated for emergency injection through clothing if necessary. Intended users include untrained laypersons. (b) (4)

The same auto-injector design has been used in previous products (b) (4) (b) (4). While CDRH did not send any IRs related to other products using the (b) (4) platform, CDRH was consulted and provided input on interpreting an IR response dated 5/9/2024 about other products using the (b) (4) platform. This IR and the applicant response are documented in this memo in appendix A. Based on the information provided in that response, it was recommended that (b) (4) was the only product currently marketed

which used an identical device as the subject NDA. CDER/DPV initiated a review of all adverse event reports for (b) (4) to investigate possible device problems, with a particular focus on the safety cap.
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☑ **Yes** ☐ **No**

5. FILING REVIEW

CDRH performed Filing Review	☑
CDRH was not consulted prior to the Filing Date; therefore CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description		**Present**		
		Yes	**No**	**N/A**
Description of Device Constituent		x		
Device Constituent Labeling		x		
Letters of Authorization		x		
Essential Performance Requirements defined by the application Sponsor (3.2.P.5)		x		
Design Requirements Specifications included in the NDA / BLA by the application Sponsor		x		
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file. (3.2.P.7)		x		
Risk Analysis supplied in the NDA / BLA by the application Sponsor 3.2.P.3.5		x		
Traceability between Design Requirements, Risk Control Measures and V&V Activities (Appendix 16)		x		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing (MAF (b) (4) -A003)	x		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	x		
	Reliability	x		
	Biocompatibility (review deferred to CDER)	x		
	Sterility (review deferred to CDER)	x		
	Software			x
	Cybersecurity			x
	Electrical Safety			x
	EMC/RF Wireless			x
	MR Compatibility			x
	Human Factors (review deferred to CDER-DMEPA)	x		
	Shelf Life, Aging and Transportation	x		
	Clinical Validation	x		
	Human Factors Validation (review deferred to CDER-DMEPA)	x		
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	x		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)	x		
	CAPA Procedure	x		
	Control Strategy provided for EPRs	x		

Table 58: Design Control Elements

Design Control Elements	Documentation	Location	
		MAF (b) (4)	NDA
Design Inputs / Specification	PD-URS-0011-Product Requirements	Appendix 2	
Design Output Specifications (Device Description and Diagrams)	Diagrams and Engineering Prints NAI Specification	Sections 1,2, & 3 Appendix 1	 3.2.P..5.1
Design Verification Activities	PD-RPT-0584 - Biocompatibility Report QA-PLN-0122 - Design Verification Plan for (b) (4) PD-RPT-0580 - (b) (4) Dist. Report PD-RPT-0648 - ISO 11608-1 Report T=24mo AA PD-RPT-0680 - (b) (4) ISO 11608-1 Report (Cool, Standard and Warm Conditioning) PD-RPT-0586 - (b) (4) Aging DVT Report QA-PLN-0134 – (b) (4) Reliability Plan PD-RPT-0643 - (b) (4) Reliability Summary Report	Appendix 3 Appendix 10 Appendix 19 Appendix 15 Appendix 18 Appendix 14 Appendix 12 Appendix 4	 3.2.P.7
Design Validation Plan/Summary Report	PD-RPT-0655 - Sharps Study PD-RPT-0689 - Human Factors Summary Report	Appendix 13 Appendix 17	 5.3.5.4
Risk Management File	Device Risk Assessment Process HF summary report (NAMSA report) QA-RSK-0042 - User FMEA (URRA) QA-RSK-0029 - Clinical Hazard Analysis (CHA) MF-RSK-0083 - Process FMEA	Section 2	 5.3.5.4 5.3.5.4 5.3.5.4 3.2.P.3.5
Traceability matrix - Design Verification Trace Matrix	QA-RPT-0234 - Auto-injector Design Verification Trace Matrix QA-RPT-0261 – Nalmefene Hydrochloride Injection, Auto-injector, 1.5 mg Verification Trace Matrix	Appendix 16	 3.2.P.7

Reviewer Comment

Required information is found both in the NAI and MAF (b) (4). Table 58 in the Overall Quality Summary lists the location of most test reports. The device master file is extensive (b) (4). Amendment 3 was submitted in November 2023 to provide the necessary data for the Nalmefene 1.5mL injection. This amendment includes reliability testing to support the emergency use indication.

5.2. Facilities Information

Firm Name:	(b) (4)
Address:	

FEI:	(b) (4)
Responsibilities:	(b) (4)

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted (b) (4). The inspection covered both drug CGMPs and medical device QS and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☑ A post-approval inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☐ An inspection is not required because A recent medical device inspection of the firm was acceptable.

Firm Name:	Purdue Pharmaceuticals L.P.
Address:	4701 International Blvd. W. Wilson, NC 27893, USA
FEI:	3002960808
Responsibilities:	Release of drug product. – While this statement is ambiguous, the firm has stated they are complying with 21CFR part 4. This statement identifies the site a combination product manufacturer. The firm later clarified in response to a CDER CMC IR that they are performing administrative release only. No device EPR testing will take place at this site.

Inspectional History
An analysis of the firm's inspection history over the past 2 years:
☑ Inspection was conducted 7/26/2022 to 8/11/2022. The inspection covered drug CGMP and was classified VAI.

☐ An analysis of the firm's inspection history over the past 2 years showed that it has never been inspected.

☐ N/A - the manufacturing site does not require an inspection at this time given the risk of the combination product

Inspection Recommendation:
☐ A choose an item inspection is required because:
The firm is responsible for major activities related to the manufacturing and/or development of the final combination involving the device constituent part; and,
A recent medical device inspection of the firm has not been performed.

☑ An inspection is not required because The firm is not responsible for major activities related to the manufacturing and development of the final combination product or the device constituent part.

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☑ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☑ No ☐ UNK
Is the final combination product meant for emergency use?	☑ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☑ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☑ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☑ Yes ☐ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☑ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☑ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

Table 1: Manufacturing, Packaging and Testing Sites

Site Name	Site Address	Federal Establishment Indicator (FEI) / DUNS number / cGMP	Drug Master File	Manufacturing Step(s) or Type of Testing [Establishment function]
Pre-Filled Syringes and Assembled Auto-Injectors				
(b) (4) Quality System is certified to 21 CFR Part 4.4(b)(1) complying with Part 210/211 and compliance with sections 820.20, 820.30, 820.50, 820.100, 820.170 and 820.200 are not applicable.	(b) (4)	DUNS: (b) (4) FEI: (b) (4) cGMP Certification	NA	(b) (4)
(b) (4)	(b) (4)	DUNS: (b) (4) FEI: (b) (4) cGMP Certification	NA	
		DUNS: (b) (4) FEI: (b) (4) cGMP Certification	NA	
		DUNS: (b) (4) FEI: (b) (4) cGMP Certification	NA	
		DUNS: (b) (4) FEI: (b) (4) cGMP Certification	NA	

ICC2400130
NDA 218590 ,Nalmefene
Purdue Pharma

Site Name	Site Address	Federal Establishment Indicator (FEI) / DUNS number / cGMP	Drug Master File	Manufacturing Step(s) or Type of Testing [Establishment function]
(b) (4)	(b) (4)	DUNS: (b) (4) FEI: ISO 15378 Certification ISO 13485 Certification	(b) (4)	(b) (4)
		N/A – Analytical Development studies only	NA	
		N/A development lab only	NA	
		ISO 10993	(b) (4)	
Assembled Auto-Injector Only				
(b) (4)	(b) (4)	DUNS: (b) (4) FEI: cGMP Certification	NA	
	(b) (4)	DUNS: (b) (4) FEI: cGMP Certification	MAF # (b) (4)	

Referen

Site Name	Site Address	Federal Establishment Indicator (FEI) / DUNS number / cGMP	Drug Master File	Manufacturing Step(s) or Type of Testing [Establishment function]
Purdue Pharmaceuticals L.P. Compliance with to sections 820.20, 820.30, 820.50, 820.100, 820.170 and 820.200	4701 International Blvd. W. Wilson, NC 27893, USA	FEI: 3002960808 DUNS: 132080875 cGMP certification	NA	Release of the drug product

NA – Not applicable

Reviewer Comment
A total of 11 sites are listed in the NAI, but only these two state that their quality systems will comply fully with 21 CFR part 4. Another facility, [redacted] (b) (4) is responsible for primary packaging of the pre-filled syringes. This facility states that their quality system is complying with 21 CFR Part 4.4(b)(1) only. Based on the information available it does not appear that this facility qualifies as a combination product manufacturing facility.

The other eight facilities listed are device component manufacturers/testing labs, or drug manufacturers/testing labs.

The device is an emergency use auto-injector for opioid overdose. Pediatric patients are included in the subject population. Failure of the device is likely to result in a severe adverse event for the patient, including death.

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION

Acceptable for Filing: ☑ Yes ☐ No (Convert to a RTF Memo) ☐ N/A

Facilities Inspection Recommendation:
☐ (PAI) Pre-Approval Inspection ☑ Post-Approval Inspection ☐ Routine Surveillance
☑ No Inspection ☐ N/A

Site(s) needing inspection:
[redacted] (b) (4) **Site: post-approval**
Purdue Pharmaceutical Site: no inspection

Reviewer Comments
The [redacted] (b) (4) site was previously inspected in [redacted] (b) (4). While the inspection was designated VAI only as single observation was made for inadequate design change procedures. An extensive supplement submitted to the MAF in [redacted] (b) (4) includes an updated quality system. Because all FDA observations in this 483 are resolved with new information in this submission, a post-approval inspection can be performed.

The Purdue Pharmaceutical Site was identified as conducting product release, but it was clarified through communication with the CDER CMC team that this is only administrative product release. A device inspection of this site is not needed.

A facilities inspection recommendation was communicated to CDER in [(b) (4)] on [(b) (4)]. A post-approval inspection was recommended for the [(b) (4)] site [(b) (4)]. Please refer to that CDRH memo for detailed rationale for the inspection recommendations.
Refuse to File Deficiencies: ☐ Yes ☑ No ☐ N/A **74-Day Letter Deficiencies:** ☐ Yes ☑ No ☐ N/A

	Date Sent: Click or tap to enter a date.	**Date/Sequence Received:** Click or tap to enter a date.
Information Request #		
Sponsor Response	Reviewed in Choose an item. Section	

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	**Adequate?**		
	Yes	**No**	**N/A**
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	x		
Drug name is visible on device constituent and packaging	x		
Device/Combination Product Name and labeling is consistent with the type of device constituent	x		
Prescriptive Statement/Symbol on device constituent	x		
Warnings	x		
Contraindications	x		
Instructions for Use	x		
Final Instructions for Use Validated through Human Factors	X – full review deferred to DMEPA		
Electrical Safety Labeling/Symbols			x
EMC Labeling/Symbols			x
Software Version Labeling			x
MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			x

Reviewer Comments
Draft labeling is consistent with the device as prescribed. Final review of the insert and carton labeling is deferred to CDER DMEPA.

6.3. Clinical Labeling Review

The following Clinical Labeling Review was completed by ☐ Insert Consultant Name ; The full memo is located in Appendix B. ☐ The Lead Reviewer Below is a summary of the review & recommendation:

6.4. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments CDRH has no device specific labeling concerns.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	x		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	x		
Mitigations are adequate to reduce risk to health	x		
Version history demonstrates risk management throughout design / development activities	x		
Design Inputs/Outputs	**Yes**	**No**	**N/A**
Design requirements / specifications document present (essential performance requirements included)	x		
Design Verification / Validation Attributes	**Yes**	**No**	**N/A**
Validation of essential requirements covered by clinical and human factors testing	x		
To-be-marketed device was used in the pivotal clinical trial			X – no pivotal trial, HF and bioequivalence are used
Bioequivalence Study utilized to-be-marketed device	x		
Verification methods relevant to specific use conditions as described in design documents and labeling	x		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)	x		
Traceability demonstrated for specifications to performance data	x		

Table 1: Design Control Elements

Design Control Elements	Documentation	Location	
		MAF (b) (4)	NDA
Design Inputs / Specification	PD-URS-0011-Product Requirements	Appendix 2	
Design Output Specifications (Device Description and Diagrams)	Diagrams and Engineering Prints NAI Specification	Sections 1,2, & 3 Appendix 1	 3.2.P.5.1
Design Verification Activities	PD-RPT-0584 - Biocompatibility Report QA-PLN-0122 - Design Verification Plan for (b) (4) PD-RPT-0580 - (b) (4) Dist. Report PD-RPT-0648 - ISO 11608-1 Report T=24mo AA PD-RPT-0680 - (b) (4) ISO 11608-1 Report (Cool, Standard and Warm Conditioning) PD-RPT-0586 - (b) (4) Aging DVT Report QA-PLN-0134 – (b) (4) Reliability Plan PD-RPT-0643 - (b) (4) Reliability Summary Report	Appendix 3 Appendix 10 Appendix 19 Appendix 15 Appendix 18 Appendix 14 Appendix 12 Appendix 4	 3.2.P.7
Design Validation Plan/Summary Report	PD-RPT-0655 - Sharps Study PD-RPT-0689 - Human Factors Summary Report	Appendix 13 Appendix 17	 5.3.5.4
Risk Management File	Device Risk Assessment Process HF summary report (NAMSA report) QA-RSK-0042 - User FMEA (URRA) QA-RSK-0029 - Clinical Hazard Analysis (CHA) MF-RSK-0083 - Process FMEA	Section 2	 5.3.5.4 5.3.5.4 5.3.5.4 3.2.P.3.5
Traceability matrix - Design Verification Trace Matrix	QA-RPT-0234 - Auto-injector Design Verification Trace Matrix QA-RPT-0261 – Nalmefene Hydrochloride Injection, Auto-injector, 1.5 mg Verification Trace Matrix	Appendix 16	 3.2.P.7

Reviewer Comments
The design control process is well documented. Relevant documents are found in both the NDA and MAF (b) (4).
Reliability plan is included in MAF (b) (4) appendix 12.

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Needle Shield Removal	Needle shield will be removed from the syringe assembly when the safety cap is removed from the auto-injector with a twisting and pulling motion.
Safety Cap Removal Torque	The maximum rotational torque to separate the auto-injector cap from the auto-injector shall be (b) (4) when the device label is applied.
Trigger (Activation) Force	The maximum force to fully depress (b) (4) to initiate the auto-injector delivery sequence shall be less than (b) (4).
Exposed Needle Length	The nominal extension length of the auto-injector shall be (b) (4) mm.
Device Triggers	The auto-injector must activate dose administration if full Needle Guard retraction is achieved.
Delivered Volume	The auto-injector design shall meet ISO 11608-1:2022 dose accuracy requirements for a type D1 injector system, clause 7.2.3.2.1, 7.4.2.2, and 7.4.5. Auto-injector shall deliver at least 0.50 mL.
Injection Time	When the syringe in the autoinjector is filled per specification, 7.11.12, the time taken by the auto-injector to deliver the full contents of the syringe shall not be greater than (b) (4).
Viewing Window Occlusion	The auto-injector shall be designed to completely occlude the viewing window/area to the syringe upon completion of dose delivery.

Reviewer Comments

The device EPRs are acceptable. Previous reviews have noted that the activation force specification is high at (b) (4), but difficulty with triggering the device was not reported in the human factors study, which included pediatric users. The device is activated by fully depressing (b) (4) so the user does not need to press a button like some other auto-injector designs. A higher activation force may be acceptable with this device design.

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y – details in MAF (b) (4)
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	Y – details in MAF (b) (4)
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Biocompatibility review deferred to CDER

Applying Human Factors and Usability Engineering to Medical Devices	Usability review deferred to DMEPA

Standards and guidance adherence for the (b) (4) is summarized in MAF- (b) (4) rev 2, section 4.

4. PERFORMANCE TESTING – GENERAL USE INJECTOR CONSIDERATIONS

No performance standards have been developed specifically for syringe needle introducers. The following product related standards and guidance documents were used in the development and testing of the device:

- *FDA Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features* – August 9, 2005. This guidance was used as a reference when determining the device testing and sample size requirements.
- *FDA Guidance for Industry and FDA Staff: Technical Considerations for Pen, Jet and Related Injectors intended for Use with Drugs and Biological Products* – June 2013. This guidance was used as a reference when determining the device testing and sample size requirements.
- *FDA Draft Guidance for Industry and FDA Staff: Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA: Guidance for Industry and Food and Drug Administration* April 2020. This guidance was used as a reference when determining the device testing and sample size requirements to ensure product reliability.
- ASTM D4169-22 - Standard Practice for Performance Testing of Shipping Containers and Systems.
- ASTM F1980-21 - Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices
- ISO 11608-1:2022 - Needle-based injection systems for medical use — Requirements and test methods—Part 1: Needle-based injection systems.
- ISO 11608-5:2022 - Needle based injection systems for medical use – Requirements and test methods – Part 5: Automated Functions.
- ISO 23908:2011 - Sharps injury protection — Requirements and test methods — Sharps protection features for single-use hypodermic needles, introducers for catheters and needles used for blood sampling.

The device is considered designation "D1" per ISO 11608-1:2022 and the following environmental conditions were tested:

Table 7: Environmental Conditioning Tests

Test	Description
Operating Temperature (warm, cool and standard atmosphere)	To simulate extreme in-use environment conditions • Warm - 5+/-3°C, no humidity requirement • Standard - 23+/-5°C, RH 50 +/-25% • Cool – 40+/-2°C, RH 50 +/-10%
Extreme Conditions of Use[1] (Drop – Free fall Testing)	To simulate potential for dropping the device from a countertop storage location • Drop each autoinjector once in each of the three axes from a one meter height. See ISO 11608-1
Extreme Storage[1] Temperatures (Dry Heat and Cold Storage)	To simulate potential temperature excursions during storage • Place devices in an environmental chamber for a minimum of 96 hours at acceptable high and low storage temperatures as stated in the instructions for use. See ISO 11608-1. Dry heat tested at 25°C and cold storage tested at 15°C.
Vibration[1]	Vibrate autoinjector samples in each of the three axes in accordance with IEC 60068-2-6 and Table 7 in ISO 11608-1.
Transport[1] (Distribution Testing)	To simulate conditions during transport ASTM D4169 schedule DC 13, Assurance Level II with following test schedule sequence: • 1st: Schedule A – Manual Handling (1st Drop Sequence) • 2nd: Schedule C – Vehicle Stacking • 3rd: Schedule F – Loose Load Vibration • 4th: Schedule E – Vehicle Vibration • 5th: Schedule J – Concentrated Impact • 6th: Schedule A – Manual Handling (2nd Drop Sequence) • 7th: Schedule I – Low Pressure High Altitude Testing
Functional Stability[1] (Shelf life)	Samples accelerated aged per ASTM F1980-16/DP04-220. Samples aged at 40 ± 2°C at ambient RH for 259 days to achieve 24 months equivalent real time.

[1]Samples for these conditions were conditioned and tested in conjunction with the reliability testing reported in Appendix 4 PD-RPT-0643. This resulted in pre-conditions being stacked and in some cases, performed at levels that exceed the requirements of ISO 11608-1. This was done to be efficient with test samples and represents a worst-case approach.

Environmental use temperatures used for testing are 15 and 25ºC. Extreme storage temperature limits are 5 and 40ºC.

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA, or ANDA: Guidance for Industry and Food and Drug Administration Staff	Y	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Device EPRs are appropriate. Appropriate justification has been provided for EPR specifications.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

8. RISK ANALYSIS

8.1. Risk Management Plan

Reviewer Comments

The overall risk analysis plan is documented in MAF(b) (4)-Am03 rev 02.

Risk Assessment

The NAI development process aligns with EN ISO 14971:2019, *Medical Devices - Application of Risk Management to Medical Devices*, in which failure modes of the product and their associated clinical harms are identified and controlled. The following documents are generated through the application of risk management during development of the auto-injector and are maintained within the design history file.

Document	Description of Risk Management Activity
Risk Management Plan	Scope of the planned RM activities, identifying and describing the combination product and the life-cycle phases for which each element of the plan is applicable.
Clinical Hazard Analysis	Identification of the potential hazards and harms associated with the NAI and the corresponding clinical severity.
Design FMEA	Assessment of individual component failure modes of the auto-injector and the associated probability and severity relative to the clinical harm.
Process FMEA	Assessment of the manufacturing process, identification of failure modes associated with incorrect manufacturing and assembly steps and the probability, detectability and severity relative to the corresponding clinical harm.
User FMEA	Assessment of the required user steps, identification of user errors and the associated probability and severity relative to the corresponding clinical harm.
Risk Management Report	Document the risk control activities have been implemented and the benefit-risk analysis has been completed.

The risk management activities outlined in this section are documented throughout the NDA.

8.2. Hazard Analysis and Risk Summary Report

(b) (4)

Reviewer Comments

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION

Filing Deficiencies:	Mid-Cycle Deficiencies:	Final Deficiencies:
☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A	☐ Yes ☑ No ☐ N/A

Reviewer Comments

Device risk analysis is acceptable. Design and manufacturing risks are analyzed separately. No individual manufacturing steps have unacceptable residual risk. Risk analysis documents for clinical hazards and user FMEA have been included, but review is deferred to CDER/DMEPA.

CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No

DESIGN VERIFICATION REVIEW

8.4. Performance/Engineering Verification

Built in template tables were not utilized for this review. Design verification summaries for EPR and non-EPR specifications have been provided.
Document (b) (4) RPT-0261 located in 3.2.P.7 is a key device design document. It contains a summary traceability matrix for all design verification activities. The following Summary is copied from that document:

1.0 EXECUTIVE SUMMARY

Design verification activities were completed to meet the Product Requirements for (b) (4) Combination Product per PD-URS-0011 Rev 007. Testing samples for both Pre-filled Syringe (PFS) and (b) (4) autoinjector were from registration batches, and they represented commercial PFS and (b) (4) autoinjector. All PFS and autoinjector testing was completed and met the commercial acceptance criteria.

2.0 PURPOSE

The purpose of this document is to summarize all testing activities that have been completed and demonstrate that the product requirements listed in PD-URS-0011 are satisfied for the (b) (4) combination product.

Device EPRs have been verified across three production lots at T=0, 3M, 6M, and 12M. Results of these tests were provided in qa-rpt-0261-design-verification-tracability-matrix. No out of specification results were reported for any design verification tests.

Reliability testing is documented separately in MAF (b) (4) -Am03 Appendix 12.
Reliability Report Executive Summary:

I. EXECUTIVE SUMMARY

Reliability of the [redacted] (b) (4) Auto-Injector was assessed per [redacted] (b) (4) Reliability Plan [redacted] (b) (4) -PLN-0134. This report addresses the recommendations of the end of phase 1 meeting held with the FDA on March 31st, 2022 and the FDA draft guidance, "*Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA, or ANDA: Guidance for Industry and Food and Drug Administration Staff*" issued April 2020.

Design inputs and design outputs for reliability were assessed. A fault tree for failure to deliver a successful injection was generated. The fault tree encompasses design and manufacturing related failure modes. The basic events were analyzed to determine the probability of failure. The basic event probabilities were used to calculate a system reliability level of [redacted] (b) (4); see Appendices A, B, and C. This reliability level meets the requirement of a less than 1/100,000 (reliability ≥ 99.999%) failure rate to deliver a successful injection on the first attempt.

Testing was conducted to support the fault tree model for reliability. Attribute outputs and variable data essential performance requirements (EPRs) were tested following worst-case foreseeable preconditioning. All devices successfully delivered a dose and all variable data was within specification. Testing has been completed at T=0 and T=24mo accelerated aged (AA) time points. Additional testing is planned at Real Time Aged (RT)=24mo.

Total life cycle reliability was assessed for the [redacted] (b) (4) auto-injector. Fault trees and a Manufacturing control plan (MF-PLN-0056) for the EPRs related to reliability were generated. A summary of the Corrective And Preventive Actions (CAPA) process, change control process, and post-market procedures applicable to the [redacted] (b) (4) autoinjector is included in this report. The assessment of these controls and procedures demonstrates that adequate controls are in place to ensure reliability is maintained throughout the product's life cycle.

The information presented in this report demonstrates that the [redacted] (b) (4) auto-injector is reliable with respect to successfully delivering a dose on the first attempt with in-specification EPR performance. Reliability has been achieved and will be maintained throughout the product's life cycle.

4.7. TEST RESULTS

Table 13 below summarizes the results of reliability testing that has been completed for the (b) (4) Auto-Injector.

Table 13: Summary of Reliability Test Results

PRD Ref #	Test	Acceptance Criteria	Results		Pass/Fail
			Time Point (Report) T=0 (PD-RPT-0592)	Time Point (Report) T=24mo AA (PD-RPT-0642)	
7.1.3	Needle Shield Removal	600 of 600 shall strip the Needle Shield from the syringe upon safety cap removal.	600 of 600 samples tested stripped the Needle Shield from the syringe upon safety cap removal	600 of 600 samples tested stripped the Needle Shield from the syringe upon safety cap removal	Pass
7.1.6	Safety Cap Removal Torque	A 95%/99.99% Tolerance Interval shall be no more than (b) (4)	(b) (4)		Pass
7.2.1	Activation Force	A 95%/99.99% Tolerance Interval shall be no more than (b) (4)			Pass
7.2.4	Exposed Needle Length	A 95%/99.99% Lower tolerance Interval shall be greater than or equal to (b) (4) A 95%/99.99% Upper tolerance Interval shall be less than or equal to (b) (4)			Pass
7.2.5	Device Triggers	600 of 600 must successfully trigger if full needle guard retraction is achieved.	600 of 600 samples tested successfully triggered and expelled drug when injected through 3 layers of cotton duck cloth	600 of 600 samples tested successfully triggered and expelled drug when injected through 3 layers of cotton duck cloth	Pass
7.2.6	Needle Penetrates Clothing Device Activates	600 of 600 must successfully trigger and expel drug when injected through 3 layers of cotton duck cloth.	600 of 600 samples tested successfully triggered and expelled drug when injected through 3 layers of cotton duck cloth	600 of 600 samples tested successfully triggered and expelled drug when injected through 3 layers of cotton duck cloth	Pass

PRD Ref #	Test	Acceptance Criteria	Results		Pass/Fail
			Time Point (Report) T=0 (PD-RPT-0592)	Time Point (Report) T=24mo AA (PD-RPT-0642)	
7.2.7	Delivered Volume	A 95%/99.99% Tolerance Interval shall be no less than (b) (4)	(b) (4)		Pass
7.2.8	Ejection Time	A 95%/99.99% Tolerance Interval shall be no more than (b) (4)			Pass
7.2.10	Viewing Window Occlusion	600 of 600 sample's viewing windows must completely occluded follow the injection, confirming the device delivered full contents of the syringe	600 of 600 sample's viewing windows tested successfully became occluded upon completion of dose delivery	600 of 600 sample's viewing windows tested successfully became occluded upon completion of dose delivery	Pass

Variable EPRs must pass a 95/99.99% confidence/reliability tolerance interval. Variable EPRs are: Safety Cap Removal Torque, Activation Force, Delivered Volume, and Injection Time.

Attribute EPRs are tested pass/fail only and must pass a 95/99.999% confidence/reliability conformance level. Attribute EPRs are: Needle Shield Removal, Device Triggers, Needle Penetrates Clothing, and Viewing Window Occlusion.

The sample size for attribute testing was determined using k-factor. This method used the fault tree analysis, which included 62 faults. For each fault, the number of standard deviations between the nominal result and the failure limit was determined. Then, the sample size needed to achieve (b) (4) reliability was calculated for each fault. (b) (4) was determined to be the minimum fault level reliability needed to achieve a system level reliability of 99.999%. The highest sample size determined by this calculation was 308. 600 samples (per timepoint) was selected as a conservative sample size based on this analysis. An example calculation is provided on page 46 of the (b) (4) Reliability Summary Report.

Sample pre-conditioning included eight total groups, which are described using the table below. The report notes that specific conditioning for air particulates was not tested because the IFU states “store in a clean dry place” and additionally the device is kept in a box prior to use. Conditioning of aged devices was performed under “uncontrolled conditions”, therefore those groups have accumulated some air particle exposure.

Table 10: Test Matrix

Sample Group	T = 0					T = 24 months (AA)[1]				
	1	2	3	4	Total	5	6	7	8	Total
Pre-Conditioning										
Distribution Testing	X	X	X	X	NA	X	X	X	X	NA
24 Month Aging	NA					X	X	X	X	
Cyclical temperature & humidity excursion	X	X	X	X		X	X	X	X	
Vibration	X	X	X	X		X	X	X	X	
Crush	X	X	X	X		X	X	X	X	
Free Fall (Drop)	X	X	X	X		X	X	X	X	
Activation Conditions										
Vertical (needle guard down)	X	X			NA	X	X			NA
Horizontal			X	X				X	X	
Low (15°C)	X		X			X		X		
High (25°C)		X		X			X		X	
Through Clothing and Membrane	X	X	X	X		X	X	X	X	
Sample Sizes										
Needle Shield Removal	240	240	60	60	600	240	240	60	60	600
Device Triggers	240	240	60	60	600	240	240	60	60	600
Viewing Window Occlusion	240	240	60	60	600	240	240	60	60	600
Needle Clothing Penetration	240	240	60	60	600	240	240	60	60	600
Exposed Needle Length	30	30	30	30	120	30	30	30	30	120
Activation force[2]	60	60	0	0	120	60	60	0	0	120
Ejection Time[2]	60	60	0	0	120	60	60	0	0	120
Delivered Volume	30	30	30	30	120	30	30	30	30	120
Safety Cap Removal Torque[2]	60	60	0	0	120	60	60	0	0	120
Sample Group Total	240	240	60	60	600	240	240	60	60	600

[1]Table 10 describes test matrix performed for the current summary report revision. This matrix does not include real timepoint groups.

Reliability Test Results:

For each EPR, sample means for test groups were compared using a t-test. If means were statistically equivalent, the groups were pooled for additional analysis. If means were different, the groups were analyzed individually.

All distributions were evaluated for normality. If the data set passed normality, a 95% confidence, 99.99% reliability tolerance interval was calculated and compared to the acceptance criteria. Non-normal data required transformation of both the data and the acceptance criteria to determine reliability.

Although the sponsor did not report any device EPRs which failed to meet the reliability specification (see Table 13 at the beginning of this section) several groups could not be pooled because sample means were statistically different (safety cap removal torque, activation force, delivered volume).

Safety cap removal torque data was non-normal for group 2 (high environmental injection temp) at both T=0 and T=24mo. The non-normal data sets were first compared to a set of distributions to determine the best fit.

Table 10: Group 2 Goodness of Fit Test

Distribution	AD	P	LRT P
Normal	4.922	<0.005	
Box-Cox Transformation	1.007	0.011	
Lognormal	7.080	<0.005	
3-Parameter Lognormal	4.921	*	0.000
Exponential	20.553	<0.003	
2-Parameter Exponential	13.723	<0.010	0.000
Weibull	2.722	<0.010	
3-Parameter Weibull	1.542	<0.005	0.001
Smallest Extreme Value	1.540	<0.010	
Largest Extreme Value	7.818	<0.010	
Gamma	6.366	<0.005	
3-Parameter Gamma	24.784	*	1.000
Logistic	2.839	<0.005	
Loglogistic	4.273	<0.005	
3-Parameter Loglogistic	2.843	*	0.000
Johnson Transformation	0.502	0.199	

For T=0, Group 2 the Johnson Transformation was the best fit, although it only had a p-value of 0.199. This transformation requires that both the distribution and specification be transformed using the same function. The transformation changed the upper tolerance limit specification (b) (4). The calculated 99.99% tolerance interval for the transformed dataset was (b) (4). Both numbers were then fed through the inverse of the Johnson Transformation to produce numbers that can be compared to the original specifications. This is how the result of (b) (4) reported in table 13 was produced. Based on the p-value the use of the Johnson Transformation to model this data is marginal, but acceptable given that none of the devices tested was close to the upper specification limit. The raw mean for this test group was (b) (4) and the distribution was non-normal due to low outliers. There is no lower bound specified for the cap removal torque for the final finished device. There is a device label applied which holds the safety cap on. Design verification does include testing for a minimum cap removal torque specification (b) (4) for unlabeled devices to prevent the cap being dislodged during transport.

Safety cap removal torque data at T=24mo showed a similar pattern. The two groups were not equivalent. Group 1 was normal and met the specification. Group 2 was again non-normal and the Johnson Transformation provided the best fit, with a p-value of 0.374. Following the same transformation -> inverse transformation process used at T=0, an upper tolerance limit of (b) (4) was produced. This is many times higher than the specification of (b) (4).

Because this data did not meet the specification, an additional 60 samples were tested and data was segregated [(b) (4)]. Devices from [(b) (4)] were included in the expanded sample. Data was again non-linear but now none of the evaluated distributions provided a good fit. Sample means [(b) (4)] were significantly different than cavities 3 and 4. The [(b) (4)] data was normal and met the specification with an UTL of [(b) (4)] [(b) (4)] were then pooled together and this distribution was normal and met the specification with an UTL of [(b) (4)]

The safety cap design used in this product is identical to another product already on the market, [(b) (4)]. CDER reviewed all adverse event reports involving [(b) (4)] and provided a report documenting all device related events. In total, 263 unique US cases were identified, with 34 classified as user error. Per the applicant, approximately [(b) (4)] units of [(b) (4)] have been distributed. There are no reports of difficulty removing the cap causing a missed dose.

Due to differences between the PFS components, drugs, user populations, and control strategies, it is not clear if the other device adverse event reports for [(b) (4)] have any applicability for the proposed Nalmefene AI.

Fault-Tree Analysis

A fault tree analysis of top-level events causing a failure was provided. Top-level events were: unable to remove safety cap, unable to trigger, trigger prematurely, fluid not delivered, fluid not delivered to injection site, drug not delivered in timely manner, and needle shield removal. Each of these top level events corresponds with a device EPR. A secondary fault tree was conducted for each top-level even to determine basic events. Additional analysis was then used to estimate the probability of each event and cumulative probabilities were used to determine the overall [(b) (4)] reliability. The manufacturing control strategy is documented in MF-PLN-0056. The control strategy is broken down by device EPR, and includes direct references to specific events in the fault tree analysis.

5.0 MANUFACTURING CONTROL STRATEGY

The following table shows the summary for Essential Performance Requirements (EPR) testing for release.

Table 3: EPR Release Testing Summary

EPR	PRD	Sub-Assembly Release	Final Assembly Release
Safety Cap Removal Torque	7.1.6	X	X
Needle Shield Removal	7.1.3	X	X
Activation Force	7.2.1	X	X
Delivered Volume	7.2.7	NA[1]	X
Exposed Needle Length	7.2.4	NA[1]	X
Device Activation	7.2.5	X	X
Ejection Time	7.2.8	NA[1]	X
Viewing Window Occlusion	7.2.10	X	X
Successful Injection	7.5.16	NA[1]	X

[1]Drug properties, syringe fill process, and the pre-filled syringe are primary contributors to these EPRs. Testing after final assembly with syringe lot is appropriate.

Due to the non-normal results obtained in the reliability study, only the control strategy (b) (4) is copied below because of the results of the reliability testing. (b) (4)

The control strategies for the other device EPRs are similar.

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8.4.1. *Essential Performance Requirement Evaluation*

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method Acceptable (Y/N)	Validation (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)

Reviewer Comment

8.4.2. *Verification of Design Inputs Evaluation*

Design Input	Design Output	Verification Method	Results/Deviations	Adequately Verified (Y/N)	Validated through Clinical, Human Factors or Other	Adequately Validated (Y/N)

Reviewer Comment

8.4.3. *Evaluation of Test Methods*

Title:	
Scope/Objective & Acceptance Criteria:	
Methods	

Results:	
Conclusions/ Reviewer Comments:	
Acceptable:	☐Yes ☐No

Reviewer Comment

8.5. Design Verification Review Conclusion

DESIGN VERIFICATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☐ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Design verification is adequate. Testing has been supplied to support overall device reliability of 99.999%. Cap removal torque testing failed to meet the specification with 99.99% reliability when devices were analyzed as a pooled sample, but segregating test articles by (b) (4) produced normal distributions which met the requirement. The control strategy for this EPR includes attribute and variable testing on lot release for both the device (b) (4) and the final finish combination product.		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

8.6. Discipline Specific Sub-Consulted Review Summary

☑ No Additional Discipline Specific Sub-Consults were requested
☐ The following additional Discipline Specific Sub-Consults were requested:

9. CLINICAL VALIDATION REVIEW

9.1. Review of Clinical Studies Clinical Studies

☑ There is no device related clinical studies for review
☐ There are clinical studies for review

10. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	☐
Human Factors deferred to DMEPA	☑

11.FACILITIES & QUALITY SYSTEMS

11.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☑
CDRH Facilities Inspection Review was not conducted	☐

Facility Regulatory History Review	
Firm Name:	
Address & FEI:	
Responsibilities:	
Site Inspection Recommendation:	Choose an item.

Reviewer Comments
See (b) (4). CDRH recommends a post-approval inspection of (b) (4)

Facilities Review Conclusion		
The Sponsor provided adequate information about the facilities AND all inspection issues are resolved if applicable.	☑ Yes	☐ No

11.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted **Quality Management System, Combination Product Device Elements** Purdue maintains the following internal Procedures to govern the relevant quality system requirements of 21 CFR 820.	☑

QSR Section	Quality System	Relevant Procedure(s)
820.20	Management Responsibility	QSC 1_1, Development, Management and Use of the Quality Systems Compliance Manual 0-QA-043, Quality Council
820.30	Design Controls	0-GN-063, Design Control for Drug Device Combination Product Development CQA 1-39, Change Control Program
820.50	Purchasing Controls	0-MM-034, Purchasing Contract Manufacturing and Packaging Services 0-SQA-005, Supplier Auditing 0-QA-032, Implementing Quality Agreements with Third Party Suppliers (b) (4) and Finished Product 0-MM-023, Purchasing of Raw Materials 0-MM-025, Purchasing of Packaging Materials
820.100	Corrective and Preventative Actions	CQA 1-35, Corrective Action and Preventive Action (CAPA) CQA 1-34, Laboratory Investigation Procedure CQA 1-33, Deviation Processing CQA 1-40, Product Quality Complaint Investigations
820.170	Installation	Not relevant for this type of medical device
820.200	Servicing	Not relevant for this type of medical device

CDRH Quality Systems Documentation Review was not conducted	☐

11.3. Control Strategy Review

The Sponsor provided the following control strategy information regarding the EPRs of the device constituents:

Essential Performance Requirements Control Strategy Table

** The proposed acceptance criteria for the EPR may be tighter than the design input and should be assessed for adequate quality control)/ Sampling Plan (Sampling plan may be review issue depending on the product (e.g. emergency-use)*

Essential Performance Requirements	Control Strategy Description - The Sponsor provided the following description of how the essential performance requirements of the combination product are controlled through incoming acceptance, in-process control, and/or release testing activities:	Acceptable (Y/N/NA)
EPR #1		

EPR #2		
EPR …		

Reviewer Comments

Control Strategy Conclusion		
The Sponsor provided adequate information to support the manufacturing control activities for the essential performance requirements of the combination product.	☒Yes	☐No

11.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☑ No ☐ N/A	**Mid-Cycle Deficiencies:** ☐ Yes ☑ No ☐ N/A	**Final Deficiencies:** ☐ Yes ☑ No ☐ N/A
Reviewer Comments Device control strategy is documented and discussed in section 8 Design Verification within Table 3 EPR Release Testing Summary. No deficiencies were identified with the device quality system documentation provided.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☑ No		

<<END OF REVIEW>>

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/s/

SANDY TRUONG
08/09/2024 09:20:05 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING

Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*** This document contains proprietary information that cannot be released to the public***

Date of This Review:	July 15, 2024
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 218590
Product Name, Dosage Form, and Strength:	Zurnai (nalmefene) injection, 1.5 mg/0.5 mL
Applicant Name:	Purdue Pharma L.P.
FDA Received Date:	July 12, 2024
TTT ID #:	2024-8241-1
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 PURPOSE OF MEMORANDUM

Purdue Pharma L.P. submitted revised container label and carton labeling received on July 12, 2024 for Zurnai. The Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the revised container label and carton labeling for Zurnai (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.[a]

2 CONCLUSION

Purdue Pharma L.P. implemented all of our recommendations and we have no additional recommendations at this time. Additionally, we note the order in which the proprietary name, established name, routes of administration and strength are listed is per recommendation from the Agency[b].

[a] Getahun, S. Label and Labeling Review for Zurnai (NDA 218590). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 07. TTT ID: 2024-8241.

[b] Response to Information Request Dated July 08, 2024 (NDA 218590 Zurnai). Stamford (CT): Purdue Pharma L.P.; 2024 JUL 12. Available from: \\CDSESUB1\EVSPROD\nda218590\0015\m1\us\ir-response-jul-08-2024.pdf

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SOFANIT N GETAHUN
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VALERIE S VAUGHAN
07/15/2024 03:26:52 PM

FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion

****Pre-decisional Agency Information****

Memorandum

Date: July 15, 2024

To: Zachary Dezman, Clinical Reviewer
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

Sandy Truong, Regulatory Project Manager, DAAP

Lisa Basham, Associate Director for Labeling, DAAP

From: L. Sheneé Toombs, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Sam Skariah, Team Leader, OPDP

Subject: OPDP Labeling Comments for TRADENAME® (nalmefene injection), for intramuscular or subcutaneous use

NDA: NDA 218590

In response to DAAP's consult request dated March 19, 2024, OPDP has reviewed the proposed Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for TRADENAME® (nalmefene injection), for intramuscular or subcutaneous use.

PI/PPI/IFU:
OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 28, 2024, and our comments are provided below.

A combined OPDP and Division of Medical Policy Programs (DMPP) review was completed for the proposed PPI and IFU, and comments were sent under separate cover on July 11, 2024.

Carton and Container Labeling:
OPDP's review of the proposed carton and container labeling is based on the draft labeling submitted by the sponsor to the electronic document room on July 12, 2024, and we do not have any comments at this time.

Thank you for your consult. If you have any questions, please contact Sheneé Toombs at (301) 796-4174 or latoya.toombs@fda.hhs.gov.

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/s/

LATOYA S TOOMBS
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Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy

PATIENT LABELING REVIEW

Date:	July 10, 2024
To:	Sandy Truong, PharmD Senior Regulatory Project Manager **Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)**
Through:	LaShawn Griffiths, MSHS-PH, BSN, RN Associate Director for Patient Labeling **Division of Medical Policy Programs (DMPP)** Barbara Fuller, RN, MSN, WOCN Team Leader, Patient Labeling **Division of Medical Policy Programs (DMPP)**
From:	Jessica Chung, PharmD, MS Patient Labeling Reviewer **Division of Medical Policy Programs (DMPP)** L. Sheneé Toombs, PharmD, CPH Regulatory Review Officer **Office of Prescription Drug Promotion (OPDP)**
Subject:	Review of Patient Labeling: Patient Package Insert (PPI) and Instructions for Use (IFU)
Drug Name (established name), Dosage Form and Route:	ZURNAI (nalmefene injection), for intramuscular or subcutaneous use
Application Type/Number:	NDA 218590
Applicant:	Purdue Pharma, L.P.

1 INTRODUCTION

On February 7, 2024, Purdue Pharma, L.P. submitted for the Agency's review a 505(b)(2) New Drug Application (NDA) 218590 for ZURNAI (nalmefene injection). The reference listed drug (RLD) for this submission is NDA 020459 for REVEX (nalmefene hydrochloride) injection. The proposed indication for ZURNAI (nalmefene injection) is for the emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, (b) (4) (b) (4).

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on March 19, 2024, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for ZURNAI (nalmefene injection).

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on June 7, 2024.

2 MATERIAL REVIEWED

- Draft ZURNAI (nalmefene injection) PPI and IFU received on February 7, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 28, 2024.
- Draft ZURNAI (nalmefene injection) Prescribing Information (PI) received on February 7, 2024, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on June 28, 2024.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level. In our review of the IFU the target reading level is at or below an 8th grade level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APHont to make medical information more accessible for patients with vision loss. We reformatted the PPI and IFU document using the Arial font, size 10.

In our collaborative review of the PPI and IFU we:

- simplified wording and clarified concepts where possible

- ensured that the PPI and IFU are consistent with the Prescribing Information (PI)
- removed unnecessary or redundant information
- ensured that the PPI and IFU are free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the PPI meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the IFU meets the criteria as specified in both the FDA's Guidance for Useful Written Consumer Medication Information (published July 2006) and Instructions for Use-Patient Labeling for Human Prescription Drug and Biological Products (published July 2022)

4 CONCLUSIONS

The PPI and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the PPI and IFU is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the PPI and IFU.

Please let us know if you have any questions.

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/s/

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BARBARA A FULLER
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LASHAWN M GRIFFITHS
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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: June 13, 2024

TO: Rigoberto A Roca, MD
Director
Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of New Drugs

FROM: Melkamu Kebtie Getie, Ph.D., R.Ph.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Kimberly Benson, Ph.D.
Deputy Director
DGDSI
OSIS

SUBJECT: Review of Analytical RRA of [redacted] (b) (4)

1. RRA Summary

The Office of Study Integrity and Surveillance (OSIS) conducted an analytical RRA of studies NAL1004 and NAL1005 (NDA 218590, nalmefene) conducted [redacted] (b) (4)

No objectionable conditions were observed. Based on the RRA findings, there are no identified concerns regarding reliability of the data for the audited studies for the review division consideration.

2. Audited Studies

NDA 218590

Study Number: NAL1004
Study Title: "A Study to Characterize the Time Course of Reversal of Opioid (Fentanyl)-Induced Respiratory Depression Following Administration of Nalmefene Autoinjector 1.5 mg (0.94% MgCl2) Intramuscular and Narcan® 4 mg Intranasal in Healthy Subjects"

Sample analysis dates: 11/14/2022 – 5/25/2023 (nalmefene)
11/11/2022 – 1/17/2023 (naloxone)
11/21/2022 – 1/30/2023 (fentanyl)

Study Number: NAL1005
Study Title: "A Phase 1, Open Label, Randomized, Single Dose, Two-Period Crossover Study in Healthy Subjects to Compare the Pharmacokinetic Profiles of Nalmefene following Intramuscular Administration of Nalmefene Autoinjector 1.5 mg (0.94% MgCl2) versus Nalmefene Hydrochloride Injection 1 mg"
Sample analysis dates: 6/16/2023 – 7/5/2023

Analytical site: [redacted]

3. RRA Findings

OSIS Scientist Melkamu Getie-Kebtie conducted an RRA [redacted]

3.1 Previous RRA

The previous OSIS RRA [redacted], was conducted from [redacted]. At the conclusion of the RRA, an observation was discussed with the firm regarding lack of established procedure for sample reanalysis and reporting of the incurred sample reproducibility (ISR) results for the analytes in the audited study. No similar findings were observed in the current RRA.

3.2 Current RRA

The current RRA included conducting a virtual tour, auditing study related records, and interviewing the firm's management and staff.

3.3 RRA finding

At the conclusion of the RRA, I did not observe any objectionable conditions.

Melkamu Getie-Kebtie, R.Ph., Ph.D.,
Pharmacologist

Draft: MG 6/6/24, 6/10/24, 6/13/24
Edit: SA 6/6/24, 6/13/24; KB 6/10/24

OSIS File #: BE [redacted]

eNSpect Assignment ID: [redacted]
eNSpect OpID: [redacted]

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/s/

MELKAMU GETIE KEBTIE
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STANLEY AU
06/13/2024 11:56:12 AM
Secondary reviewer

KIMBERLY A BENSON
06/13/2024 11:57:26 AM

This is a corrected review that does not change the overall recommendations/conclusions of the original review dated June 7, 2024

LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 1 (DMEPA 1)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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Date of This Review:	June 7, 2024
Requesting Office or Division:	Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Application Type and Number:	NDA 218590
Product Name, Dosage Form, and Strength:	Zurnai (nalmefene hydrochloride) injection, 1.5 mg/0.5 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Purdue Pharma L.P.
FDA Received Date:	February 7, 2024, and April 19, 2024
TTT ID #:	2024-8241
DMEPA 1 Safety Evaluator:	Sofanit Getahun, PharmD, BCPS
DMEPA 1 Team Leader:	Valerie S. Vaughan, PharmD

1 REASON FOR REVIEW

As part of the approval process for Zurnai (nalmefene hydrochloride) injection, the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) requested that we review the proposed Zurnai prescribing information (PI), container label, carton labeling, and Instructions for Use for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

NDA 218590 is a 505(b)(2) NDA and the listed drug product is Revex, NDA 020459.

2 MATERIALS REVIEWED

Table 1. Materials Considered for this Label and Labeling Review

Material Reviewed	Appendix Section (For Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E -N/A
Labels and Labeling	F

N/A=not applicable for this review
*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), container label, carton labeling, and Instructions for Use may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Purdue Pharma L.P.

Note that DMEPA 1 is evaluating the HF validation study results under separate cover and based on the outcome of that review, additional label and labeling comments may be forthcoming.

4 RECOMMEDATIONS FOR DIVISION OF ANESTHESIOLOGY, ADDICTION MEDICINE, AND PAIN MEDICINE (DAAP)

Table 2. Identified Issues and Recommendations for Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
General Issues			
As currently presented the proprietary name is denoted by the place holder "TRADENAME" throughout the PI. The proposed proprietary name "Zurnai" was found conditionally acceptable on April 15, 2024. Remove the place holder "TRADENAME" and replace with the conditionally acceptable name "Zurnai."			
Full Prescribing Information – Section 3 Dosage Forms and Strengths			
1.	As currently presented, information about the package type (i.e., single dose) or the appropriate information to facilitate identification of the dosage form is not included.	A description of identifying characteristics is required by 21 CFR 201.57(c)(4)(ii) and can be used to help mitigate the risk of administering deteriorated or contaminated drug for this product.	Include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in accordance with 21 CFR 201.57(c)(4)(ii).
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	As currently presented, the appropriate information to facilitate identification of the dosage form is not included.	A description of the identifying characteristics can be used to help identify the product and is required by 21 CFR 201.57(c)(17)(iii).	Include a description of identifying characteristics of the dosage form, such as color and clarity of the solution in accordance with 21 CFR 201.57(c)(17)(iii).

5 RECOMMENDATIONS FOR PURDUE PHARMA L.P.

Table 3. Identified Issues and Recommendations for Purdue Pharma L.P. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label(s) and Carton Labeling			
1.	The format for expiration date is not defined on the carton labeling.	Clearly defining the expiration date will minimize confusion and risk for deteriorated drug medication errors.	Identify the expiration date format you intend to use. FDA recommends that the human-readable expiration date on the drug package label include a year, month, and non-zero day. FDA recommends that the expiration date appear in YYYY-MM-DD format if only numerical characters are used or in YYYY-MMM-DD if alphabetical characters are used to represent the month. If there are space limitations on the drug package, the human-readable text may include only a year and month, to be expressed as: YYYY-MM if only numerical characters are used or YYYY-MMM if alphabetical characters are used to represent the month. FDA recommends that a hyphen or forward slash be used to separate the portions of the expiration date.
2.	As currently presented the proprietary name is denoted by the place holder "TRADENAME" on the container label and carton labeling	The proposed proprietary name "Zurnai" was found conditionally acceptable on April 15, 2024.	Remove the place holder "TRADENAME" and replace with the conditionally acceptable name "Zurnai."
3.	As currently presented, the strength statement on the PDP does not	Consider revising the strength statement such that the strength statement appears as:	

Table 3. Identified Issues and Recommendations for Purdue Pharma L.P. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	include the volume of the product.	"1.5 mg/0.5 mL."	
4.	As currently presented, the (b) (4) is located above the Use Instructions. (b) (4)	Grouping of contents allows for logical sequence of information. Additionally, the Instructions for Use contains the details on administration instructions.	Above the use instructions and corresponding graphics, we recommend replacing the (b) (4) with the instruction *"Refer to Instructions for Use for additional administration details."* Additionally, we recommend relocating the (b) (4) (b) (4) to the side panel and revising from (b) (4) to *"Dosage: see Full Prescribing Information."*
Container Label			
1.	We note Step 4 of the Instruction for Use *"Call 911 and watch the person. Stay until ambulance arrives"* is not included.	This instruction should be retained on the Autoinjector label as it is an important step to ensure that the opioid overdose patient receives appropriate medical attention following the use of Zurnai.	Include Step 4 of the Instruction for Use *"Call 911 and watch the person. Stay until ambulance arrives"* on the AI label.
Instructions for Use			
1.	As currently presented the heading of the IFU document submitted with your application does not include a title/header which indicates to end user the	The title/header *"Instructions for Use"* more accurately reflects the purpose of the document.	Include the header/title *"Instructions for Use"* at the top of the document and ensure sufficient prominence of the title.

Table 3. Identified Issues and Recommendations for Purdue Pharma L.P. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	purpose of the document. (b) (4)		
2.	As currently presented, the IFU does not include information that instructs users on administering repeat doses, nor does it include information pertaining to placing patients in the recovery position.	Not consistent with the Prescribing Information.	To ensure consistency with the Prescribing Information, we recommend including instruction to users indicating when a repeat dose is necessary and placing patients in the recovery position.
3.	As currently presented, the layout for the instruction titled, *"Preparing to Inject TRADENAME"* appears cluttered. (b) (4)	The current layout decreases readability for each of the intended actions.	We recommend adding space between the statements and utilizing bullet points to increase readability. For example: (b) (4)

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table presents relevant product information for Zurnai that Purdue Pharma L.P. submitted on February 7, 2024, and the listed drug (LD).

Table 4. Relevant Product Information for Listed Drug and Zurnai		
Product Name	Revex	Zurnai
Initial Approval Date	April 17, 1995	N/A
Active Ingredient	Nalmefene hydrochloride	
Indication	For the complete or partial reversal of opioid drug effects, including respiratory depression, induced by either natural or synthetic opioids. REVEX is indicated in the management of known or suspected opioid overdose.	Emergency treatment of known or suspected opioid overdose induced by natural or synthetic opioids in adults and pediatric patients aged 12 years and older, (b) (4)
Route of Administration	Intravenous, intramuscular, and subcutaneous	Intramuscular and subcutaneous
Dosage Form	Injection	
Strength	100 mcg/mL and 1 mg/mL	1.5 mg/0.5 mL

<table>
<tr><th colspan="3">Table 4. Relevant Product Information for Listed Drug and Zurnai</th></tr>
<tr><td>Product Name</td><td>Revex</td><td>Zurnai</td></tr>
<tr><td>Dose and Frequency</td><td>Recommended Doses for Reversal of Postoperative Opioid Depression
Use 100 µg/mL dosage strength (blue label).

The goal of treatment with REVEX in the postoperative setting is to achieve reversal of excessive opioid effects without inducing a complete reversal and acute pain.
This is best accomplished with an initial dose of 0.25 µg/kg followed by 0.25 µg/kg incremental doses at 2–5-minute intervals, stopping as soon as the desired degree of opioid reversal is obtained.
A cumulative total dose above 1.0 µg/kg does not provide additional therapeutic effect.
<table>
<tr><th colspan="2">Reversal of Postoperative Opioid Depression</th></tr>
<tr><td>Body weight</td><td>mL of Revex 100 µg/mL</td></tr>
<tr><td>50 kg</td><td>0.125</td></tr>
<tr><td>60 kg</td><td>0.15</td></tr>
<tr><td>70 kg</td><td>0.175</td></tr>
<tr><td>80 kg</td><td>0.2</td></tr>
<tr><td>90 kg</td><td>0.225</td></tr>
<tr><td>100 kg</td><td>0.25</td></tr>
</table>

Management of Known or Suspected Opioid Overdose
Use 1 mg/mL dosage strength (green label).

The recommended initial dose of REVEX for non-opioid</td><td><u>Initial Dosing:</u>

The recommended dose of Auto-Injector in adults and pediatric patients aged 12 years and older is 1.5 mg delivered by intramuscular or subcutaneous injection into the anterolateral aspect of the thigh, through clothing if necessary.

<u>Repeat Dosing:</u>

Seek emergency medical assistance as soon as possible after administration of the first dose of Auto-Injector. The requirement for repeat doses depends upon the amount, type, and route of administration of the opioid being antagonized.

If the patient responds to and subsequently relapses back into respiratory depression before emergency assistance arrives, administer an additional dose using a new auto-injector and continue surveillance of the patient.

If the desired response is not obtained after 2 to 5 minutes, administer an additional dose of Auto-Injector using a new auto-injector. If there is still no response and additional doses are available, administer</td></tr>
</table>

Table 4. Relevant Product Information for Listed Drug and Zurnai		
Product Name	Revex	Zurnai
	dependent patients is 0.5 mg/70 kg. If needed, this may be followed by a second dose of 1 mg/70 kg, 2-5 minutes later. If a total dose of 1.5 mg /70 kg has been administered without clinical response, additional REVEX (nalmefene hydrochloride injection) is unlikely to have an effect. Patients should not be given more REVEX than is required to restore the respiratory rate to normal, thus minimizing the likelihood of cardiovascular stress and precipitated withdrawal syndrome. If there is a reasonable suspicion of opioid dependency, a challenge dose of REVEX 0.1 mg/70 kg should be administered initially. If there is no evidence of withdrawal in 2 minutes, the recommended dosing should be followed.	additional doses of Auto-Injector every 2 to 5 minutes using a new Auto-Injector with each dose until emergency medical assistance arrives. Additional supportive and/or resuscitative measures may be helpful while awaiting emergency medical assistance.
How Supplied	An ampul containing 1 mL of 100 µg/mL nalmefene base (Blue Label) Box of 10 (NDC 10019-315-21) An ampul containing 2 mL of 1 mg/mL nalmefene base (Green Label) Box of 10 (NDC 10019-311-22)	Each single-dose auto-injector device delivers 1.5 mg of nalmefene in 0.5 mL. Each carton contains one single-dose TRADENAME Auto-Injector. NDC 59011-xxx-xx: One carton containing one single-dose auto-injector.

Table 4. Relevant Product Information for Listed Drug and Zurnai		
Product Name	Revex	Zurnai
Storage	Controlled room temperature	Store at controlled room temperature 20°C to 25°C (68°F to 77°F), with excursions permitted between 15°C and 30°C (59°F and 86°F).
Container Closure	Ampule	Autoinjector

APPENDIX B. PREVIOUS DMEPA REVIEWS

On February 16, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, nalmefene, and 218590. Our search did not identify any previous labeling reviews.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[a] along with postmarket medication error experiences with similar products, we reviewed the following Zurnai labels and labeling submitted by Purdue Pharma L.P.

- Container label received on February 7, 2024
- Carton labeling received on February 7, 2024
- Prescribing Information (Image not shown) received on April 19, 2024, available from:
  - Clean version: \\CDSESUB1\EVSPROD\nda218590\0005\m1\us\draft-label-text-clean.docx
  - Annotated version: \\CDSESUB1\EVSPROD\nda218590\0005\m1\us\draft-label-text-redline.docx
- Patient Information (Image not shown) received on April 19, 2024, available from: \\CDSESUB1\EVSPROD\nda218590\0005\m1\us\draft-label-ppi-2024-april.docx
- Instructions for Use (Image not shown) received on April 19, 2024, available from: \\CDSESUB1\EVSPROD\nda218590\0005\m1\us\draft-label-ifu-2024-april.docx

F.2 Label and Labeling Images

Container label

[a] Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4/10/2024

TO: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct on-site inspections**

RE: NDA 218590

The Office of Study Integrity and Surveillance (OSIS) received an inspection request consult from the Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP) on March 18, 2024, for the below sites. The requested review goal date is June 25, 2024.

Rationale

Inspections or remote regulatory assessments (RRA) of the sites below are not able to be completed. Specifically, the requested review goal date of June 25, 2024, to meet the PDUFA date of August 7, 2024, does not provide sufficient time for an inspection or remote regulatory assessment (RRA) to be completed and for OSIS to submit a review to the review division.

We note OSIS's inspection history for the site listed below.

(b) (4) OSIS conducted an RRA for the site Non-responsive. The RRA was conducted under the following submission: Non-responsive.

The following objectionable condition was observed:

Non-responsive

After review of the objectionable conditions and the written response from the site, OSIS concluded that data from the reviewed studies were reliable but recommended that the review division consider requesting additional information on blood sample handling and processing from the applicant and determine the impact of the findings on data reliability. (Final OSIS Report – Non-responsive

Ohio Clinical Trials, Columbus: Although OSIS has no inspection history for this site, the PDUFA date of August 7, 2024, does not provide sufficient time for an inspection or remote regulatory assessment (RRA) to be completed and for OSIS to submit a review to the review division.

Therefore, based on the information above, the sites below will not be inspected by OSIS at this time.

Sites

Facility Type	Facility Name	Facility Address
Clinical	Ohio Clinical Trials	1380 Edgehill Road, Columbus, OH
Analytical	(b) (4)	

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/s/

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M E M O R A N D U M

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: 4/10/2024

TO: Division of Anesthesiology, Addiction Medicine, and Pain Medicine (DAAP)
Office of Neuroscience (ON)

FROM: Office of Study Integrity and Surveillance (OSIS)

SUBJECT: **Decline to conduct an on-site inspection**

RE: NDA 218590

The Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) conducted an inspection for the site in September 2022. The inspection was conducted under the following submissions: Non-responsive.

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Clinical	Novum Pharmaceutical Research Services, Inc.	3760 Pecos McLeod, Las Vegas, NV

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