

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214697Orig1s000

OTHER REVIEW(S)

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)

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Date of This Review:	August 9, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214697
Product Name, Dosage Form, and Strength:	neffy (epinephrine) nasal spray, 2 mg/0.1 mL per spray
Applicant Name:	ARS Pharma
FDA Received Date:	August 8, 2024
TTT ID #:	2022-1023-3
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

1 PURPOSE OF MEMORANDUM

ARS Pharma submitted revised blister label, carton labeling, and instructions for use (IFU) received on August 8, 2024 for neffy. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised blister label, carton labeling, and IFU for neffy (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

ARS Pharma implemented all of our recommendations and we have no additional recommendations at this time.

^a Owens L. Label and Labeling Review Memo for neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 AUG 8. TTT ID: 2022-1022-4 and 2022-1023-2.

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/s/

DAMON A BIRKEMEIER
08/09/2024 11:54:46 AM

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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)

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Date of This Review:	August 8, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214697
Product Name, Dosage Form, and Strength:	Neffy (epinephrine) nasal spray, 2 mg
Applicant Name:	ARS Pharma
FDA Received Date:	August 5, 2024; August 6, 2024; August 7, 2024
TTT ID #:	2022-1022-4 and 2022-1023-2
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT
DMEPA 1 Associate Director for Human Factors:	Ariane O. Conrad, PharmD, BCACP, CDCES, FISMP
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP

1 PURPOSE OF MEMORANDUM

ARS Pharma submitted their revised Quick Reference Guide (QRG) on the blister pack and carton labeling for Neffy on August 5, 2024, and the device label for Neffy on August 6, 2024, and Instructions for Use (IFU) for Neffy on August 7, 2024. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised QRG and IFU (Appendix A) to determine if they are acceptable from a human factors and medication error perspective. We note that revisions were made in response to recommendations provided in our prior human factors and label and labeling reviews.^a

In addition, we note that ARS incorporated changes to the IFU and blister label that were recommended by the Division of Medical Policy Programs (DMPP) (“The use of symbols and images to represent what a patient should “not” see or do are not recommended in patient labeling, as this could lead to patient confusion. Therefore, we recommend deleting the [REDACTED] (b) (4)”).^b Therefore, we also comment on our alignment with the recommendations from patient labeling from a human factors perspective.

2 DISCUSSION

Our August 7, 2024 labeling review memo included a recommendation to revise the proposed “Use in the Nose Only” statement on the device front label.^c Our recommendation was relayed to ARS via email. ARS replied with the following rationale in their August 7, 2024: *“If we make this the same as the Blister the language will likely be too long and may make it more difficult to read. Can you check if it is acceptable to keep the abbreviated language on the device itself or we may have to reduce the font which was a prior comment to increase the font.”* Thus, in this case, we find the Applicant’s rationale acceptable, and we have no additional recommendations regarding this issue at this time.

^a Owens, L. Review of Revised Label and Labeling Memorandum for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Aug 7. TTT ID: 2022-1022-3.

Barlow, M. Human Factors Study Report Review for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Jul 12. TTT ID: 2022-1023-1.

Owens, L. Review of Revised Label and Labeling Memorandum for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Jun 6. TTT ID: 2022-1022-2.

Owens, L. Label and Labeling Review for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 May 30. TTT ID: 2022-1022-1

Barlow, M. Human Factors Study Report Review for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 Jun 1. TTT ID: 2022-1023.

Owens, L. Label and Labeling Review for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 May 15. TTT ID: 2022-1022

^b Booker, N. Patient Labeling Review for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OMP, DMPP/OPDP (US); 2024 Jun 28. NDA 214697.

^c Owens, L. Review of Revised Label and Labeling Memorandum for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 Aug 7. TTT ID: 2022-1022-3.

In addition, we note that ARS incorporated changes to their QRG and IFU to address a separate communication sent by DPACC for Neffy. Of note, images regarding the “wrong use” were removed and the formatting of the instructions was revised (See table below).

Previously Reviewed in L&L Review and HF Review	Current
(b) (4)	

Per their submission, *“ARS made updates to the Neffy™ IFU and QRG following the EPI 13 study. Specifically, these were modified to better communicate the aspect of the dosing procedure related to the potential for drug loss (i.e., correct insertion angle and depth of insertion). The dosing illustrations were also updated to depict the proper dosing technique more clearly.”* Thus, the images were added to address a concern noted in their HF studies and they subsequently validated the updated labeling in a post-validation study.

Based on this information and the subsequent review of the HF results validating the user interface, we determined that ARS’s data supports the use of the “wrong use” images in the QRG and IFU as previously proposed. Thus, we advised the review division to recommend that ARS revise the Neffy QRG and IFU to retain the “wrong use” images and to revise the formatting of the information on the QRG to be consistent with formatting used in HF validation. Subsequently, DPACC agreed to send an information request to ARS requesting that the removed images in the IFU are placed back under the “Do not angle nozzle” direction in the IFU. In addition, they agreed with the recommendation to revert the layout of the numbered steps in the QRG as recommended. However, they do not agree with our recommendation to include a single “wrong use” image in the QRG because they determined that the *“QRG is cleaner to read without the ‘wrong use’ image”, “the text for ‘wrong use’ is retained in both the IFU and QRG so the information is communicated to the patient”, and “the ‘wrong use’ image only demonstrates one aspect of incorrect use (pointing towards the side wall) and not angling towards the septum.”*

3 CONCLUSION

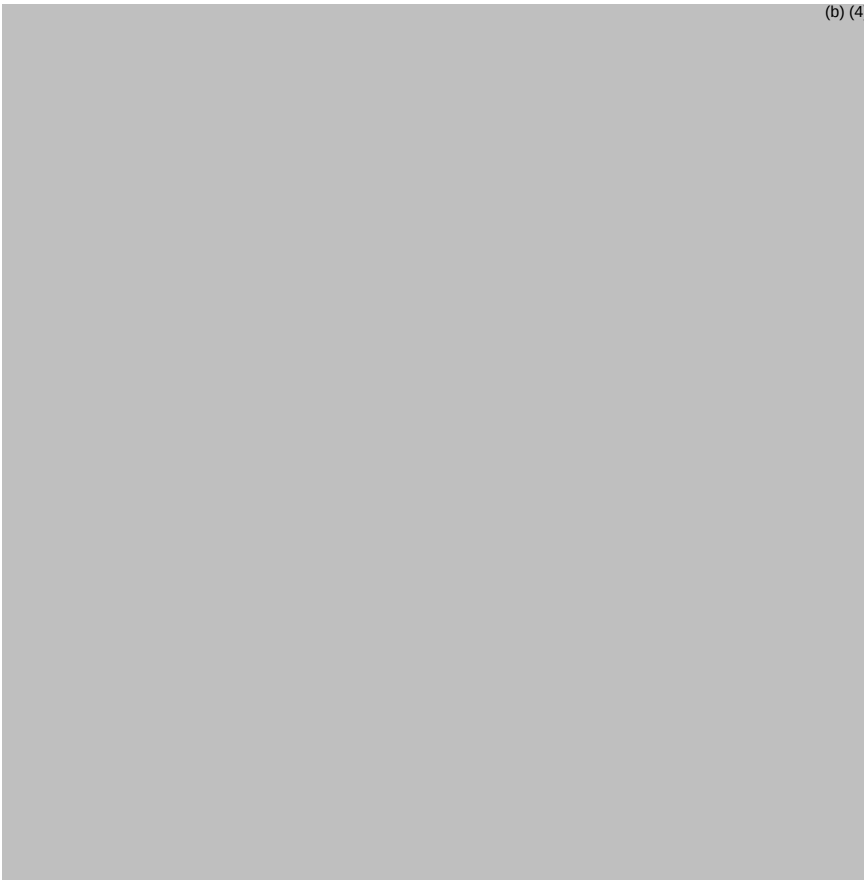
We continue to have concerns with the removal of the “(b) (4)” image from the QRG from a human factors perspective; however, we acknowledge DMPP and DPACC’s concerns regarding the images. We note that DPACC is communicating our recommendations for the “(b) (4)” images in the IFU and formatting concerns with the numbered steps in the QRG.^d

^d LaRose, J. Advice/Information Request for Label IR #6 NDA 214697 Resubmission. Silver Spring (MD): FDA, CDER, OND, DPACC (US); 2024 Aug 8. NDA 214697.

APPENDIX A. LABELS AND LABELING

- Instructions for Use received on August 7, 2024, available from <\\CDSESUB1\EVSPROD\nda214697\0082\m1\us\draft-labeling-text-ifu.pdf>
- Device label received on August 6, 2024
- Blister label received on August 5, 2024
- Carton labeling received on August 5, 2024

Device Label:



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/s/

ARIANE O CONRAD
08/08/2024 01:36:48 PM

LISSA C PRINGLE-OWENS
08/08/2024 01:38:10 PM

DAMON A BIRKEMEIER
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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)

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Date of This Review:	August 7, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214697
Product Name, Dosage Form, and Strength:	neffy (epinephrine) Nasal Spray, 2 mg/0.1 mL per spray
Applicant Name:	ARS Pharma
FDA Received Date:	August 5, 2024
TTT ID #:	2022-1022-3
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

ARS Pharma submitted revised container labels and carton labeling received on August 5, 2024 for neffy. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels and carton labeling for neffy (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to labeling comments and recommendations sent by DPACC on August 2, 2024.^a

2 CONCLUSION

ARS Pharma previously implemented all of our recommendations^b; however, the revised device front label can be improved to minimize the risk of medication errors.

3 RECOMMENDATIONS FOR ARS PHARMA

A. Container Label

1. Revise the device front label from 'Use in the Nose only' to read 'For Use in the Nose Only' to maintain consistency with the blister label and carton labeling.

^a <https://dartrts.fda.gov/dartrts/ViewDocument?documentId=090140af8075d5df>

^b Owens, L. Label and Labeling Review for neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 JUN 06. TTT ID: 2022-1022-2.

APPENDIX A. IMAGES OF LABELS AND LABELING RECEIVED ON AUGUST 5, 2024

Prescribing Information

<\\CDSESUB1\EVSPROD\nda214697\0080\m1\us\draft-labeling-text-package-insert-clean.pdf>

Instructions for Use

<\\CDSESUB1\EVSPROD\nda214697\0080\m1\us\draft-labeling-text-ifu.pdf>

Patient Information

<\\CDSESUB1\EVSPROD\nda214697\0080\m1\us\patient-information-leaflet.pdf>

Container Label(s)

Blister



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/s/

LISSA C PRINGLE-OWENS
08/07/2024 09:22:51 AM

DAMON A BIRKEMEIER
08/07/2024 09:26:01 AM

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 12, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214697
Product Type:	Combination Product (Drug-Device)
Product Name, Dosage Form and Strength:	Neffy ^a (epinephrine) nasal spray, 2 mg
Device Constituent:	Aptar Nasal Spray Device
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ARS Pharma
FDA Received Date:	April 2, 2024; April 18, 2024
TTT #:	2022-1023-1
DMEPA 1 Team Leader (Acting):	Matthew Barlow, RN, BSN
DMEPA 1 Deputy Director:	Jason Flint, MBA, PMP
DMEPA 1 Director:	Mishale Mistry, PharmD, MPH

^a The proposed proprietary name, Neffy, was found conditionally acceptable on October 27, 2022.

1. REASON FOR REVIEW

This review evaluates the human factors (HF) validation study report and labels and labeling submitted under NDA 214697 for Neffy (epinephrine) nasal spray.

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
Labels, Labeling, and Packaging	Appendix C

N/A=not applicable for this review

1.1 PRODUCT INFORMATION

Table 2 presents relevant product information for Neffy that ARS Pharma submitted on April 2, 2024.

Table 2. Relevant Product Information for Neffy	
Initial Approval Date	N/A
Active Ingredient	epinephrine
Indication	indicated for emergency treatment of allergic reactions (Type I), including anaphylaxis, in adult and pediatric patients who weigh ≥ 30 kg.
Route of Administration	Intranasal
Dosage Form	Nasal spray
Strength	2 mg
Dose and Frequency	One spray of Neffy (2 mg epinephrine) administered into one nostril. Administer second dose of Neffy in the same nostril with a new nasal spray after approximately (b) (4) minutes in absence of clinical improvement or (b) (4) after initial dose.
How Supplied	Neffy nasal spray: 2 mg/0.1 mL of epinephrine is supplied in a carton containing two (2) blister packages each with a single-dose spray device for 1 time use (NDC 82580-020-02).
Storage	Store at 68°F to 77°F (20°C to 25°C). Excursions permitted up to 122°F (50°C).

	Do not freeze. Neffy freezes below 5°F (-15°C). If Neffy freezes, it will not deliver drug. (b) (4)
Container Closure/ Device Constituent (including figure)	(b) (4)
Intended Users	Patients (adults and pediatrics), caregivers, naïve passersby, and Healthcare professionals (HCPs)
Intended Use Environment	Home; public

The proposed optional carrying case is a zippered case. When opened, the Quick Reference Guide is located on one side (the Quick Reference Guide is the same as that of the blister package) and the opposite side contains two 'molds', where two nasal sprays (removed from the blister package) are intended to be placed.



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

On May 1, 2024, we searched for previous DMEPA reviews and FDA/Applicant interactions relevant to this current review using the terms, NDA 214697, IND 139091, and ARS1. The identified reviews and FDA/Applicant interactions are provided below.

- On September 4, 2019, the Applicant submitted an HF validation study protocol, and we provided our review and feedback on November 1, 2019^b.
- On February 5, 2020, the Applicant submitted a revised protocol and responses to our November 1, 2019 recommendations; however, initially the Applicant stated they did not submit the protocol for the Agency's review/feedback. On February 24, 2020, the Applicant sent an email stating they would now wait for any additional feedback from the Agency. On April 10, 2020, we provided our review and recommendations to the Sponsor's responses and revised protocol^c.
- The Applicant submitted NDA 214697 on August 19, 2022; HF validation study results and post-validation supplemental HF study results were included as part of the submission.
- On June 2, 2023, we completed our review of the HF validation study results and post-validation supplemental HF study results^d. We determined the results were acceptable; however, we had additional labeling recommendations to address the noted use issues.
- On April 18, 2023, the Applicant submitted a proposed optional carry case for the proposed epinephrine nasal spray product, which would not be packaged with the proposed epinephrine nasal spray product. On July 6, 2023, the Applicant submitted additional information and graphics of the proposed optional carry case.
- On July 18, 2023, we informed the Applicant that they will need to submit the proposed carry case to the NDA as a supplement because, "the use of this material and labeling will need to be reviewed for human factors and stability considerations"^e.
- On September 19, 2023, we informed the Applicant that a supplemental NDA is not required for the carry case, as it was determined to be optional, and the Applicant was not proposing to provide it with the intend-to-market user interface and packaging. Additionally, we communicated concerns regarding their proposed carry case along with recommendations for their consideration^f.

^b Barlow, M. HF Validation Study Protocol Review for epinephrine nasal spray (IND 139091). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 01. RCM No.: 2019-1851.

^c Barlow, M. Review Revised HF Protocol and Responses for epinephrine nasal spray (IND 139091). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 10. RCM No.: 2019-1851-1.

^d Barlow, M. HF Results Review for epinephrine nasal spray (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1(US); 2023 JUN 02. RCM No.: 2022-1023.

^e Larose, J. Information Request for epinephrine nasal spray. Silver Spring (MD): FDA, CDER, OND< DPACC (US); 2023 July 18. NDA 214697.

^f Larose, J. Information Request for epinephrine nasal spray. Silver Spring (MD): FDA, CDER, OND< DPACC (US); 2023 September 19. NDA 214697.

- On September 19, 2023, the application received a Complete Response (CR) due to clinical, clinical pharmacology, and product quality deficiencies⁸.
- On April 2, 2024, the Applicant submitted their CR response under NDA 214697, which included two additional “post-validation supplemental” human factors studies, which are the focus 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 study 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 updated labeling (blister pack Quick Reference Guide and Instructions for Use) proposed in the resubmission. Table 4 presents a summary of the “post-validation supplemental study for updated labeling” and “post-validation supplemental study for carrying case” studies design, and our discussion of methodology concerns (as applicable). Note, we did not review the protocol for either of these HF studies. See Appendix A for more details on the study design.

Table 3. Comparison of Labeling (Blister Pack Quick Reference Guide and Instructions for Use)	
Labeling evaluated in previous HF validation study	Labeling evaluated in “post-validation supplemental study”
Top Row: Blister pack quick reference guide (QRG) (this information is also presented on the back panel of the carton labeling)	Top Row: Blister pack quick reference guide (QRG) (this information is also presented on the back panel of the carton labeling)
Bottom Row: IFU steps and “Important Information” section	Bottom Row: IFU steps and “Important Information” section

⁸ Larose, J. Complete Response for epinephrine nasal spray. Silver Spring (MD): FDA, CDER, OND< DPACC (US); 2023 September 19. NDA 214697.

Table 4. Study Methodology for Human Factors (HF) Validation Study		
“Post-Validation Supplemental Study for Updated Labeling” Design	“Post-Validation Supplemental Study for Carrying Case” Design	DMEPA Discussion of Methodology Concerns
User Group(s) • Adult patients (n=4) • Adult caregivers (n=4) • Pediatric patients [10-17 years of age] (n=8)	User Group(s) • Adult patients (n=4) • Adult caregivers (n=4) • Pediatric patients [10-17 years of age] (n=8)	Generally, we recommend that distinct user groups (e.g., adult patients vs. adult caregivers vs. pediatric patients) have a minimum of 15 participants. See Sections 3.1 and 3.2 below for further discussion.
Training No training provided	Training No training provided	N/A
Test Environment & Materials Test room setup to reflect the conditions of a home dining room environment along with a soundtrack of escalating beeps to simulate stress during an anaphylactic emergency	Test Environment & Materials Test room setup to reflect the conditions of a home dining room environment along with a soundtrack of escalating beeps to simulate stress during an anaphylactic emergency	N/A
Sequence of Study Simulated Use Scenario 1: Onset of Anaphylaxis Simulated Use Scenario 2: Persisting Symptoms Root Cause Analysis of Simulated-Use Issues Knowledge Questions	Sequence of Study Simulated Use Scenario 1 and 2: Receipt and Preparation the Carrying Case Simulated Use Scenario 3: Onset of Anaphylaxis Simulated Use Scenario 4: Persisting Symptoms	We note the Applicant did not evaluate all tasks related to the safe and effective use of the proposed product.

	Root Cause Analysis of Simulated-Use Issues	
	Knowledge Questions	

3. RESULTS AND ANALYSIS

In this section, we have carefully reviewed each study report including the methodology, the Applicant's URRAs, the use issues, 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.

3.1 DISCUSSION OF METHODOLOGY ISSUES

We acknowledge the two submitted post-validation HF studies were conducted to evaluate the following: 1) proposed labeling instruction update for the user to administer the second dose in the same nostril as the first dose was administered in ("post-validation supplemental study for updated labeling"), and 2) the proposed optional carrying case. However, we note the Applicant did not recruit 15 participants per distinct user group in each study. Per guidance^h, we generally recommend that each distinct user group includes at least 15 participants for HF validation studies. Additionally, we note that in the study evaluating the optional carrying case, the Applicant did not account for a scenario where the user who packed the carrying case is not the same as the user administering the product (e.g., naïve passersby, HCPs such as a school nurse), as these users would have different tasks. Furthermore, the Applicant did not include multiple simulated use environments (e.g., public restaurant/food court and a home environment).

3.2 ANALYSIS AND CONCLUSION

In the "post-validation supplemental study for updated labeling", one pediatric patient participant noted some difficulty pushing the plunger; however, per the report, this participant was able to push the plunger for both doses without moderator intervention. Additionally, each participant administered the second dose in the same nostril as the first dose. As stated in Section 3.1 above, the Applicant did not recruit 15 participants per distinct user group in each study. However, in reviewing the "Post-Validation Supplemental Study for Updated Labeling" and "Post-Validation Supplemental Study for Carrying Case" study reports, it appears each adult participant (both patients and caregivers) (n=16) and each pediatric patient participant (n=16), in both studies, comprehended the instruction to

^h See FDA Guidance for Industry and Food and Drug Administration Staff *Applying Human Factors and Usability Engineering to Medical Devices*, February 2016. Available from <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/applying-human-factors-and-usability-engineering-medical-devices>.

administer the second dose in the same nostril. Based on our discussions with our clinical colleagues from the Division of Pulmonology, Allergy, and Critical Care (DPACC), the risk of administering the second dose in the opposite nostril as the first dose is acceptable because the majority of patients will only need one dose, and that delivering a second dose in a different nostril is an acceptable risk based on pharmacokinetic data from the non-nasal allergen challenge test. Therefore, considering the unmet public health need for alternative routes of administration for epinephrine that may increase use and reduce time to administration, along with the totality of HF data, and the clinical team's benefit/risk determination, in this particular instance, we find the proposed user interface supports the safe and effective use of the proposed product.

We acknowledge there were no use issues with the supplemental HF study evaluating the optional carrying case; however, we remain concerned that in the instance that the zipper malfunctions, users would be unable to open the case. For this product, such a delay could lead to prolonged anaphylaxis and death. Therefore, considering the methodology issues discussed above (Section 3.1), coupled with the aforementioned inherent design issues with the optional carrying case (e.g., utilization of a zipper), we are unable to determine if the optional carrying case supports the safe and effective use of the proposed product. However, we note that as the optional carrying case is not how the product would be dispensed, it is out of the purview of the Agency for review.

Additionally, we note the Applicant did not receive the labeling recommendations from our June 2, 2023 reviewⁱ. Thus, these recommendations should be communicated to the Applicant.

4. CONCLUSION AND RECOMMENDATIONS

Based on our review of the "Post-Validation Supplemental Study for Updated Labeling" and "Post-Validation Supplemental Study for Carrying Case", we find that the revised labeling supports safe and effective use of the proposed product.

We note the Applicant did not receive our labeling recommendations from our June 2, 2023 review^j. Thus, we recommend these recommendations are communicated to the Applicant (See Section 4.1). These changes can be implemented without submitting additional HF validation testing results for Agency review.

With respect to the proposed optional carrying case, we are unable to determine whether it supports safe and effective use, due to study methodology concerns. However, regardless of the study methodology, we remain concerned that the zipper closure mechanism can malfunction, and such a delay in care may lead to prolonged anaphylaxis and death.

ⁱ Barlow, M. HF Results Review for epinephrine nasal spray (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1(US); 2023 JUN 02. RCM No.: 2022-1023.

^j Barlow, M. HF Results Review for epinephrine nasal spray (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1(US); 2023 JUN 02. RCM No.: 2022-1023.

4.1 RECOMMENDATIONS FOR ARS PHARMA

Based on the totality of the human factors (HF) data, we find the proposed user interface supports the safe and effective use of the proposed product. However, we are unable to determine whether the optional carrying case supports the safe and effective use of the proposed product, as the study methodology does not allow for a comprehensive evaluation of the modified user interface that the use of the optional carrying case invites. We continue to have concerns with the design of proposed optional carrying case, especially with the risk of zipper malfunction, and refer you to our September 19th 2023 communication which outlines our high-level concerns.

APPENDICES:

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

- The HF study results report for updated labeling and background information can be accessed in EDR via: [\\CDSESUB1\EVSPROD\nda214697\0066\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5353-rep-analys-data-more-one-stud\ars-neffy-vt3-503\ars-neffy-vt3-503-re.pdf](\\CDSESUB1\EVSPROD\nda214697\0066\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5353-rep-analys-data-more-one-stud\ars-neffy-vt3-503\ars-neffy-vt3-503-re.pdf)
- The HF study results report for the proposed optional carrying case and background information can be accessed in EDR via: [\\CDSESUB1\EVSPROD\nda214697\0066\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5353-rep-analys-data-more-one-stud\ars-neffy-vt4-503\vt4-503-validation-report.pdf](\\CDSESUB1\EVSPROD\nda214697\0066\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5353-rep-analys-data-more-one-stud\ars-neffy-vt4-503\vt4-503-validation-report.pdf)
- The use-related risk analysis can be accessed in EDR via: [\\CDSESUB1\EVSPROD\nda214697\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\hr-ir\ars-neffy-urra-501.pdf](\\CDSESUB1\EVSPROD\nda214697\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\hr-ir\ars-neffy-urra-501.pdf)

APPENDIX B. INFORMATION REQUESTS ISSUED DURING THE REVIEW

On 4/17/2024, we issued an Information Request (IR) to request the protocol for both HF studies submitted on 4/2/24, a side-by-side comparison of the changes made to the user interface since our previous review, and the comprehensive URR. On 4/18/2024, the Applicant provided an acceptable response on that can be accessed in EDR via:

- HF study protocol for the updated labeling: [\\CDSESUB1\EVSPROD\nda214697\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\vt3-503\protocol-ars-neffy-vt3-103.pdf](\\CDSESUB1\EVSPROD\nda214697\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\vt3-503\protocol-ars-neffy-vt3-103.pdf)
- HF study protocol for the optional carrying case: [\\CDSESUB1\EVSPROD\nda214697\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\vt4-503\protocol-ars-neffy-vt4-101.pdf](\\CDSESUB1\EVSPROD\nda214697\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\vt4-503\protocol-ars-neffy-vt4-101.pdf)
- Side-by-side comparison of user interface changes: [\\CDSESUB1\EVSPROD\nda214697\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\hr-ir\hf-ir-response-17-april-2024.pdf](\\CDSESUB1\EVSPROD\nda214697\0068\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\hr-ir\hf-ir-response-17-april-2024.pdf)

APPENDIX C. LABELS, LABELING, AND PACKAGING

C.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^k along with postmarket medication error experiences with similar products, we reviewed the following Neffy labels and labeling submitted by ARS Pharma on April 2, 2024 and June 4, 2024

- Container label
- Blister/QRG label
- Carton labeling
- Instructions for Use, available from <\\CDSESUB1\EVSPROD\nda214697\0066\m1\us\neffy-ifu.docx>
- Prescribing Information (Image not shown) received on, available from <\\CDSESUB1\EVSPROD\nda214697\0066\m1\us\draft-labeling-text-package-insert-clean.docx>

C.2 Label and Labeling and Packaging Images

Container label(s) (Front and Back)



^k Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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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 Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: June 28, 2024

To: Ji LaRose, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Critical Care (DPACC)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Quynh-Nhu Capasso, PharmD
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): NEFFY (epinephrine nasal spray)

Dosage Form and Route: nasal spray

Application Type/Number: NDA 214697

Applicant: ARS Pharmaceuticals Inc.

1 INTRODUCTION

On April 2, 2024, ARS Pharmaceuticals Inc. submitted for the Agency's review a Response to Complete Response (CR) Letter, to the original New Drug Application (NDA) 214697 for NEFFY (epinephrine nasal spray). The proposed indication for NEFFY (epinephrine nasal spray) is for the treatment of type I allergic reactions, including anaphylaxis, in adult and pediatric patients who weigh 30 kg or greater.

On August 19, 2022, the Applicant submitted original NDA 214697 and on September 19, 2023, the Division of Pulmonary, Allergy, and Critical Care (DPACC) issued a CR letter for NDA 214697 due to outstanding Clinical/Clinical Pharmacology and Product Quality deficiencies.

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 DPACC on April 9, 2024, and April 8, 2024, respectively, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for NEFFY (epinephrine nasal spray).

2 MATERIAL REVIEWED

- Draft NEFFY (epinephrine nasal spray) PPI and IFU received on April 2, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on June 14, 2024.
- Draft NEFFY (epinephrine nasal spray) PPI and IFU received on April 2, 2024, revised by the Review Division throughout the review cycle, and received by OPDP on June 14, 2024.
- Draft NEFFY (epinephrine nasal spray) Prescribing Information (PI) received on April 2, 2024, revised by the Review Division throughout the review cycle, and received by DMPP on June 14, 2024.
- Draft NEFFY (epinephrine nasal spray) Prescribing Information (PI) received on April 2, 2024, revised by the Review Division throughout the review cycle and received by OPDP on June 14, 2024.
- Approved Adrenaclick (epinephrine injection) comparator labeling dated February 4, 2021.

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.

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.

In our collaborative review of the PPI and IFU we have:

- 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 and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the PPI is consistent with the approved comparator labeling where applicable.

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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06/28/2024 09:21:03 AM

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

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

Memorandum

Date: June 28, 2024

To: Ji Hyun LaRose, Regulatory Project Manager
Division of Pulmonology and Critical Care (DPACC)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for NEFFY® (epinephrine nasal spray)
[resubmission]

NDA: 214697

Background:

In response to DPACC's consult request dated April 8, 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 NEFFY® (epinephrine nasal spray).

PI/PPI/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on June 14, 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 June 28, 2024.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on June 14, 2024, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov

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/s/

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ICC2400340 NDA214697, Epinephrine nasal spray ARS PHARMACEUTICALS INC

Instructions	Submission Information		
Date	6/12/2024		
To:	JI HYUN LAROSE (CDER- OND)		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	Other
From	Gang Peng OPEQ/OHT3/DHT3C		
Through (Division) *Optional	Shruti Mistry OPEQ/OHT3/DHT3C		
Subject	NDA214697, Epinephrine nasal spray ICC2400340		
	Final Recommendation Date: 6/12/2024 ☒ 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)
Gang Peng -S	Shruti N. Mistry -S	2024.06.12 22:05:53 -04'00'

Remove Buttons

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA214697 S66
Sponsor	ARS PHARMACEUTICALS INC
Drug/Biologic	Epinephrine nasal spray
Indications for Use	Immediate and emergency treatment of allergic reactions (Type I), including anaphylaxis
Device Constituent	Nasal Spray
Related Files	ICC2200794 _ ICC2200768, IND139091, ICC2200768

Review Team	
Lead Device Reviewer	Gang Peng

Important Dates	
Final Lead Device Review Memo Due	6/28/2024
Interim Due Dates	Meeting/Due Date
FDA Action (Resubmission Class 2)	October 2, 2024

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 <u>Notes</u>
	Yes	No	NA	
Device Description			x	
Labeling			x	
Design Controls			x	
Risk Analysis			x	
Design Verification			x	
Reliability			x	
Consultant Discipline Reviews	x			Updated biocompatibility is adequate to address our original additional comments
Clinical Validation			x	
Human Factors Validation			x	
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:

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	☒

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3. PURPOSE/BACKGROUND

3.1. Scope

ARS PHARMACEUTICALS INC is requesting approval of Epinephrine nasal spray. The device constituent of the combination product is a Nasal Spray.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

requesting review of the resubmission class 2 for neffy, previous CR

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 Biocompatibility additional comment response

This review will not cover the following review areas:

All other areas not associated with the biocompatibility additional comment in the CR letter

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

- ICC2200794 ICC2200768 -CDRH consulted for facilities and device review which resulted in the current biocompatibility additional comment
Note that originally CDRH had hold deficiencies which were subsequently resolved. As a result, only the current biocompatibility additional comment remains. See the 7/23/24 CDRH Consult Memo "Epinephrine nasal spray.NDA214697.CDRH-OPEQ" for additional background.
- IND139091, ICC2100293, ICCR00071790: CDRH consulted for ARS-1 as it relates to (b) (4) as a comparator for the IND and an increase in concentration of the drug product from 1mg to 2mg.
- IND139091, ICC1900261, ICCR2019-04684: CDRH consulted for ARS-1

3.2.1. Related Files

The firm has referenced the following submissions: IND 139091; (b) (4)
(b) (4) and NDA 204200

NDA024200 RLD- Adrenalin (epinephrine injection)

3.3. Indications for Use

Combination Product	Indications for Use
Epinephrine nasal spray	Immediate and emergency treatment of allergic reactions (Type I), including anaphylaxis
Nasal Spray	Delivery of the Drug Product

3.4. Materials Reviewed

Sequence	Module(s)
66 ml	1. complete-response
66 ml	1. multi module info amend
66 m4	4.2 2300243

4. DEVICE DESCRIPTION

4.1. Device Description

The Neffy development program was initially focused on a 1 mg strength formulation. Subsequently, based on clinical studies, it was determined that a 2 mg strength was optimal for adults and adolescents greater than 30 kg. The combination product is intended to be indicated for patients 4 years and older.

The drug substance is a white to almost white crystalline powder. (Module 2.3.S.7. Stability. Table 2, page 2/3).

The drug product is an aqueous solution that is (b) (4) filled into a unit dose 400uL type (b) (4) glass vials and closed with a (b) (4) rubber stopper and then assembled into a unit dose sprayer (UDS) device. The device is a (b) (4) dispenser delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 100 µL per actuation. After a single actuation, the unit dose system is then considered depleted and discarded. Each UDS consists of an actuator which consists of (b) (4) and a container holder. After assembly, the UDS device is secondary packaged into individual single use blisters composed of (b) (4) and peel open blister lidding. There is a 125 µL overfill. (Module 2.3.P.1).

Anticipated mean peak plasma levels (Cmax) after administration of intranasal *neffy* 2 mg are between approximately 421 pg/mL (self-administration) and 485 pg/mL (HCP-caregiver administration) from primary ARS studies in adults. Pediatric exposures are approximately 540 pg/mL (Cmax) based on data from EPI 10 in children 30 kg or greater.

The container closure system for Neffy® (epinephrine nasal spray) consists of Type (b) (4) glass (b) (4) vials (0.4 mL) supplied by (b) (4) and sealed using a (b) (4) rubber plunger supplied by Aptar Pharma, France. ARS utilizes two suppliers for the unit dose device for Neffy. First, the Aptar device which has been commercially available and used for close to 20 years in other approved products on the US

APPEARS THIS WAY ON ORIGINAL

market, such as Imitrex (sumatriptan nasal spray), Narcan (naloxone hydrochloride) Nasal Spray, and Valtoco (diazepam nasal spray). Narcan and Valtoco are also similar to Neffy as they are formulations intended for emergency treatment of a life-threatening condition. Second, the (b) (4) device which has been developed specifically as a (b) (4)

The proposed shelf life is 24 months.

The neffy 1 mg formulation is the same as the neffy 2 mg formulation except for (b) (4) and increase in epinephrine content to achieve a higher dose.

4.2. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION	
Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments There are no issues with the device description; the device description was adequate in the previous ICC220786 review and has not changed. I included the relevant information from the previous review memo.	
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No	

4.3. Discipline Specific

Biocompatibility-CR Letter Additional Comment

DEVICE

In your submission, you included cytotoxicity, sensitization, and irritation testing for the Aptar device constituent part of the proposed combination product. Additionally, you

provided cytotoxicity and sensitization testing for the (b) (4) device constituent part of the proposed combination product. However, you did not provide irritation testing for the (b) (4) device constituent part of the proposed combination product. An adequate irritation assessment is important because exposure to the device (if it includes even a small amount of an irritant) can result in a localized non-specific inflammatory response which can lead to redness, swelling, itching, dryness, cracking of the skin, blistering or pain. Therefore, provide methods and results from irritation testing of the (b) (4) device constituent part of the proposed combination product (e.g., according to a recognized standard such as ISO 10993-10). Refer to recommendations in Attachment A of FDA's Biocompatibility Guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process'" (<https://www.fda.gov/media/85865/download>) for devices with your nature and duration of tissue contact.

Company Response:

(b) (4) completed the additional irritation testing study ((b) (4) Study Number 2300243) as APPEARS THIS WAY ON ORIGINAL recommended by the Agency.

This study was an intranasal local tolerance study in rats with two extracts of the (b) (4) (b) (4) device or two placebos (saline and cottonseed oil). The report is also filed to DMF (b) (4)

Results from this study did not indicate any abnormalities or toxicity from either the two extraction APPEARS THIS WAY ON ORIGINAL

media nor controls. There were also no adverse clinical observations, nor any macroscopic or microscopic compound-related tissue changes. Compared to both polar and nonpolar controls each test extract mean score for macroscopic assessment was zero (0 = no irritation response). No histopathology finding was noted to be different then controls with test APPEARS THIS WAY ON ORIGINAL extracts as outlined in the report.

Based on this study repeat administration of extracts of the (b) (4) device manufactured APPEARS THIS WAY ON ORIGINAL

by (b) (4) did not result in any irritation or histopathologic findings of concern and all evaluations were similar to both saline and oil controls in this study. Therefore, repeat intranasal administration of (b) (4) is deemed to not have potential to cause irritation or other toxic effects.

From the (b) (4) Study Number 2300243:

Intranasal Local Tolerance Study in Rats with Two Extracts of (b) (4)

44.93 cm² / test item (patient contacting area);

102.06 cm² / test item (total area)

On the sponsor's request, only the patient contacting area was considered for the calculation of the extract ratio. In total a ratio of 6 cm² of sample to 1 mL of extraction medium was used.

the assembly of (b) (4) was extracted together with the (b) (4)

Extraction conditions: 37 ± 1 °C for 72 ± 2 h, under agitation

Vehicles: Saline and Cottonseed oil

6 wistar rats per group

Negative control with just vehicle used

two daily intranasal administrations of the polar or nonpolar test item extract into the left nostril for 3 consecutive days

Observations: neither erythema/eschar formation nor oedema, score of 0 for all animals

Reviewer Comment

As requested in the additional comment of the CR letter, the firm has provided irritation testing.

From the testing, I note:

- The firm extracted using only the patient contacting area with a 6cm² ratio. This is acceptable as it does not dilute the sample. This will actually result in a more concentrated sample compared with extracting with the entire device's surface.
- The extraction condition and vehicles chosen are representative of the clinical use of the device
- No observations of concern (clinical/irritation/weight change) were reported, the test is deemed to pass

Overall, I do not have any concerns with the provided irritation testing. The ISO 10993 standards do not specify specific testing for intranasal irritation in the way that it does for skin, ocular, genital, etc irritation. However, the general operation is the same (applying extract to the intended clinical use area). Based on the test report provided, the methodology is valid to determine intranasal irritation. The additional comment has been resolved. No further device concerns remain.

Discipline:	Date Sent:	Date/Sequence Received:
Consultant:	Click or tap to enter a date.	Click or tap to enter a date.
Information Request #		
Sponsor Response		
Reviewer Comments		
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

Follow-On Deficiency	Date Sent:	Date/Sequence Received:
Discipline:		
Consultant:		
Information Request #		

Sponsor Response	
Reviewer Comments	
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

Add Additional Information Request

☐ **No Additional Information Requests – Finalize Consultant Deficiency Review Section**

Insert Discipline Review Section

☐ **No Additional Disciplines**

<<END OF REVIEW>>

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/s/

JI HYUN LAROSE
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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:	June 6, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214697
Product Name, Dosage Form, and Strength:	neffy (epinephrine) Nasal Spray, 2 mg/0.1 mL per spray
Applicant Name:	ARS Pharma
FDA Received Date:	June 4, 2024
TTT ID #:	2022-1022-2
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 PURPOSE OF MEMORANDUM

ARS Pharma submitted revised container labels and carton labeling received on June 4, 2024 for neffy. The Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the revised container labels and carton labeling for neffy (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

ARS Pharma did not implement our recommendations. Specifically, regarding our recommendation to capitalize the proprietary name, “neffy” ARS Pharma stated that “neffy” with the lowercase “n” is intentional, has specific meaning, is the official trademark, and that they do not agree presenting the proprietary name “neffy” in all lowercase impacts readability of the name. In this case, we find the Applicant’s rationale acceptable at this time.

Additionally, ARS Pharma provided acceptable clarification regarding the numbers (b) (4) and (b) (4) located on the device labels. They state that the numbers represent the approved label part numbers at the manufacturing facility. We note that this description provides the clarification we requested.

Our remaining recommendations were implemented, and we have no additional recommendations at this time.

^a Owens, L. Label and Labeling Review for neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2024 MAY 30. TTT ID: 2022-1022-1.

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/s/

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DAMON A BIRKEMEIER
06/07/2024 12:31:33 PM

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)

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

Date of This Review:	May 30, 2024
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214697
Product Name, Dosage Form, and Strength:	Neffy (epinephrine) Nasal Spray, 2 mg/0.1 mL per spray
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant Name:	ARS Pharma
FDA Received Date:	April 2, 2024; May 20, 2024
TTT ID #:	2022-1022-1
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Damon Birkemeier, PharmD, FISMP, NREMT

1 INTRODUCTION

As part of the approval process for Neffy (epinephrine) Nasal Spray, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Neffy Prescribing Information (PI), Patient Package Insert (PPI), Instructions for Use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 BACKGROUND

Neffy (epinephrine) is a proposed 505(b)(2) drug product and the Listed Drug (LD) is Adrenalin (epinephrine), NDA 204200 and NDA 019430. We note that the container label and carton labeling contain a QR code. An Information Request (See Appendix D) was sent via email on May 17, 2024, to request clarification on the information the user will obtain from the QR code.

1.2 REGULATORY HISTORY

ARS Pharma previously submitted NDA 214697 on August 19, 2022, which received a Complete Response letter on September 19, 2023, due to issues with Clinical/Clinical Pharmacology and Product Quality.^a

Thus, ARS Pharma submitted a Class 2 Resubmission on April 2, 2024.^b

2 MATERIALS REVIEWED

This section lists the materials considered for our review of NDA 214697.

Table 1. Materials Considered for this Label and Labeling Review	
Materials Reviewed	Appendix Section
Relevant Product Information	A
Labels and Labeling	B
Previous DMEPA Reviews	C
Information Request	D

3 CONCLUSION

We note that our recommendations from our previous review^c were not conveyed to ARS Pharma during the last review cycle.

We re-evaluated the proposed Neffy Instructions for Use (IFU) and Patient Package Insert (PPI) and determined that they are acceptable from a medication error perspective.

^a LaRose, J. on behalf of Kelly Stone, MD, PhD. Complete Response for NDA 214697. Silver Spring (MD): FDA, CDER, OND, Division of Pulmonology, Allergy, and Critical Care (DPACC) (US); 2023 SEP 09.

^b Resubmission (NDA 214697). San Diego (CA): ARS Pharma; 2024 APR 02. Available from: <\\CDSESUB1\EVSPROD\nda214697\0066\m1\us\coverletter.pdf>.

^c Owens, L. Label and Labeling Review for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 15. TTT ID No.: 2022-1022.

However, the Neffy proposed container label, prescribing information (PI) and carton labeling 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 for the Division of Pulmonology, Allergy, and Critical Care (DPACC) in Table 2 and for ARS Pharma in Table 3. 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.

Table 2. Identified Issues and Recommendations for the Division of Pulmonology, Allergy, and Critical Care (DPACC)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	It is not clear which NDC # is being referred to in the statement “Neffy nasal spray: 2 mg/0.1 mL of epinephrine is supplied in a carton containing two (2) blister packages each with a single-dose spray device for 1 time use (NDC 82580-020-02).”	The product is intended to be dispensed as an intact carton containing two devices.	We recommend ensuring the NDC # listed corresponds to the NDC # corresponding to the carton of two devices as opposed to the NDC for the individual device.

Table 3. Identified Issues and Recommendations for ARS Pharma (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Labels and Carton Labeling			
1.	The proprietary name is presented in all lowercase on the container labels, device labels, and carton labeling.	As presented, this presentation decreases readability.	We recommend revising the presentation of the proprietary name from all lowercase (e.g., neffy) to title case (e.g., Neffy).
2.	The linear barcode is missing on the container	The drug barcode is often used as an additional verification during the	Add the product’s linear barcode to each individual container label and carton

Table 3. Identified Issues and Recommendations for ARS Pharma
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	label, device label, and carton labeling.	medication use process; therefore, it is an important safety feature that should be part of the label and is a requirement per 21 CFR 201.25(c)(2).	labeling in accordance with 21CFR 201.25(c)(2). The bar code should be placed in a conspicuous location where it will not be difficult to read because of distorted text. Additionally, the barcode should be placed in an area where it will not be damaged because it appears at the point of label separation (e.g., perforation).
3.	The device labels contain the numbers (b) (4) and (b) (4)	As presented, these numbers may cause confusion.	Clarify the meaning of these numbers or remove them to prevent confusion.
Carton Labeling			
4.	The carton does not have a statement “dispense in this sealed carton”.	The lack of this statement may result in dispensing and administration errors. Dispensing the device without the carton circumvents the safety features of the carton labeling and may lead to medication errors and safety concerns.	We recommend adding the statement “Dispense in this sealed carton” on the principal display panel of the carton.
5.	The strength expression is not in a prominent location on the PDP.	As presented the strength may be overlooked.	We recommend relocating the product strength to a more prominent location on the PDP, directly below the product established name.
6.	The Recommended Dosage statement is missing from carton labeling.	This is a requirement per 21 CFR 201.55 that labels for prescription drugs bear a statement of the recommended dosage.	Add the recommended dosage statement: “Recommended Dosage: see Prescribing Information.” to the side panel in accordance with 21 CFR 201.55.

Table 3. Identified Issues and Recommendations for ARS Pharma
(entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
7.	Repetitive statement (b) (4) (b) (4)	There is potential for the user to overlook the word (b) (4)	Delete the repetitive statement (b) (4) from the side panel.
8.	The route of administration on the PDP lacks clarity and prominence.	The route of administration may be overlooked and misunderstood.	Revise the route of administration statement on the PDP to read: "Use in the Nose only (Single-Use)" and increase the prominence of the statement.
9.	On the top and side panel the strength is located between the proprietary name and the established name.	There should not be an interruption between the proprietary name and the established name.	You may: 1. Revise the strength presentation so that there is no interruption between the proprietary name and the established name. -or- 2. The name and strength may be deleted from the side and top panel as it displayed as required on the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. RELEVANT PRODUCT INFORMATION

Table 4 presents relevant product information for Neffy received on April 2, 2024 from ARS Pharma.

Table 4. Relevant Product Information for Neffy	
Initial Approval Date	N/A
Active Ingredient	epinephrine
Indication	emergency treatment of allergic reactions (Type I), including anaphylaxis, in adult and pediatric patients who weigh ≥ 30 kg.
Dosage Form	Nasal Spray
Strength	2 mg/0.1 mL per spray
Route of Administration	intranasal
Dose and Frequency	• one spray of neffy (2 mg/0.1 mL of epinephrine) administered into one nostril. • (b) (4) • Administer second dose of neffy in the same nostril with a new nasal spray after approximately (b) (4) minutes in absence of clinical improvement or (b) (4) (b) (4) after initial dose.
How Supplied	carton containing two (2) blister packages each with a single-dose spray device for 1 time use
Storage	Store at 68°F to 77°F (20°C to 25°C). Excursions permitted up to 122°F (50°C).

APPENDIX B. LABELS AND LABELING

B.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Neffy labels and labeling submitted by ARS Pharma.

- Prescribing Information received on April 2, 2024, available from <\\CDSESUB1\EVSPROD\nda214697\0066\m1\us\annotated-draft-labeling-text-tc.pdf>
- Patient Package Insert received on April 2, 2024, available from <\\CDSESUB1\EVSPROD\nda214697\0066\m1\us\patient-information-leaflet.pdf>
- Instructions for Use received on April 2, 2024, available from <\\CDSESUB1\EVSPROD\nda214697\0066\m1\us\draft-labeling-text-ifu.pdf>
- Container label received on August 19, 2022, and April 2, 2024
- Carton labeling received on April 2, 2024

^d Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

APPENDIX C. PREVIOUS DMEPA REVIEWS

On May 6, 2024, we searched for previous DMEPA reviews relevant to this current review using the terms, Neffy. Our search identified one previous review^e, and we considered our previous recommendations to see if they are applicable for this current review.

^e Owens, L. Label and Labeling Review for Neffy (NDA 214697). Silver Spring (MD): FDA, CDER, OSE, DMEPA 1 (US); 2023 MAY 15. TTT ID No.: 2022-1022.

APPENDIX D. INFORMATION REQUEST

- The following Information Request (IR) was sent to ARS Pharma on May 17, 2024:

Please clarify/provide the information that the user will obtain from the QR code. A response is requested within 5 business days.

A response to the IR was received on May 20, 2024, available from:

<\\CDSESUB1\EVSPROD\nda214697\0070\m1\us\coverletter.pdf>

[\\CDSESUB1\EVSPROD\nda214697\0070\m5\53-clin-stud-rep\535-rep-effic-safety-stud\\[REDACTED\]5354-other-stud-rep\qr-code\neffy-training-video-script.pdf](\\CDSESUB1\EVSPROD\nda214697\0070\m5\53-clin-stud-rep\535-rep-effic-safety-stud\[REDACTED]5354-other-stud-rep\qr-code\neffy-training-video-script.pdf)

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/

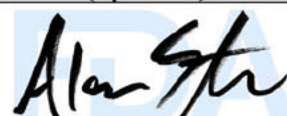
LISSA C PRINGLE-OWENS
05/30/2024 04:20:20 PM

DAMON A BIRKEMEIER
05/30/2024 04:23:12 PM

DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM – STREAMLINED

Date:	7/23/2023		
To:	Ji LaRose		
Requesting Center/Office:	CDER/OND	Clinical Review Division:	Other
From:	Porsche Bennett OPEQ/OHT3/DHT3C		
Through (Division): *optional	CAPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C		
Subject:	Consult for Submission: NDA214697, Epinephrine nasal spray ICC2200794_ICC2200768 ICCR00868571_ICCR00870331		
Recommendation:	Final Recommendation Date: 8/23/2023 ☐ 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 1. ☐ Device Constituent Parts of the Combination Product are Not Approvable		

Digital Signature Concurrence Table

Reviewer	Team Lead (TL)	Division (optional)
Porsche P. Bennett -S Digitally signed by Porsche P. Bennett -S Date: 2023.08.23 09:45:12 -04'00'		

1. DEVICE POST MARKET COMMITMENT RECOMMENDATION

PMC: Provide biocompatibility irritation testing for the nasal spray device constituent part for all device suppliers.

Committed schedule:

Draft Protocol Submission: Not Applicable

Final Protocol Submission: Not Applicable

Study Completion: 09/2023

Final Report Submission: 11/2023

2. SUBMISSION OVERVIEW

Table 1. Submission Information	
Consult Identification #	ICCR00868571 ICCR00870331
Consult Request Link	Facilities Review: Neffy® (epinephrine nasal spray) is an aqueous solution in a single use container. The solution is a (b) (4) filled into unit dose 400 µL Type (b) (4) glass vials and closed with a (b) (4) rubber stopper and then assembled into a Unit Dose Sprayer (UDS) device. The device is a (b) (4) dispenser delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 100 µL per actuation. Neffy is indicated for the immediate and emergency treatment of allergic reactions (Type I), including anaphylaxis. Please assign a CDRH reviewer to assess the device-related facilities. The CDER facility reviewer, Suzanne Hudak, has requested a due date of 2 weeks from the submission of this consult request. Please advise if that is feasible. https://force-dsc.lightning.force.com/lightning/r/Case/5003d000004qK84AAE/view Engineering Review: Requesting CDRH consult of the nasal device for neffy (epinephrine nasal spray) for NDA 214697. This is an original priority review with goal date: 2/17/2023. Advisory Committee is planned for 12/8/2022. https://force-dsc.lightning.force.com/lightning/r/Case/5003d000004hgpeAAA/view
ICC tracking #	ICC2200794 ICC2200768
Submission Number	NDA214697
Sponsor	ARS PHARMACEUTICALS INC
Drug/Biologic	Epinephrine nasal spray
Indications for Use	Immediate and emergency treatment of allergic reactions (Type I), including anaphylaxis
Device Constituent	Nasal Spray
Related Files	IND139091, Original review prior to extension (Refer to Appendix A below)

2. CDRH REVIEW

Background:	CDRH conducted a facilities and engineering review and provided CDER a final review memo on May 23, 2023 as the firm did not provide adequate data, information, and responses to information requests by the end of the expedited review cycle, dated June 19, 2023. CDRH recommended CR deficiencies and additional comments to be included in the CR letter as well as comments to the review team for consideration when the firm responds to the CR deficiencies and submission comes off CR hold. Thursday, May 25, 2023, 3:00 PM-4:00 PM, a meeting was held between FDA and the firm to discuss the outstanding deficiencies which included CDER Drug product inadequacies as well as CDRH device inadequacies. As the original review was under an expedited review clock, it was concluded after the meeting with the firm that the sponsor would possibly be able to adequately respond the information requests with additional time, with the submission being on a standard review clock. Therefore, CDER gave the firm additional time to respond to the drug product and device deficiencies and extended the review clock to that of a standard review. The major deficiencies were included in a letter as information requests (IRs) and issued to the firm prior to the May 25th meeting and were also discussed in the meeting. The minor deficiencies were sent to the firm as information requests on, June 7, 2023, after the
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meeting once it was determined that FDA would extend the review clock to August 19, 2023. The firm committed to providing a response all device IRs during the extended review clock to enable an approvability decision.

The final original memo included the following conclusions:

Comments to the review team:

- Drug Product Comment #1: The firm did not test spray content uniformity post transportation simulation with rationale provided that the drug product is aqueous and spray content uniformity testing is also covered by delivered dose testing. CDRH defers the requirement of spray content uniformity testing to the CDER DP reviewer.
- Clinical Comment #1: The firm appears to have included the 2mg combination product using the Aptar device in clinical PK studies; however, it does not appear that the (b) (4) device was used in clinical studies. The decision for validation of the device through clinical studies using the (b) (4) device constituent part is deferred to CDER.
- Labeling Comment #1: It appears that the instructions for use, container label, and carton label do not have the intended users stated on the labels. For example, the patient information leaflet includes the intended users as adults and children 66lbs and greater. However, the other labeling does not include a weight minimum or age. CDRH defers the requirement for the labeling to include the intended users to CDER.
- Labeling Comment 2: The labeling does not appear to include an Rx Only statement, the use period once the device is removed from the blister packaging, and instructions regarding shaking of the combination product in alignment with labeling recommendations per FDA's guidance, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, section V- labeling considerations, pages 37-45. CDRH defers the requirement for the labeling to include the Rx statement, the use period once removed from packaging, and instructions regarding shaking of the device to CDER.

Major deficiencies recommended to be included in CR letter:

- Device CR Deficiency 1: You indicate that your firm intends to utilize the nasal actuator and container holder components manufactured by (b) (4) (b) (4) and therefore you have referenced Device Master File (DMF) (b) (4) however, the referenced DMF did not include biocompatibility test reports. In response to the biocompatibility information request sent to your firm April 20, 2023, you provided the summary biocompatibility reports for the (b) (4) device, and you also indicated that the full biocompatibility reports were subsequently included in DMF (b) (4). However, the provided biocompatibility reports did not include irritation testing. As your device is intended to be a mucosal membrane contacting nasal spray, per FDA's Guidance "Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" APPEARS THIS WAY ON ORIGINAL (<https://www.fda.gov/media/85865/download>) irritation testing should be conducted given the contact type and duration. Irritation testing is needed to determine the safety of the proposed combination product. Therefore, provide an irritation test report for the (b) (4) device.

- CR Deficiency 2:

In your response to information request 1 sent to your firm March 20, 2023, you included a fault tree analysis and associated reliability calculations. The fault tree analysis and calculations are inadequate for the following reasons:

a.

b.

c.

d.

e.

f.

(b) (4)

Additionally, please provide the following supportive documents:

- a. Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. Outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g., DFMEA, UFMEA, Fault Tree Analysis).
 - b. Provide a trace matrix that shows traceability between design requirements, risk control measures and verification and validation activities
- CR Deficiency 3: In your submission you included document “control-critical-steps” that list in-process controls for each stage of manufacturing of the combination product; however, you do not appear to detail in your submission in-coming inspection activities and testing conducted for lot release for FDA to determine the complete control strategy for the proposed combination product. FDA needs to ensure reliability specifications will be maintained for all essential performance requirements as they can impact the overall reliability of the combination product. Detail the control strategy for the proposed combination product, discussing in-coming inspection, in-process controls, and lot release testing.

Minor deficiencies recommended to be included in CR letter “below the line” as additional considerations:

- Device Minor Deficiency 1: In your submission for the proposed combination product, you have not provided information on your cGMP compliance approach. Your marketing application should contain a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>). Provide detail of your cGMP approach.
- Device Minor Deficiency 2: You have not provided a summary of your Corrective and Preventive Action (CAPA) procedure in accordance to 21CFR820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. Summarize the procedure(s) for your CAPA System and ensure the following elements are included:
 - a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
 - b. Procedures should include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems;
 - c. Procedures should include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification

	for use of nonconforming product and the signature of the individual(s) authorizing the use; d. Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems; e. Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems; f. Investigation of nonconformities and their causes; g. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities; h. Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device; and i. Requires all documentation of all CAPA activities.							
Objective of this Memo:	The purpose of this review is to determine adequacy of the firm's response to the device deficiencies included in the letter issued to the firm and discussed during the sponsor meeting held May 25, 2023, as well as the information requests sent to the firm on June 7, 2023. Based on the adequacy of the firm's response to the device deficiencies an approval recommendation will be provided to CDER as it relates to the device constituent part of the combination product. Modules Reviewed during this review: • Sequence 0042, SDN 42, Received 2023-05-30 • Sequence 0044, SDN 44, Received 2023-06-05							
Review Comments:	<table border="1"> <tr> <td></td><td>Date Sent: 5/24/2023</td><td>Date/Sequence Received: 5/30/2023</td></tr> <tr> <td>Information Request #1</td><td colspan="2" rowspan="2"></td></tr> <tr> <td></td></tr> </table>		Date Sent: 5/24/2023	Date/Sequence Received: 5/30/2023	Information Request #1			
	Date Sent: 5/24/2023	Date/Sequence Received: 5/30/2023						
Information Request #1								

	Sponsor Response	(b) (4)	
	Reviewer Comments	The firm did not provide any additional data, particularly any testing and data in lieu of sensitization testing. Therefore, the applicant has not adequately demonstrated device safety at this time in accordance to ISO10993-1: 2018, <i>Biological evaluation of medical devices — Part 1: Evaluation and testing within a risk management process</i>. Given the device is intended for emergency use as opposed to continuous or prolonged use, and the benefit of a patient receiving the emergency use drug product outweighs the risk of potential irritation, a PMC appears reasonable to support an approvability decision.	
	Response Adequate:	☐ Yes ☒ No, See Device PMC #1 in section 1	

		Date Sent: 5/24/2023	Date/Sequence Received: 6/5/2023	
	Information Request #2	(b) (4)		

**Sponsor
Response**

	Reviewer Comments	The FTA was updated with a top level event of (b) (4) (b) (4) followed by a second level that consist of all essential performance requirements (EPR), and subsequent levels that consist of events that can occur (b) (4). The overall reliability of the combination product is stated to be (b) (4) %. (b) (4) The sponsor appears to have adequately responded to the information request, demonstrating the overall reliability of the proposed combination product to be (b) (4) %.	
	Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	
	Information Request #3	Date Sent: 5/24/2023	Date/Sequence Received: 3/22/2023
	Sponsor Response	(b) (4)	
	Reviewer Comments	The firm's control strategy demonstrates that the component suppliers are manufacturing product according to	

		specification and providing CoA's for each batch. Also, the firm appears to have adequate in-coming inspection steps and in-process controls. Lastly, the firm stated in the Epinephrine nasal spray specification in 3.2.P.5.1, Table that all device EPRs (dose delivered-Tier 1, dose delivered- Tier 2, droplet size distribution, pump delivery- Tier 1, pump delivery- Tier 2, spray pattern and actuation force) are tested on release. Therefore, the overall control strategy for the proposed combination product appears adequate.	
	Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	
		Date Sent: 6/7/2023	Date/Sequence Received: 3/22/2023 (b) (4)
	Information Request #1		
	Sponsor Response		

	Reviewer Comments	The firm's response is adequate; therefore, this information request is deemed resolved.	
	Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	
		Date Sent: 6/7/2023	Date/Sequence Received: 3/22/2023
	Information Request #2	(b) (4)	

	Sponsor Response	(b) (4)
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		(b) (4)
Review Recommendation:	The device constituent part of the proposed combination product, Epinephrine nasal spray, 2mg, “Neffy” appears to be adequate for the approval of the combination product with a post market commitment for irritation testing of the (b) (4) device.	

Reviewer Comments	The firm’s response is adequate; therefore, this information request is deemed resolved.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

---END OF REVIEW---

Appendix A: Original CDRH Review Prior to Extension

67 Page(s) has been Withheld As A Duplicate Copy Of The "ICC2200768" dated 05/09/23 Which Is Located In This Other Review Section Of This NDA Approval Package Under signature date 05/12/23.

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/

JI HYUN LAROSE
09/11/2023 09:18:14 AM

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

PATIENT LABELING REVIEW

Date: August 29, 2023

To: Ji LaRose, PharmD
Regulatory Project Manager
Division of Pulmonary, Allergy, and Critical Care (DPACC)

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Quynh-Nhu Capasso, PharmD
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): neffy (epinephrine nasal spray)

Dosage Form and Route: nasal spray

Application Type/Number: NDA 214697

Applicant: ARS Pharmaceuticals Inc.

1 INTRODUCTION

On August 19, 2022, ARS Pharmaceuticals Inc. submitted for the Agency's review an original New Drug Application (NDA) 214697 for neffy (epinephrine nasal spray). The proposed indication for neffy (epinephrine nasal spray) is for treatment of allergic reactions (Type I), including anaphylaxis, in adult and pediatric patients who weigh ≥ 30 kg.

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 Pulmonary, Allergy, and Critical Care (DPACC) on August 26, 2022, for DMPP and OPDP to review the Applicant's proposed Patient Package Insert (PPI) and Instructions for Use (IFU) for NEFFY (epinephrine nasal spray).

DMPP conferred with the Division of Medication Error Prevention and Analysis (DMEPA) and a separate DMEPA review of the IFU was completed on June 1, 2023.

2 MATERIAL REVIEWED

- Draft neffy (epinephrine nasal spray) PPI and IFU received on August 19, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on August 16, 2023.
- Draft neffy (epinephrine nasal spray) PPI and IFU received on August 19, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on August 16, 2023.
- Draft neffy (epinephrine nasal spray) Prescribing Information (PI) received on August 19, 2022, revised by the Review Division throughout the review cycle, and received by DMPP on August 16, 2023.
- Draft neffy (epinephrine nasal spray) Prescribing Information (PI) received on August 19, 2022, revised by the Review Division throughout the review cycle, and received by OPDP on August 16, 2023, and August 24, 2023.
- Approved Adrenaclick (epinephrine injection) comparator labeling dated February 4, 2021.

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.

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.

In our collaborative review of the PPI and IFU we have:

- 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 and IFU meet the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)

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.

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/

NYEDRA W BOOKER
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QUYNH-NHU D CAPASSO
08/29/2023 10:57:11 AM

LASHAWN M GRIFFITHS
08/29/2023 10:59:29 AM

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

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

Memorandum

Date: August 29, 2023

To: Ji Hyun LaRose, Regulatory Project Manager
Division of Pulmonology and Critical Care (DPACC)

From: Quynh-Nhu Capasso, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Adewale Adeleye, Team Leader, OPDP

Subject: OPDP Labeling Comments for NEFFY® (epinephrine nasal spray)

NDA: 214697

Background:

In response to DPACC's consult request dated April 26, 2022, 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 NEFFY® (epinephrine nasal spray).

PI/PPI/IFU:

OPDP's review of the proposed PI is based on the draft labeling emailed to OPDP on August 24, 2023, 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 August 29, 2023.

Carton and Container Labeling:

OPDP's review of the proposed carton and container labeling is based on the draft labeling emailed to OPDP on August 16, 2023, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact Quynh-Nhu Capasso at quynh-nhu.capasso@fda.hhs.gov

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

/s/

QUYNH-NHU D CAPASSO
08/29/2023 11:23:36 AM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
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Office of New Drugs
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M E M O R A N D U M

From: Ndidi Nwokorie, MD Medical Officer
Division of Pediatrics and Maternal Health (DPMH)
Office of Rare Diseases, Pediatrics, Urologic and Reproductive
Medicine (ORPURM)
Office of New Drugs (OND)

Through: Mona Khurana, MD, Pediatric Team Leader
DPMH, ORPURM, OND

To: Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)

Subject: Description of Approved Pediatric Population in Labeling

Applicant: ARS Pharmaceuticals, Inc.

Application number: NDA 214697

Drug: Neffy (epinephrine nasal spray)

Drug Class: A (b) (4) alpha and beta-adrenergic receptor agonist

Proposed Indication: For the emergency treatment of allergic reactions (Type I), including anaphylaxis, in adult and pediatric patients who weigh 30 kg (66 lbs) or greater

Proposed Dosage: 2 mg (one spray) into one nostril. May repeat in (b) (4) minutes if no response or inadequate response

Route of administration: Intranasal

Dosage Form: Single dose Solution

Dosage Strengths: 2mg/0.1ml

Materials Reviewed:

Documents entered in to DARRTS

- Under NDA 214697 on June 6, 2023
 - NDA 214697 DPMH Consult Request FRM-CONSULT-18
- Under IND 139091 on April 15, 2020
 - DPMH Memorandum for ARS-1 (epinephrine spray)

Documents submitted under NDA 214697 to DocuBridge on August 19, 2022

- Cover Letter
- Introduction to Summary
- Note-to-Reviewer (Reviewer's Guide)

Consult Request:

DPACC consulted DPMH to assist with language to describe the approved pediatric population in Section I (Indications and Usage) of the human prescription drug and biological product labeling for this product.

I. Background of the Neffy Product

ARS Pharmaceuticals, Inc, (hereby known as Applicant) submitted a new drug application (NDA) on August 19, 2022, for *neffy*® 2mg (epinephrine nasal spray) for the emergency treatment of allergic reactions (Type I) under the 505b2 regulatory pathway.¹ The Applicant is relying on FDA's previous findings of safety and efficacy for Adrenalin® (epinephrine) Injection (NDA 204200) and EpiPen (NDA 019430) as the listed drugs (LD).

Epinephrine is a non-selective alpha and beta-adrenergic receptor agonist that acts by reversing the pathological response to the histamine cascade caused by an antigen.²

The Applicant is developing Neffy (epinephrine nasal spray) as a needle-free alternative to dosing epinephrine in an allergic emergency to reduce the apprehension patients may have regarding self-injections, potentially reducing dosing delays and consequently improving outcomes during an allergic emergency.³

Epinephrine was first used to treat anaphylaxis in the 1960's.³ Use of epinephrine at that time was based on empiric observations and expert opinions. To date, no prospective, controlled clinical trials have been performed to substantiate the use of epinephrine for treatment of anaphylaxis.³ However, subsequent epinephrine drug products since the 1960's have relied on extensive clinical experiences to support the safe and effective use of all approved routes of administration in the treatment of severe allergies and anaphylaxis.³

Due to both ethical and practical reasons, randomized, controlled clinical trials cannot be conducted to assess the efficacy of epinephrine for the treatment of severe allergic reactions and anaphylaxis.

For the purpose of this application, the Applicant provided pivotal data from multiple phase 1 trials in adult healthy volunteers and adult and pediatric patients with type 1 allergies that compared the pharmacokinetic (PK) profile of this product to approved epinephrine injection products and characterized the PK and pharmacodynamic (PD) relationship of this product.³ These consisted of the following trials:

- Four primary clinical pharmacology trials in adult and pediatric patients with type 1 allergies who weighed at least 30 kg that evaluated whether Neffy 2 mg would achieve comparable exposures as injection epinephrine products with caregiver administration, self-administrations, and in worse case situations such as in the presence of nasal congestion or rhinorrhea.
- Five phase 1 trials characterizing the PK and tolerability of Neffy 1 mg
- One dose-ranging pilot trial in 26 healthy adult volunteers that evaluated Neffy doses ranging from 1.0 mg to 2 mg (1.0 mg, 1.3 mg, 1.5 mg, 1.8 mg, and 2 mg).³

¹ Cover Letter submitted to DocuBridge on August 19, 2022

² Note-to-Reviewer (Reviewer's Guide) submitted to DocuBridge on August 19, 2022

³ Introduction to Summary submitted to DocuBridge on August 19, 2022

The Applicant is relying on pivotal clinical data collected in 42 pediatric patients 8 years of age and older weighing at least 30 kg with severe type I allergies to support approval of this efficacy supplement.³ These patients consisted of the following:

- 26 pediatric patients 30 kg and greater who were dosed with Neffy 1 mg
- 16 pediatric patients 30 kg or greater who were dosed with Neffy 2 mg

(b) (4)

II. Discussion of the appropriate approach to describe approved pediatric population in labeling

FDA guidance⁴ and regulation⁵ requires pediatric use information to be described in the Pediatric Use subsection and included in other sections of labeling as appropriate. The regulations state that the pediatric information in labeling must not be false or misleading.⁶ When data support the use of a drug for a pediatric indication, pediatric use information must be placed in relevant sections of labeling including Indications and Usage, Dosage and Administration, Adverse Reactions, Use in Specific Populations, Clinical Pharmacology, and Clinical Studies, as well as any other sections that may be appropriate.⁴ The remainder of this memorandum will focus on advice given regarding Section 1: Indication and Usage.

FDA guidance states that if a drug is indicated for a specific pediatric population, the indication statement should specify the ages of the indicated pediatric age group.⁴ In general, labeling content, including the approved population, is derived from clinical data submitted in the marketing application.

Collectively, the pediatric PK and PD data included in this sNDA demonstrated that pediatric patients weighing 30 kg or greater who were dosed with Neffy 2 mg resulted in exposures that are slightly greater than that achieved in the adult population with the same dose. Although observed data were collected in patients down to 8 years of age, the Division discussed with DPMH the acceptability of generalizing the data down to patients younger than 8 years of age who would meet the minimum weight threshold given that there would be no anticipated age-related differences on drug disposition between the 4 to less than 8 year age group and the greater than 8 year age group for this drug if the intended dose was correctly administered. Population (POP) PK and Physiologically Based Absorption Model (PBAM) analyses suggested that the Neffy 2 mg dose will provide therapeutic exposures of epinephrine in children 30 kg or greater, further supporting the generalizability of the observed data to patients meeting the minimum weight threshold of 30 kg regardless of age.

⁴ Pediatric Information Incorporated Into Human Prescription Drug and Biological Product Labeling Guidance for Industry

⁵ 21 CFR 201.57(c)(9)(iv)(B), (C), and (D)

⁶ Section 505(d), 505(e) of the FD&C Act

The Division proposed the following Indication statement for section 1 of product labeling:

NEFFY is indicated for emergency treatment of allergic reactions (Type I), including anaphylaxis, in adult and pediatric patients who weigh 30 kg (66 lbs) or greater.

DPMH agrees with the approach taken by the Division. The Applicant plans to use an approved nasal spray device³ (Aptar nasal dose sprayer) that is not fit-for-purpose in patients less than 4 years of age.⁷ Therefore, the Agency agreed⁷ to waive pediatric assessment for patients less than 4 years of age on the basis that the device would not be appropriate for younger patients. However, being agnostic on age and including a body weight restriction only, the concern that the product may be administered to patients less than 4 years of age is mitigated by the fact that a body weight of 30 kg represents 95th percentile for children 6 years and 9 months of age. Therefore, it is unlikely that a patient younger than 4 years of age would be 30 kg and thus be administered this product.

The Applicant plans to submit supporting data to extend the approved indication down to 4 years of age and a body weight of 15 kg. Further consideration could be made to revise the indicated population to include an age restriction of 4 years for this product following review of that supplement.

There is precedent for approving products for pediatric use based on a minimum weight restriction that is agnostic on age. One recent example is the 2021 FDA approval of Morphine Sulfate tablets (NDA 022207) for pediatric use. The labeling for this NDA 022207 is silent on the age of the approved pediatric population and includes only the weight restriction in the Indication statement.

DPMH participated in labeling discussions and provided recommended labeling for the pediatric population for Neffy (epinephrine nasal spray) in accordance with 21 CFR 201.57(c)(9)(iv). DPMH's input will be reflected in the final labeling and approval letter. The final labeling will be agreed upon with the application holder and may not fully reflect changes suggested here or during labeling discussion.

⁷ DPMH Memorandum under IND 139091 entered in DARRTS on April 15, 2020

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/

NDIDI N NWOKORIE
08/09/2023 05:32:42 PM

MONA K KHURANA
08/09/2023 11:46:25 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

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Division of Pediatrics and Maternal Health Review

Date: 7/20/2023 **Date consulted:** 6/15/2023

From: Katherine Kratz, MD, Medical Officer, Maternal Health
Division of Pediatrics and Maternal Health (DPMH)

Through: Miriam Dinatale, DO, Team Leader, Maternal Health, DPMH
Lynne P. Yao, MD, OND, Division Director, DPMH

To: Division of Pulmonology, Allergy and Critical Care (DPACC)

Drug: Neffy (epinephrine nasal spray)

NDA: 214697

Applicant: ARS Pharmaceuticals, Inc.

Subject: Pregnancy and Lactation Labeling

Indication: Emergency treatment of allergic reactions (Type I) including anaphylaxis in adult and pediatric patients who weigh ≥ 30 kg

Materials

Reviewed:

- DPMH consult request dated 6/15/2023. DARRTS Reference ID: 5191502.
- Applicant's submitted background package and proposed labeling for NDA 214697, submitted 8/19/2022. Sequence Number (SN) 0001.
- United States Prescribing Information (USPI) for Adrenalin (epinephrine injection) 1 mg/mL, for intramuscular, subcutaneous, and intravenous use, revised 6/2022.
- USPI for EpiPen (epinephrine injection), for intramuscular or subcutaneous use And EpiPen Jr (epinephrine injection), for intramuscular or subcutaneous

use, revised 2/2023.

- DPMH review of Epinephrine Injection USP, NDA 209359 by Christos Mastroyannis, M.D., dated 11/8/2017. DARRTS Reference ID: 4178799.
- DPMH review of Epinephrine Injection USP, NDA 204200/S-009 by Christos Mastroyannis, M.D., dated 11/6/2018. DARRTS Reference ID: 4345859.

Consult Request: “ARS submitted an NDA for Neffy, an intranasal epinephrine for the treatment of anaphylaxis. They are relying on the 505(b)(2) pathway and using Adrenalin and EpiPen as the two listed drugs. During labeling review, the Division noticed that the PLLR section of Adrenalin and EpiPen do not align. Specifically, the Division has questions in terms of Section 8.1, Adrenalin has a section describing the use of epinephrine during labor or delivery that is not present in EpiPen labeling. The Division would like DPMH feedback as to whether this language should be included in all epinephrine labeling and as to if there is any reason as this was included in Adrenalin and not EpiPen.”

I. INTRODUCTION AND BACKGROUND

On August 19, 2022, the applicant, ARS Pharmaceuticals, Inc., submitted a 505(b)(2) New Drug Application (NDA) for Neffy (epinephrine nasal spray) for the treatment of type 1 allergic reactions including anaphylaxis. The applicant posits that their nasal spray is a needle-free option that is “faster to administer, easier to carry and more convenient to use.”¹ The Reference Listed Drugs (RLDs) are Adrenalin (epinephrine) Injection under NDA 204200 and EpiPen under NDA 019430. DPACC consulted the DPMH Maternal Health Team on June 15, 2023, to assist with the Pregnancy and Lactation subsections of labeling.

Relevant Regulatory History

- Epinephrine predates both the original Federal Food and Drugs Act of 1906 (prohibited the sale of adulterated or misbranded drugs), the Food Drug & Cosmetic Act (FD&C Act) of 1938 (required that marketed drugs demonstrate safety) and the Kefauver-Harris amendment in 1962 to the FD&C Act (required that drugs demonstrate both safety and efficacy for approval). Since epinephrine predates 1938, it was not subject to the Drug Efficacy Study Implementation (DESI) review that was put in place following the 1962 amendments to the FD&C Act to evaluate drugs approved by the agency as safe between 1938 and 1962.²
- 1939: FDA approved epinephrine injection.
- 2017: DPMH conducted a consult review for epinephrine injection under NDA 209359.
- 2018: DPMH conducted a consult review for epinephrine injection under NDA 204200 (one of the RLDs).
- DPMH was not consulted for NDA 019430, the second RLD.

Drug Characteristics³

¹ NDA 214697, SN 0001, Nonclinical Overview, page 3.

² Division of Pulmonary, Allergy and Rheumatology Products (DPARP) Summary of Review for Regulatory Action, NDA 204200 by Lydia Gilbert-McClain, MD, dated 12/7/2012. DARRTS Reference ID: 3227628.

³ NDA 214697, SN 0001, Proposed Prescribing Information, under review by DPACC.

Drug class	Alpha- and beta-adrenergic agonist (sympathomimetic agent)
Mechanism of action	Acts on the alpha and beta-adrenergic receptors
Dosage form	Single use intranasal spray
Dose	2 mg of epinephrine in 0.1 mL solution
Molecular weight	183.21 g/mol
Half-life	< 5 minutes (based on Adrenalin labeling)
% protein bound	Not assessed (confirmed with DPACC clinical pharmacology team)
Bioavailability	Not assessed (confirmed with DPACC clinical pharmacology team)

Labeling of RLDs^{4,5}

- The labelings for both RLDs are in the PLLR format.
- There is no boxed warning for either RLD.
- There is no contraindication for pregnancy or lactation for either RLD.
- Serious adverse reactions for Adrenalin:³
 - Local necrosis
 - Aggravation of angina pectoris or ventricular arrhythmias
- Serious adverse reactions for EpiPen:⁴
 - Injection related injury
 - Skin and soft tissue infections
 - Aggravation of angina pectoris or ventricular arrhythmias
- 8.1, Pregnancy:
 - There are no human data for either RLD.
 - There are Clinical Considerations for disease associated maternal and/or embryo/fetal risk and labor or delivery for Adrenalin. Note: EpiPen does not contain a Clinical Consideration for labor or delivery.
 - The labor or delivery subsection states, “Epinephrine usually inhibits spontaneous or oxytocin induced contractions of the pregnant human uterus and may delay the second stage of labor. Avoid epinephrine during the second stage of labor. In dosage sufficient to reduce uterine contractions, the drug may cause a prolonged period of uterine atony with hemorrhage. Avoid epinephrine in obstetrics when maternal blood pressure exceeds 130/80 mmHg. Although epinephrine may improve maternal hypotension associated with septic shock and anaphylaxis, it may result in uterine vasoconstriction, decreased uterine blood flow, and fetal anoxia.”

Reviewer comment:

Maternal blood pressure is critical for uteroplacental perfusion, and adequate uteroplacental perfusion is required for fetal oxygenation. Epinephrine is a first-line treatment for hypotension related to anaphylaxis (see below), and treatment is necessary to maintain maternal blood pressure. Thus, timely treatment with epinephrine in the case

⁴ USPI for ADRENALIN (epinephrine injection) 1 mg/mL, for intramuscular, subcutaneous, and intravenous use, revised 6/2022.

⁵ USPI for EPIPEN® (epinephrine injection), for intramuscular or subcutaneous use and EPIPEN Jr® (epinephrine injection), for intramuscular or subcutaneous use, revised 2/2023.

of severe, life-threatening anaphylaxis is an important message to prescribers. It is important to underscore that the risks of uterine vasoconstriction, decreased uterine blood flow and fetal anoxia are potential risks, as there are sources that suggest that the overall effect of epinephrine is to increase uteroplacental perfusion.^{6,7,8} See the Discussions and Conclusions section below for labeling recommendations related to whether the Labor or Delivery section that appears in Adrenalin labeling should be included in the labeling of subsection 8.1 for Neffy.

- There is a Clinical Consideration for disease associated maternal and/or embryo/fetal risk for Adrenalin and EpiPen.
- There are animal data for both RLDs:
 - Adrenalin: Epinephrine caused teratogenic effects (including gastroschisis) in rabbits dosed at 15 times the maximum recommended human dose (MHRD) during organogenesis. Teratogenic effects, embryonic lethality, and delayed skeletal ossification were seen in mice at 3 times the MRHD. Reduced litter sizes and delayed ossification occurred in hamsters at 2 times the MRHD.
 - EpiPen: Epinephrine caused teratogenic effects (including gastroschisis and embryolethality) in rabbits dosed at 40 times the MRHD. Teratogenic effects and embryonic lethality were seen in mice at 8 times the MRHD. Teratogenic effects occurred in hamsters at 7 times the MRHD.
- 8.2, Lactation
 - There are no human or animal data for either RLD.
- There are no existing pregnancy testing or contraception recommendations.
- There are no known drug-drug interactions with hormonal contraceptives.

II. REVIEW

PREGNANCY

Epinephrine, anaphylaxis, and pregnancy

DPMH has previously reviewed epinephrine and pregnancy.^{9,10} Past DPMH reviews summarized epinephrine use in pregnancy as follows: “Nonclinical data demonstrate that epinephrine at high doses and with prolonged exposure during organogenesis is teratogenic in rabbits, mice, and hamsters. Based on the mechanism of action, epinephrine may cause acceleration of fetal heart rate, uterine vasoconstriction, and fetal anoxia. Review of the limited published literature on human use during pregnancy did not show a clear association between epinephrine use during the 1st trimester and adverse developmental outcomes. Therefore, the information is not sufficient to determine a drug-associated risk for major birth defects or miscarriage. There are

⁶ Gei AF, Pacheco LD, Vanhook JW, Hankins GDV. The use of a continuous infusion of epinephrine for anaphylactic shock during labor. *Obstet Gynecol* 2003;102(6):1332–35. doi: 10.1016/s0029-7844(03)00167-4.

⁷ Hepner DL, Castells M, Mouton-Faivre C, et al. Anaphylaxis in the clinical setting of obstetric anesthesia: a literature review. *Anesth Analg*. 2013;117: 1357–1367.

⁸ Riley ET. Editorial I: Spinal anaesthesia for caesarean delivery: keep the pressure up and don’t spare the vasoconstrictors. *Br J Anaesth* 2004;92:459–61

⁹ DPMH review of Epinephrine Injection USP, NDA 209359 by Christos Mastroyannis, M.D., dated 11/8/2017. DARRTS Reference ID: 4178799.

¹⁰ DPMH review of Epinephrine Injection USP, NDA 204200/S-009 by Christos Mastroyannis, M.D., dated 11/6/2018. DARRTS Reference ID: 4345859.

risks to the mother and fetus associated with hypotension associated with septic shock. Treatment should not be delayed for a life-threatening condition due to potential risks from epinephrine use.”

In terms of anaphylaxis in pregnancy, the prevalence among pregnant individuals has been reported as 1.6 to 3.8 per 100,000 pregnancies.^{11,12,13} Maternal mortality from anaphylaxis is estimated to be 0.9 per 100,000 live births.¹⁰ The most common causes of anaphylaxis during pregnancy are antibiotics and anesthetics.^{14,15} Pregnancy does not alter the clinical findings, course, or the medical management associated with anaphylaxis. Epinephrine is considered first-line treatment for anaphylaxis in pregnant individuals as it is in nonpregnant individuals.¹⁶

Nonclinical Experience

The applicant conducted a literature review of reproductive and developmental toxicity for epinephrine. The applicant cited the National Toxicology Program for nonclinical data for epinephrine and provided information that appears in current labeling in addition to the following data:

- 1) Administration of 25-100 µg of epinephrine by intraperitoneal injection to pregnant rats during gestation days 15-21 resulted in fetal bradycardia, fetal hypotension, and increased fetal serum potassium levels; these findings were attributed to epinephrine-induced impairment of blood flow.
- 2) Epinephrine reduced uteroplacental circulation in monkeys.
- 3) Prenatal epinephrine exposure in rats and mice failed to demonstrate epinephrine-mediated alterations in postnatal behavior.

The applicant conducted a reproductive and developmental toxicity study in rats with the excipient in the nasal spray called dodecylmaltoside (DDM). In the study with DDM, there was no difference in the percentage of pre- and post-implantation loss or mean live litter sizes. There was no difference in mean fetal weight. There were no external, visceral, or skeletal malformations. The NOAEL was ≥ 30 mg/kg/day.¹⁷

The reader is referred to the full Pharmacology/Toxicology review by Dr. Carol Galvis.

¹¹ McCall SJ, Bunch KJ, Brocklehurst P, D'Arcy R, Hinshaw K, Kurinczuk JJ, Lucas DN, Stenson B, Tuffnell DJ, Knight M. The incidence, characteristics, management and outcomes of anaphylaxis in pregnancy: a population-based descriptive study. *BJOG*. 2018 Jul;125(8):965-971. doi: 10.1111/1471-0528.15041. Epub 2018 Jan 3. PMID: 29193647; PMCID: PMC6033185.

¹² Mulla ZD, Ebrahim MS, Gonzalez JL. Anaphylaxis in the obstetric patient: analysis of a statewide hospital discharge database. *Ann Allergy Asthma Immunol*. 2010 Jan;104(1):55-9. doi: 10.1016/j.anai.2009.11.005. PMID: 20143646.

¹³ McCall SJ, Kurinczuk JJ, Knight M. Anaphylaxis in Pregnancy in the United States: Risk Factors and Temporal Trends Using National Routinely Collected Data. *J Allergy Clin Immunol Pract*. 2019 Nov-Dec;7(8):2606-2612.e3. doi: 10.1016/j.jaip.2019.04.047. Epub 2019 May 16. PMID: 31102701; PMCID: PMC6848914.

¹⁴ Simionescu AA, Danciu BM, Stanescu AMA. Severe Anaphylaxis in Pregnancy: A Systematic Review of Clinical Presentation to Determine Outcomes. *J Pers Med*. 2021 Oct 22;11(11):1060. doi: 10.3390/jpm11111060. PMID: 34834412; PMCID: PMC8623240.

¹⁵ Reiner K, Zah Bogović T, Čačić M, Mihaljević S, Krišto B. Anaphylaxis during pregnancy. *Psychiatr Danub*. 2019 Mar;31(Suppl 1):60-62. PMID: 30946719.

¹⁶ Schatz, M et al. Anaphylaxis in pregnant women. UpToDate. Topic 393, version 23.0. Accessed 6/28/23.

¹⁷ NDA 214697, SN 0001, Nonclinical Overview, page 18.

Review of Pharmacovigilance Database

The applicant did not provide pharmacovigilance data.

Review of Literature

Applicant's review:

The applicant did not provide a review of the clinical literature.

DPMH review:

DPMH conducted a search of published human studies in PubMed from 2018 (the date of the most recent DPMH review of epinephrine) to the present to identify publications that have not been previously reviewed by DPMH. The following search terms were used: “epinephrine” and “pregnancy,” “pregnancy outcomes,” “birth defects,” “malformations,” “stillbirth,” or “spontaneous abortion.” The results of the literature search are as follows:

- Two literature reviews^{18,19} indicated that the available data are limited and that maternal and fetal outcomes are dependent on rapid treatment with epinephrine and c-section. One of the reviews¹⁸ concluded that “the negative neurologic outcomes of the fetus are mostly due to delayed caesarean delivery or inadequate doses of adrenaline during anaphylaxis.”
- Two case reports^{20,21} described the use of intramuscular epinephrine in the first and second trimesters of pregnancies without adverse maternal or fetal outcomes.
- A randomized, controlled trial²² that compared a continuous epinephrine infusion to a continuous phenylephrine infusion during labor to maintain blood pressure during spinal anesthesia demonstrated no increase in fetal acidosis with epinephrine as compared to phenylephrine and no impact on uterine contractility.

DPMH also searched Micromedex,²³ Reprotox,²⁴ TERIS,²⁵ and Shepard's²⁶ and no new information was identified.

¹⁸ Reiner K, Zah Bogović T, Ćaćić M, Mihaljević S, Krišto B. Anaphylaxis during pregnancy. *Psychiatr Danub*. 2019 Mar;31(Suppl 1):60-62. PMID: 30946719.

¹⁹ Simionescu AA, Danciu BM, Stanescu AMA. Severe Anaphylaxis in Pregnancy: A Systematic Review of Clinical Presentation to Determine Outcomes. *J Pers Med*. 2021 Oct 22;11(11):1060. doi: 10.3390/jpm11111060. PMID: 34834412; PMCID: PMC8623240.

²⁰ Tan E, O'Sullivan M, Crozier T, Kolawole H, Mantas S, Said M, Rueter K, Frith K, Barnes S. Acute management of anaphylaxis in pregnancy. *Aust J Gen Pract*. 2022 Jun;51(6):405-408. doi: 10.31128/AJGP-03-21-5918. PMID: 35637583.

²¹ Wu SS, Abraham T, Michaud C, Peppers B, Ward A, Buchner SE, Teba CV, Tcheurekdjian H, Hostoffer R, Jhaveri D. Fetal response to intramuscular epinephrine for anaphylaxis during maternal penicillin desensitization for secondary syphilis. *J Matern Fetal Neonatal Med*. 2018 Aug;31(16):2223-2225. doi: 10.1080/14767058.2017.1336221. Epub 2017 Jun 20. PMID: 28562129.

²² Wang YB, Yang ZY, Zhang WP. Comparison of Continuous Infusion of Epinephrine and Phenylephrine on Hemodynamics During Spinal Anesthesia for Cesarean Delivery: A Randomized Controlled Trial. *Clin Ther*. 2020 Oct;42(10):2001-2009. doi: 10.1016/j.clinthera.2020.08.004. Epub 2020 Aug 26. PMID: 32861500.

²³ Truven Health Analytics information, <http://www.micromedexsolutions.com>. Accessed 6/28/23.

²⁴ Reprotox Website: www.Reprotox.org. Accessed 6/28/23.

²⁵ TERIS database, Truven Health Analytics, Micromedex Solutions. Accessed 6/28/23.

²⁶ Shepard's database, Truven Health Analytics, Micromedex Solutions. Accessed 6/28/23.

Reviewer comment:

The applicant did not provide any new data to inform labeling of epinephrine use during pregnancy. DPMH concludes from their review that epinephrine does not appear to be associated with adverse maternal or fetal outcomes. See the Discussions and Conclusions section below for labeling recommendations for 8.1.

LACTATION

Nonclinical Experience

The applicant did not provide nonclinical data related to lactation in their submission. In the most recent review by DPMH,²⁷ it was noted that animal data demonstrate that intraarterial epinephrine can decrease serum oxytocin and inhibit milk production.^{28,29}

The reader is referred to the full Pharmacology/Toxicology review Dr. Carol Galvis.

Review of Pharmacovigilance Database

The applicant did not provide pharmacovigilance data.

Review of Literature

Applicant's review:

The applicant did not provide a review of the clinical literature.

DPMH review:

DPMH conducted a search for published human studies from 2018 to the present in PubMed, using the search terms: “epinephrine” and “lactation” and “breastfeeding.” No relevant publications were identified.

In addition, DPMH conducted a search for epinephrine in Micromedex, Hale's *Medications and Mothers' Milk*,³⁰ Reprotox, the Drugs and Lactation Database (LactMed),³¹ and Briggs *Drugs in Pregnancy and Lactation: A Reference Guide to Fetal and Neonatal Risk*.³² The results are as follows:

- Hale's: “Although likely to be secreted in milk, [epinephrine] is almost instantly destroyed in the gastrointestinal tract. It is unlikely that any would be absorbed by the infant unless in the early neonatal period. In addition, it has a half-life of only 2 minutes.”

²⁷ DPMH review of Epinephrine Injection USP, NDA 204200/S-009 by Christos Mastroyannis, M.D., dated 11/6/2018. DARRTS Reference ID: 4345859.

²⁸ Gorewit RC, Aromando MC. Mechanisms involved in the adrenalin-induced blockade of milk ejection in dairy cattle. *Proc Soc Exp Biol Med*. 1985;180:340-7

²⁹ Song SL, Crowley WR, Grosvenor CE. Evidence for involvement of an adrenal catecholamine in the beta-adrenergic inhibition of oxytocin release in lactating rats. *Brain Res*. 1988;457:303-9.

³⁰ Hale, Thomas W. *Hale's Medications & Mothers' Milk 2021: A Manual of Lactational Pharmacology*. 19th ed. New York: Springer Publishing Company, 2020. www.halesmeds.com

³¹ Drugs and Lactation Database (LactMed). Accessed 6/28/23.

³² Briggs, Gerald G., Craig V. Towers, and Alicia B. Forinash. *Briggs Drugs in Pregnancy and Lactation: a Reference Guide to Fetal and Neonatal Risk*. 12th edition. Philadelphia, PA: Lippincott Williams & Wilkins, 2021. Print.

- LactMed: “Because of its poor oral bioavailability and short half-life, any epinephrine in milk is unlikely to affect the infant. High intravenous doses of epinephrine might reduce milk production or milk letdown. Low-dose intramuscular (such as Epi-Pen), epidural, topical, inhaled or ophthalmic epinephrine are unlikely to interfere with breastfeeding. Epinephrine is the first line-medication of choice for treatment of anaphylaxis; it should be used in the same manner in breastfeeding and non-breastfeeding patients.”

Reviewer comment:

The applicant did not provide any data from which to draw conclusions regarding the safety of epinephrine use during lactation. DPMH notes from their review that there are no animal or human data about the presence of epinephrine in milk. There are animal data suggesting that epinephrine may reduce milk production. There are no human data related to effects of epinephrine on milk production or the effect of epinephrine on the breastfed infant. Given the pharmacologic properties of epinephrine, the destruction of epinephrine by the infant’s gastrointestinal tract, and the lack of published adverse event data after decades of use, DPMH concludes that exposure is likely to minimal in the breastfed infant. See the Discussions and Conclusions section below for labeling recommendations for 8.2.

FEMALES AND MALES OF REPRODUCTIVE POTENTIAL

Nonclinical Experience

The applicant did not provide nonclinical data related to fertility in their submission. In section 13 of the current labeling for the RLDs,^{33,34} it states that epinephrine decreased implantation in female rabbits dosed subcutaneously with 1.2 mg/kg/day (15-fold the highest human intramuscular or subcutaneous daily dose) during gestation days 3 to 9.

The reader is referred to the full Pharmacology/Toxicology review by Dr. Carol Galvis.

Review of Pharmacovigilance Database

The applicant did not provide pharmacovigilance data.

Review of Literature

Applicant’s review:

The applicant did not provide a review of the clinical literature.

DPMH review:

DPMH conducted a literature search for studies in humans from 2018 to the present in PubMed, using the search terms “epinephrine” and “fertility,” “contraception,” “oral contraceptives,” “infertility” and “testosterone.” DPMH also conducted a search in Micromedex, Reprotox, and TERIS. No new publications or information was identified. The reader is referred to the most

³³ USPI for ADRENALIN (epinephrine injection) 1 mg/mL, for intramuscular, subcutaneous, and intravenous use, revised 6/2022.

³⁴ USPI for EPIPEN® (epinephrine injection), for intramuscular or subcutaneous use and EPIPEN Jr® (epinephrine injection), for intramuscular or subcutaneous use, revised 2/2023.

recent DPMH review of epinephrine³⁵ in which two publications^{36,37} related to male and female fertility were reviewed, and DPMH concluded that the study findings related to decreased male testosterone levels in the setting of epinephrine infusion and stimulation of endometrial activity with large doses of epinephrine were not clinically important.

Reviewer comment:

The applicant did not provide any data from which to draw conclusions regarding the impact of epinephrine on fertility or contraception. DPMH concludes from their review that there are limited human data related to the effects of epinephrine on fertility in males and females of reproductive potential. See the Discussions and Conclusions section below for labeling recommendations for subsection 8.3.

III. DISCUSSION AND CONCLUSIONS

Pregnancy

Epinephrine is necessary for the treatment of anaphylaxis in pregnant individuals. Failure to treat anaphylaxis may result in maternal and/or fetal death; therefore, emergency treatment with epinephrine for anaphylaxis is required as a life-saving measure for pregnant individuals and their fetuses. Nonclinical data involving epinephrine at doses higher than the maximum recommended human dose and with prolonged exposure demonstrate teratogenicity. However, clinical data over decades of use have not demonstrated adverse maternal or fetal outcomes. The “Risk Summary” in subsection 8.1 should include text explaining the human and animal data.

DPMH recommends removing the bullet from the Highlights of Prescribing Information that states,

(b) (4)

(b) (4)

Per the PLLR, DPMH recommends including a general background risk statement at the end of “Risk Summary” in subsection 8.1.

In order to explain the risk of anaphylaxis, DPMH recommends a “Clinical Considerations” section in 8.1. Although labeling for other epinephrine products indicates that epinephrine has the potential to impact the labor or delivery process by 1) decreasing uterine contractility which may either delay the second stage of labor or cause uterine atony with hemorrhage and 2) inducing uterine vasoconstriction which decreases uterine blood flow and may result in fetal anoxia, DPMH concludes that these potential risks do not outweigh the benefits of life-saving treatment with epinephrine. Thus, DPMH does not recommend including a “Labor or Delivery”

³⁵ DPMH review of Epinephrine Injection USP, NDA 204200/S-009 by Christos Mastroyannis, M.D., dated 11/6/2018. DARRTS Reference ID: 4345859.

³⁶ Levin J, Lloyd CW, Lobotsky J, et al. The effect of epinephrine on testosterone production. *Acta Endocrinol* 1967;55:184-92.

³⁷ Garrett WJ. The effects of adrenaline and noradrenaline on the intact non-pregnant human uterus: With a note on the effects of these hormones in early pregnancy. *J Obstet Gynecol* 1955;876-83.

section under “Clinical Considerations” as appears in the labeling for Adrenalin, one of the RLDs. The other RLD, EpiPen, does not contain the “Labor or Delivery” section in labeling.

There is no evidence of a new safety concern with epinephrine use in pregnancy; therefore, DPMH does not recommend issuing post-marketing requirements related to pregnancy.

Lactation

There are human data available to inform the presence of epinephrine in milk. Animal data are limited to effects on milk production, and there are no human data related to milk production or the effect on the breastfed infant. Based on the PLLR, DPMH recommends stating that there are no data on the presence of epinephrine in human milk, its effect of the drug on breastfed infant, or its effect on milk production in subsection 8.2.

Given the pharmacologic properties of epinephrine, including poor oral bioavailability and short half-life, epinephrine exposure to the breastfed infant is likely to be low. Since this drug is indicated for emergent use, the risk/benefit statement for lactation will not be included in subsection 8.2.

There is no evidence of a new safety concern with epinephrine use during lactation; therefore, DPMH does not recommend issuing post-marketing requirements related to lactation.

Females and Males of Reproductive Potential

DPMH recommends omitting subsection 8.3 for the following reasons:

- Epinephrine does not cause embryo-fetal toxicity or genotoxicity.
- Treatment with epinephrine is necessary as a life-saving measure prior to which contraception and pregnancy testing are not indicated.
- There are no reported adverse effects of epinephrine on human fertility after decades of use.

LABELING RECOMMENDATIONS

DPMH provided labeling text for subsections 8.1 and 8.2 (see below). These recommendations are largely based on the labeling for Adrenalin, except that the “Labor or Delivery” section from the Adrenalin labeling has been removed as explained in the Discussions and Conclusions section of this review. DPMH refers to the final NDA action for final labeling.

DPMH Proposed Pregnancy and Lactation Labeling

(b) (4)



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/

KATHERINE G KRATZ
07/20/2023 11:48:55 AM

MIRIAM C DINATALE
07/20/2023 02:05:33 PM

LYNNE P YAO
07/21/2023 08:02:37 AM

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:	June 1, 2023
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214697
Drug Constituent Name and Strength	Neffy (epinephrine) nasal spray, 2 mg
Product Type:	Combination Product (Drug-Device)
Device Constituent:	Aptar Nasal Spray Device
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ARS Pharma
FDA Received Date:	August 19, 2022 & October 7, 2022
OSE RCM #:	2022-1023
DMEPA 1 Human Factors Evaluator:	Matthew Barlow RN, BSN
DMEPA 1 Associate Director for Human Factors:	Jason Flint MBA, PMP

1 REASON FOR REVIEW

ARS Pharma submitted a New Drug Application (NDA) for their proposed epinephrine nasal spray drug product on August 19, 2022, under NDA 214697. This is a combination product with a proposed Aptar Nasal Spray device constituent part that is intended for immediate and emergency first-line treatment of allergic reactions (Type I) including anaphylaxis in Adults and Children ≥ 30 kg (66 lbs.).

1.1 PRODUCT DESCRIPTION

The proposed device constituent part is a unit dose nasal sprayer. The product is single-dose (one dose available in each device), and the device can only be activated once (b) (4). The product carton comes with 2 (b) (4) blister packs (each with a printed Quick Reference Guide (QRG) on the back, plus a separate Instructions for Use (IFU)). See figures 1 and 2 below.

Figure 1: Proposed Nasal Spray Device in Blister Packaging

Figure 2: Back of the Proposed Blister Tray with QRG

(b) (4)

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

On September 4, 2019, the Sponsor submitted an HF validation study protocol, and we provided our review and feedback on November 1, 2019^a. On February 5, 2020, the Sponsor submitted a revised protocol and responses to our November 1, 2019 recommendations; however, initially the Sponsor stated they did not submit the protocol for the Agency's review. On February 24, 2020, the Sponsor sent an email stating they would wait for any additional feedback from the Agency. On April 10, 2020, we provided our review and recommendations to the Sponsor's responses and revised protocol^b. The Sponsor submitted HF validation study results and post-validation supplemental HF study results on August 19, 2022, under NDA 214697, which are the focus of this review.

1.3 MATERIALS REVIEWED

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

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA and CDRH)	B
Background Information on Human Factors Engineering (HFE) Process	C
Human Factors Validation Study Report	D
Information Requests Issued During the Review	E
Labels and Labeling	F

^a Barlow, M. HF Validation Study Protocol Review for epinephrine nasal spray (IND 139091). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 01. RCM No.: 2019-1851.

^b Barlow, M. Review Revised HF Protocol and Responses for epinephrine nasal spray (IND 139091). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 10. RCM No.: 2019-1851-1.

2 OVERALL ASSESSMENT OF MATERIALS REVIEWED

The Applicant included two simulated-use HFVS (HFVS #1 and HFVS #2) in their submission to support the NDA. These two studies were separated by the actual use PK studies (e.g., self-administration PK study) EPI 12 and EPI 13, which provided additional information that was considered in the testing done for the supplemental HFVS (HFVS #2). The two HFVS were intended to provide data to support safe and effective use of the proposed product by adolescents (epinephrine-experienced and epinephrine-naïve patients) and adult lay people (epinephrine-experienced and epinephrine-naïve patients, passersby, and caregivers) without medical training, along with epinephrine experienced healthcare providers.

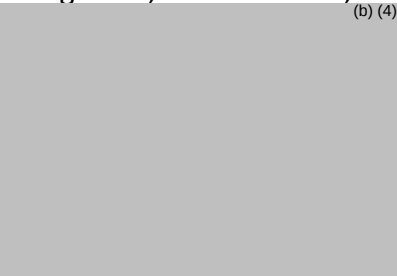
The sections below provide a summary of the study designs (Table 2 and Table 3), errors/close calls/use difficulties observed (Table 4 and table 5), and our analysis to determine if the results support a finding that the user interface design supports the safe and effective use of the proposed product.

2.1 SUMMARY OF STUDY DESIGN

Table 2. Study Methodology for Human Factors (HF) Validation Study							
Study Design Elements	Details						
Participants	User Group	N	Learning Condition	Epinephrine Experience	Nasal Spray Experience	Administration Condition In Study	Simulated Testing Environment
	Adult Patients	15	Untrained (N=15)	Experienced (N=15)	To Be Tracked During Recruitment for the Study	Self-Administer (N=15)	Home (N=15)
	Adolescent Patients	15	Untrained (N=15)	Experienced (N=15)		Self-Administer (N=15)	Home (N=15)
	Adult Naïve Patients	15	Untrained (N=15)	Naïve (N=15)		Self-Administer (N=15)	Home (N=15)
	Adolescent Naïve Patients	15	Untrained (N=15)	Naïve (N=15)		Self-Administer (N=15)	Home (N=15)
	Passers-by	15	Untrained (N=15)	Naïve (N=15)		Administer into Mock Patient (N=15)	Public (N=15)
	HCPs	15	Untrained (N=15)	Experienced (N=15)		Administer into Mock Patient (N=15)	Healthcare Setting (N=15)
	Total	90	Untrained (N=90)	Naïve (N=37) Experienced (N=53)	Representative Mix of Experienced and Naïve	Self-Administer (N=60) Administer to Mock Patient (N=30)	Public (N=15) Home (N=60) HealthCare Setting (N=15)
Training	All participants were untrained.						
Test Environment	Patients were assigned to a home environment, passers-by were assigned to a public environment, and HCPs were assigned to a hospital environment. Different room setups and different sound files were used to represent the home, a public setting, and a healthcare setting (e.g., ER). The overall room setup for the study included a table and chairs, a couch, a mayo stand (portable stand with tray) and a carry pouch that contained the devices. To represent realistic ambient noise and distraction, a laptop was used to play a sound file. The sound file played during all dosing tasks (1st and 2nd dose) and was playing when the participant entered the test room.						
Sequence of Study	- Unaided Rescue (Part 1) - Unaided Rescue (Part 2) - Debrief and Root Cause Analysis - Knowledge Task Assessment - Debrief and Root Cause Analysis						

- Final Feedback on Product and Instruction Materials

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

Study Design Elements	Details			
Participants	Group	Description	Training Provided?	Participant IDs
	Lay Adults (n = 15)	Age 18 + who have a Type 1 allergy	No	A01 - A15
	Adolescents (n = 15)	Age 10 to 17 who have a Type 1 allergy	No	J1 - J15
	Adolescents (n = 15)	Age 10 to 17 who have a Type 1 allergy	Yes	J16 - J30
	Lay Caregiver (n = 15)	Age 18 + who have a child with a Type 1 allergy	No	C01 - C15
Training	Only 15 of the 60 participants were shown the training video prior to the simulated-use portion of the study. These 15 participants were all adolescent participants. These adolescent patients were shown the video, on a laptop, but were not provided any additional information from the moderator.			
Test Environment	Sessions were conducted in a research lab test room setup to reflect the conditions of a home dining room environment simulating a situation in which someone may have inadvertently eaten something for which they have an allergy. The Neffy™ devices did not include any solution (only air, not actual drug), but all participants were expected to treat the devices as having drug. A soundtrack was played that is typical for this environment with loud noise that included public environmental elements, such as dishes being done, conversations, and TV sounds. (b) (4)  Participants were provided with commercially representative product configurations including: - o Neffy™ Nasal Spray Device (with QRG on backing) - o Carton - o Standalone IFU			
Sequence of Study	• Participant Enrollment • Session Introduction • Training Video (Trained Adolescent Arm Only, n=15) • Simulated-Use scenario 1 (1st Dose) • Simulated-Use scenario 2 (2nd Dose)			

	- o Only the following tasks were evaluated in the simulated-use scenarios: ▪ Insert nasal spray straight into nostril ▪ Insert nasal sprayer nozzle into nose up to fingers ▪ Call medical professional • Root Cause Analysis of Simulated-Use Issues • Knowledge Questions
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3 RESULTS AND ANALYSES

Table 4 describes the HF validation study results, ARS Pharma’s analyses of the results, and DMEPA 1’s analyses and recommendations. Table 5 describes the post-validation supplemental HF study results, ARS Pharma’s analyses of the results, and DMEPA 1’s analyses and recommendations.

During our review of the supplemental HF validation study results, we noted 6 participants experienced a use error related to the device “popping” out of the nostril prematurely for tasks 1 and 2 (see table 5). As such, on March 20, 2023, we sent an information request (IR) requesting further information about these use errors and a rationale for the occurrence, as this use issue was not noted in the previous HF validation study or any of the actual use studies. On March 22, 2023, the Applicant provided the following response:

“This was mainly in untrained adolescents. One potential explanation is that in the primary HF validation study and the real-world clinical studies EPI 12 and EPI 17, the device either contained saline or active drug. Thus, the device had a vial and liquid in the device. For the post-validation supplemental study (ARS-Neffy-VT-503) the devices were empty (‘air-filled’) and thus much lighter than those used in the primary HF validation study and ‘real-world’ EPI 12 and EPI 17 studies where there were no dosing errors reported. These later studies are also consistent with other HF validation studies and real-world use of the Aptar Unit Dose Sprayer which is the identical sprayer used for many other products... Thus, the errors may have been caused by the much lighter weight of the device that during activation made it less stable for subjects during administration.”

Although it’s unclear whether the root cause of this use error could be solely attributed to the lighter weight of the device as proposed by the sponsor, it is plausible, based on the results from both HF studies, the Applicant’s information, and our expert analysis, that the air-filled device contributed to the occurrence of this use error in some way, and may be test artifact. We discuss this issue further in table 4 and the conclusion section.

Table 4: HF Validation Study Results

Legend: UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis

Participants ID: P=participant

Scenario Type: Results from Both Scenarios of Unaided Rescue #1 and #2 and Knowledge Task Assessment are combined in the table below

Information Supplied by Applicant	DMEPA's Findings and Recommendations								
<u>Task 1: Dispose of Nasal Spray</u> <table border="1" data-bbox="225 441 625 594"> <tr> <th>Errors:</th><th>Participant Type:</th></tr> <tr> <td>UE (n=1)</td><td>1 experienced adolescent patient</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </table>	Errors:	Participant Type:	UE (n=1)	1 experienced adolescent patient	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=1)	1 experienced adolescent patient								
CC (n=0)									
UD (n=0)									
Observed error(s): P17 did not initially throw away the used nasal spray device.									
Risk associated with Task Errors (Per Applicant URRRA): User not disposing of nasal spray can lead to user attempting to reuse the nasal spray leading to no dose and harm	We note the URRRA is not complete because the Applicant did not specify the clinical impact of no dose. However, given the intended use of this product and what is known clinically regarding anaphylaxis, we note that dose omission could result in death or other serious adverse events for some patients.								
Relevant RCA/Subjective Feedback/Observation: - When prompted by the moderator as to what he would do with the device when he was done dosing, he stated he would not recycle it, but he did not know what else he would do. He did not state he would throw it away, nor did he initially attempt to dispose of it. When later asked again what he would do with a used device, with the full IFU available to him, he correctly stated he would dispose of the device in the household trash. - Our root cause analysis leads us to believe that the error is not attributed to the IFU, labelling, or device, but rather the participant not having any disposal information available to him, as disposal is not presented on the rescue device QRG.									
Applicant Comment and Current Mitigations: We do not believe further mitigation is needed to address this error. The IFU has a devoted section with an image related to disposal of the used product (see image below). Also, when an adolescent patient is prescribed a rescue medicine, the parent and HCP would review the use and disposal process with the adolescent; it would be knowledge the user would have prior to use of the rescue device. Furthermore, when the IFU was available to the participant, he was able to identify that the used device should be disposed of into household trash.	We do not agree with the justification that an adolescent patient prescribed the product would always receive education by the HCP. There is published literature to suggest that is in fact not always the case currently when patients are prescribed epinephrine autoinjectors for anaphylaxis. However, based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.								
<u>Task 2: Give a Second Dose</u> <table border="1" data-bbox="225 1537 625 1778"> <tr> <th>Errors:</th><th>Participant Type:</th></tr> <tr> <td>UE (n=10)</td><td>2 naïve adult patients, 5 experienced adolescent patients, 2 naïve adolescent patients, 1 naïve passerby</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </table>	Errors:	Participant Type:	UE (n=10)	2 naïve adult patients, 5 experienced adolescent patients, 2 naïve adolescent patients, 1 naïve passerby	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=10)	2 naïve adult patients, 5 experienced adolescent patients, 2 naïve adolescent patients, 1 naïve passerby								
CC (n=0)									
UD (n=0)									
Observed error(s): P17, P22, P23, P24, P29, P31, P42, P58, P59, and P73 gave the second dose in the same nostril as the first dose.									

Risk associated with Task Errors (Per Applicant URRRA): No harm in administering the second dose (b) (4)									
Relevant RCA/Subjective Feedback/Observation: - P17 stated he just did not know during the scenario. - P22 stated that he dosed (b) (4) - P23 she stated it was because she panicked, and that was the first thing that came to her mind to do, without having referenced the QRG. - P24 stated he dosed (b) (4) because in an emergency he would likely be trying to get his medicine as soon as possible and would not think about (b) (4) he was giving it in. He also stated he only skimmed the QRG and missed that instruction. - P29 stated he did read the statement but forgot. - P31 missed this instruction when he first read the QRG. - P42 did not remember reading the instruction, so they gave it in (b) (4) thinking it be more effective that way, based on their own experience. - P59 stated he dosed (b) (4) - P73 stated he did not dose (b) (4) because he had not fully read the QRG because he had forgotten his reading glasses. - Our root cause analysis leads us to believe that the error is not attributed to the IFU, labelling, or device, but rather it was a result of participants attempting to go off of memory or personal experience, without referring to the QRG. Participants who committed this use error either did not initially read the information, skimmed over it, or read it and forgot it.									
Applicant Comment and Current Mitigations: - We do not believe further mitigation is needed to address this error. (b) (4) - Furthermore, all participants who read and referred to the QRG when giving the second dose successfully dosed (b) (4) without any difficulty comprehending the information. - Although, this task is critical, dosing (b) (4) will not harm the patient and after the first dose, a medical professional would have already been contacted.	We discussed this use issue with our clinical colleagues, and they stated that based on the data there are no clinical concerns with administering a second dose of epinephrine nasal spray (b) (4) Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.								
Knowledge Task 1 under Unaided Rescue Part 2: Under what condition or when would you need to give a second dose? <table border="1" data-bbox="225 1554 625 1707"> <thead> <tr> <th>Errors:</th><th>Participant Type:</th></tr> </thead> <tbody> <tr> <td>UE (n=1)</td><td>1 experienced adolescent</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </tbody> </table>	Errors:	Participant Type:	UE (n=1)	1 experienced adolescent	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=1)	1 experienced adolescent								
CC (n=0)									
UD (n=0)									
Observed error(s): P17 initially stated he did not know the answer; however, when later presented with the device and instructional materials, he was able to successfully find the answer.									
Risk associated with Task Errors (Per Applicant URRRA):	We note the URRRA is not complete because the Applicant did not specify the clinical impact of an underdose or delay in dose. However, given the								

If a user does not know what conditions to administer a second dose, this may lead to an underdose/delay and patient harm.	intended use of this product and what is known clinically regarding anaphylaxis, we note that dose delay or underdose could result in death or other serious adverse events for some patients.
Relevant RCA/Subjective Feedback/Observation: The result of the participant attempting to go off of memory when answering the Knowledge Task question. The participant had already disposed of the QRG when initially asked this Knowledge Task but was successfully able to identify when to give a second dose when the IFU and QRG was available to him.	
Applicant Comment and Current Mitigations: - We do not believe further mitigation is needed to address this error. The IFU and QRG both have a dedicated statement instructing the user to give a second dose after (b) (4) minutes if symptoms get worse or reoccur, with “(b) (4) minutes” highlighted in bold lettering. - Furthermore, no other participants in the study incorrectly answered this Knowledge Task, demonstrating that the information is clearly presented as is.	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.

Table 5: Post-Validation Supplemental HF Study Results

Legend: UE = use error; CC = close call; UD = use difficulty; URRRA = use-related risk analysis; RCA = root cause analysis

Participants ID: A = adult patient; J = adolescent patient

Scenario Type: Results from Both Scenarios of Unaided Rescue #1 and #2

Information Supplied by Applicant	DMEPA’s Findings and Recommendations								
<u>Task 1: Insert Tip</u> <table border="1"> <tr> <td>Errors:</td><td>Participant Type:</td></tr> <tr> <td>UE (n=3)</td><td>1 adult patient, 1 adolescent patient (2 errors)</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </table>	Errors:	Participant Type:	UE (n=3)	1 adult patient, 1 adolescent patient (2 errors)	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=3)	1 adult patient, 1 adolescent patient (2 errors)								
CC (n=0)									
UD (n=0)									
Observed error(s): - A01 used his dominant hand but switched nostrils using a contralateral approach which resulted in the tip inserted at an angle. When attempting to insert and push the plunger, the tip slipped out of the nostril as he only had the tip at the very edge of the nostril. - J09 had difficulty inserting the tip of the device during both dose simulations. Since she was unable to insert the tip fully it popped out when she proceeded to the “press plunger” step.									
Risk associated with Task Errors (Per Applicant URRRA): The potential harm associated with these use issues would be no dose leading to patient harm.	We note the URRRA is not complete because the Applicant did not specify the clinical impact of no dose. However, given the intended use of this product and what is known clinically regarding anaphylaxis, we note that dose omission could result in death or other serious adverse events for some patients.								
Relevant RCA/Subjective Feedback/Observation: - A01 stated he was “freaking out” during the simulation and felt like he needed to hurry to get the medicine in and that he should have taken his time. - J09 said she felt the tip was too big to fit into her nose properly. The Sponsor noted that other participants, with seemingly smaller noses, did not report their noses being too small.									
Applicant Comment and Proposed Mitigations: None	We consulted our colleagues in the Center for Devices and Radiological Health (CDRH), who confirmed that the device constituent has the same								

	dimensions as the device constituent for other approved nasal spray products that utilize the same Aptar device constituent part used in similar populations. Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.								
Task 2: Hold Straight <table border="1"> <tr> <th>Errors:</th><th>Participant Type:</th></tr> <tr> <td>UE (n=5)</td><td>4 untrained adolescents, 1 trained adolescent</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </table>	Errors:	Participant Type:	UE (n=5)	4 untrained adolescents, 1 trained adolescent	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=5)	4 untrained adolescents, 1 trained adolescent								
CC (n=0)									
UD (n=0)									
Observed error(s): - During the first dose, when pushing the plunger in, the unanticipated force resulted in J05 and J08 reflexing such that the tip came out of the nose. - J04 and J07 had the same experience of the tip popping out when they press the plunger in during the second dose. - J24, a trained adolescent, was unable to hold it in straight.									
Risk associated with Task Errors (Per Applicant URRRA): The potential harm associated with these use issues would be no dose and underdose which would lead to patient harm.	We note the URRRA is not complete because the Applicant did not specify the clinical impact of no dose or underdose. However, given the intended use of this product and what is known clinically regarding anaphylaxis, we note that dose omission could result in death or other serious adverse events for some patients.								
Relevant RCA/Subjective Feedback/Observation: - J05 reported that she must not have inserted the tip far enough. - J08 reported that the "click" sound "freaked" her out such that she lost grip on the device. - J24 stated that by using his less dominant hand he did not have as firm a grip on the device so that when it "snapped" he was unable to hold it in straight. - The force required to press the plunger (i.e., "snapping of the plunger") can be unanticipated by users which can result in the hand and arm reflexing in response such that the sprayer "pops" out of the nose unintentionally.	See our discussion regarding these use issues in Section 3 and Section 4.								
Applicant Comment and Proposed Mitigations: None	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find the residual risk acceptable and have no recommendations at this time.								
Task 3: Call Medical <table border="1"> <tr> <th>Errors:</th><th>Participant Type:</th></tr> <tr> <td>UE (n=1)</td><td>1 adult patient</td></tr> <tr> <td>CC (n=0)</td><td></td></tr> <tr> <td>UD (n=0)</td><td></td></tr> </table>	Errors:	Participant Type:	UE (n=1)	1 adult patient	CC (n=0)		UD (n=0)		
Errors:	Participant Type:								
UE (n=1)	1 adult patient								
CC (n=0)									
UD (n=0)									
Observed error(s): During the first dose administration, A01 did not report that he would call for medical attention even after the moderator probed around the issue a few times. He re-read the IFU and noted it said he should call for help but that he did not see this information during his initial review.	This was considered a close call by the Sponsor; however, due to moderator probing and prompting, we consider this a use error.								
Risk associated with Task Errors (Per Applicant URRRA): The potential harm associated with no calling for medical/emergency professionals is no additional treatment leading to prolonged or rebound anaphylaxis.	Given the intended use of this product and what is known clinically regarding anaphylaxis, we note that rebound anaphylaxis could result in death or other serious adverse events for some patients.								
Relevant RCA/Subjective Feedback/Observation:									

Upon initial review, the call for medical attention section was not conspicuous enough to grab A01's attention. His lack of regard for the need of this step could have also contributed to this.	
Applicant Comment and Proposed Mitigations: None	Based on our review of the current mitigations in place along with the provided root cause and subjective feedback, we find additional mitigations should be implemented to improve emphasis of this important information. See Section 4.1.

4 CONCLUSION AND RECOMMENDATIONS

Some participants in the supplemental HF study experienced use errors related to angling the device in the nostril or premature removal of the device from the nostril. Based on the Applicant's use-related risk analysis (URRA) it is not clear what impact angling of the device has. Additionally, the supplemental human factors study may not have fully assessed the use error of wrong angle of insertion because the device used in this study was not filled with liquid. However, we note that this error does not appear to noticeably lower the epinephrine PK profile based on a subgroup analysis of available PK data performed by our clinical pharmacology colleagues. Thus, this use error does not appear to have a meaningful clinical impact.

Regarding the use errors related to premature removal of the device from the nostril observed in the supplemental HFVS #2. We note that the Applicant's URRA indicates that premature removal of the device while pressing the plunger may lead to partial dose or no dose. In some cases, these were due to a startle reaction due to unanticipated force, or the noise associated with depressing the spray plunger. We also note that this error was not observed in the HFVS #1 or the actual use PK studies. The Applicant attributes the observation of this error in the supplemental HFVS #2 to the air-filled device used only in this study, which seems plausible and may indicate study artifact, as we note that this error was not observed in the HFVS #1 or the actual use PK studies. Furthermore, we considered that use errors related to premature removal are not unique to the proposed product as this type of error occurs with other intranasal emergency use products using the same device constituent parts, as well as some epinephrine injection products. In this case, we do not have reason to determine there is a greater risk associated with this product as compared to other intranasal emergency use products using the same device constituent parts or epinephrine injection products.

We considered the impact of the aforementioned use errors, and given the above considerations in totality, we determined the residual risk is acceptable, and we do not think additional risk mitigation measures related to the user interface design will likely further reduce the residual risk for the identified use errors related to angling the device and premature removal of the device.

Furthermore, in both HFVS #1 and HFVS #2, we note that there were multiple use errors regarding the failure to call a medical professional. To address this use error, we recommend that the Applicant implement labeling revisions to further emphasize the need to call for emergency medical help. See Section 4.1 for our recommendations.

4.1 RECOMMENDATIONS FOR ARS PHARMACEUTICALS

Our evaluation of the proposed packaging, label and labeling identified areas of vulnerability that may lead to medication errors. We have provided recommendations below, and we recommend that you implement these recommendations prior to approval of this NDA.

Please note that if you further modify the product user interface or device constituent parts beyond addressing the enclosed recommendations, please submit your updated use-related risk analysis and your determination for HF data requirements for your product for Agency review.

- A. QRG on Blister Pack, Instructions for Use (IFU), and QRG on Carton Labeling
 - a. Based on the root cause analysis and subjective feedback for the task of calling medical in the HF validation study and post-validation supplemental HF study, we recommend revising the quick reference guide to improve emphasis of this important information. Consider making this information a step and separating it from the current boxed information on the QRG. Additionally, we recommend revising the language to read “Contact Emergency Services immediately after use” on the carton labeling, QRG, and IFU, as emergency medical professionals should be contacted. Furthermore, this language is consistent with other epinephrine products.
 - b. We recommend removing the language (b) (4) from the instructions, as it may be unclear to a user what might constitute (b) (4).
- B. IFU
 - a. We recommend revising the title of Step 1C to read as follows: “Insert *nozzle* into a nostril until your fingers touch your nose (see Figure 1C)” to emphasize the nozzle and not just the tip of the nozzle should be inserted into nostril. This is also consistent with the revisions to the QRG.
 - b. We recommend placing the instruction "Keep Neffy in its clear plastic case until ready to use" under the important information of the IFU, as the QRG is on the back of the blister pack, which would provide users with instructions on how to administer the product.
- C. Carton labeling
 - a. We recommend placing the instruction “Keep Neffy in its clear plastic case until ready to use” on the back panel. Consider placing it above the images depicting the use of the product.
- D. All Labeling (Carton, Container, IFU, QRG etc.)
 - a. We note you use both (b) (4) and “single-dose” throughout the labeling. We recommend revising the package term from (b) (4) to the appropriate package term “single-dose” throughout to maintain consistency with

terminology. See *Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors* (May 2022)^c.

^c Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. 2022. Available from: <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/safety-considerations-container-labels-and-carton-labeling-design-minimize-medication-errors>

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 5 presents relevant product information for Neffy that ARS Pharmaceuticals submitted on 8/19/2022.

Table 5. Relevant Product Information	
Initial Approval Date	N/A
Therapeutic Drug Class or New Drug Class	(b) (4) alpha and beta-adrenergic receptor agonist
Active Ingredient (Drug or Biologic)	epinephrine
Indication	Immediate and emergency first-line treatment of allergic reactions (Type I) including anaphylaxis in Adults and Children ≥ 30 kg (66 lbs.)
Route of Administration	intranasal
Dosage Form	nasal spray
Strength	2 mg
Dose and Frequency	(b) (4) a single intranasal (into the nose) administration of 2.0 mg epinephrine. In the absence of clinical improvement or (b) (4) after the initial treatment, a second dose of neffy may be administered approximately (b) (4) minutes (b) (4) after the first dose.
How Supplied	neffy 2 mg (NDC 82580-(b) (4)-02) is supplied as a carton containing two (2) blister packages each with a single spray device.
Storage	Store below 77°F (25°C). Excursions permitted up to 122°F (50°C). Do not freeze. neffy freezes below 5°F (-15°C). (b) (4) (b) (4)
Container Closure/Device Constituent	Aptar nasal spray device, single-dose.
Intended Users	Patients (adults and pediatrics), Caregivers, Naïve Passersby, and HCPs
Intended Use Environment	Home; Public

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On October 3, 2022, we searched the L:drive and AIMS using the terms, 139091 ARS1 to identify reviews previously performed by DMEPA or CDRH.

B.1.2 Results

Our search identified two previous reviews^{d,e}, and we confirmed that our previous recommendations were implemented or considered.

^d Barlow, M. HF Validation Study Protocol Review for epinephrine nasal spray (IND 139091). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2019 NOV 01. RCM No.: 2019-1851.

^e Barlow, M. Review Revised HF Protocol and Responses for epinephrine nasal spray (IND 139091). Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2020 APR 10. RCM No.: 2019-1851-1.

APPENDIX C. BACKGROUND INFORMATION ON HUMAN FACTORS ENGINEERING PROCESS

See Appendix D

APPENDIX D. HUMAN FACTORS VALIDATION STUDY RESULTS REPORT

The HF study results report can be accessible in EDR via:

[\\CDSESUB1\EVSPROD\nda214697\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\arsp0685-2\arsp0685-2-validation.pdf](\\CDSESUB1\EVSPROD\nda214697\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\arsp0685-2\arsp0685-2-validation.pdf)

The Post-Validation HF Supplemental study results report can be accessible in EDR via:

[\\CDSESUB1\EVSPROD\nda214697\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\ars-neffy-vt-503\ars-neffy-vt-503-post-validation-suppl-study.pdf](\\CDSESUB1\EVSPROD\nda214697\0001\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\ars-neffy-vt-503\ars-neffy-vt-503-post-validation-suppl-study.pdf)

APPENDIX E. INFORMATION REQUESTS ISSUED DURING THE REVIEW

- Sponsor's October 7, 2022 Response to Agency's October 4, 2022 IR accessible in EDR via:
[\\CDSESUB1\EVSPROD\nda214697\0010\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\hr-ir\response-to-hf-information-request.pdf](\\CDSESUB1\EVSPROD\nda214697\0010\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\hr-ir\response-to-hf-information-request.pdf)
- Sponsor's January 10, 2023 Response to Agency's January 5, 2023 IR accessible in EDR via:
[\\CDSESUB1\EVSPROD\nda214697\0019\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\hr-ir\response-to-01-05-23-hf-ir.pdf](\\CDSESUB1\EVSPROD\nda214697\0019\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\hr-ir\response-to-01-05-23-hf-ir.pdf)
- Sponsor's March 22, 2023 Response to Agency's March 20, 2023 IR accessible in EDR via:
[\\CDSESUB1\EVSPROD\nda214697\0028\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\hr-ir\03-20-2023-hf-response.pdf](\\CDSESUB1\EVSPROD\nda214697\0028\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\hr-ir\03-20-2023-hf-response.pdf)
- Sponsor's April 5, 2023 Response to Agency's March 28, 2023 IR accessible in EDR via:
[\\CDSESUB1\EVSPROD\nda214697\0033\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ \(b\) \(4\) 5354-other-stud-rep\hr-ir\hf-response-28-march.pdf](\\CDSESUB1\EVSPROD\nda214697\0033\m5\53-clin-stud-rep\535-rep-effic-safety-stud\ (b) (4) 5354-other-stud-rep\hr-ir\hf-response-28-march.pdf)

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,^f along with postmarket medication error data, we reviewed the following Neffy labels and labeling submitted by ARS Pharmaceuticals.

- Container label received on August 19, 2022
- Carton labeling received on August 19, 2022
- Instructions for Use received on August 19, 2022, available from <\\CDSESUB1\EVSPROD\nda214697\0001\m1\us\draft-labeling-text-ifu.pdf>
- Prescribing Information (Image not shown) received on August 19, 2022, available from <\\CDSESUB1\EVSPROD\nda214697\0001\m1\us\prescribing-information-neffy.docx>

F.2 Label and Labeling Images

(b) (4)



^f Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/

MATTHEW J BARLOW
06/02/2023 07:53:05 AM

JASON A FLINT
06/02/2023 08:07:16 AM

MEMORANDUM

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

DATE: May 23, 2023

TO: Sally Seymour, M.D.
Director
Division of Pulmonology, Allergy, and Critical Care
(DPACC)
Office of Immunology and Inflammation (OII)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI, OSIS

SUBJECT: Routine Clinical Inspections of Institute for Asthma
and Allergy, P.C., Chevy Chase, MD and University of
South Florida, Tampa, FL

** Please note that the EIR review of the clinical inspection of Children's Hospital Colorado, Aurora, CO (Study Site #01) covering the same study was previously submitted on April 3, 2023.*

Inspection Summary

Per the request of OND/OII/DPACC, OSIS arranged inspections of clinical portion of **Study EPI 10 (NDA 214697, Epinephrine nasal spray)** conducted at Institute for Asthma and Allergy, P.C., Chevy Chase, MD and University of South Florida, Tampa, FL.

- For Institute for Asthma and Allergy, P.C., the ORA Investigators observed objectionable conditions and issued a one-item Form FDA 483 regarding the lack of the second-parent's signature in the informed consent forms (ICF). In addition, six verbal items were discussed with the site's management at the inspection closeout.
- For University of South Florida, no objectionable conditions were observed. No Form FDA 483 was issued and no verbal item

was discussed with the clinical site's management at the inspection close-out.

After reviewing the inspectional findings and response to Form FDA 483 from Institute for Asthma and Allergy, I recommend that the review division should determine the impact of the lack of adequate informed consent on the reliability of the study data from the site.

In addition, the review division should determine if there is any impact of the concomitant medications on subject safety for Subject (b) (6)

Please note that according to Table 14 in study report for EPI 10, a single-parent signature on the ICF was obtained for 7 out of 10 subjects enrolled at **Study Site #01 (Children's Hospital Colorado, Aurora, CO)**, and 2 out of 28 subjects enrolled at **Study Site #03 (University of South Florida, Tampa, FL)**. These were reported as protocol deviations. Form FDA 483 was not issued at the close-out of either of those inspections, and no exhibits were collected for these deviations during those inspections.

Inspected Study

NDA 214697

Study Number: EPI 10

Study Title: "A Single-Period, Single-Dose Study of the Pharmacokinetics and Pharmacodynamics of Epinephrine After Administration of Intranasal ARS-1 to Pediatric Subjects with Systemic Allergies"

Study Dates: July 17, 2020 - March 15, 2021* (interim)

**The study continued to enroll subjects until June 2022.*

**Clinical Site #1: Institute for Asthma and Allergy (IAA), P.C.
(Study Site #02)**

2 Wisconsin Circle, Suite 250
Chevy Chase, MD 20815

Clinical Investigator: Huamin Henry Li, M.D., Ph.D.

Scope of Inspection

ORA Investigators David Chon and Lucilla Facchin audited the clinical portion of **Study EPI 10** at Institute for Asthma and Allergy, P.C., Chevy Chase, MD from March 20 to 24, 2023.

This was the first FDA BIMO BA/BE inspection of the clinical site. Dr. Li was previously inspected under the Clinical Investigators and Sponsor-Investigators Compliance Program in November 2016 and no Form FDA 483 was issued at the inspection closeout.

The current inspection included a review of the following items: organization of the firm, study administration and responsibility, subjects' records and good documentation practice including study source records, informed consent records, electronic case report forms (eCRFs); test article accountability and disposition; and study sample collection, processing, and storage.

Inspectional Findings

Investigators Chon and Facchin observed objectionable conditions and issued a one-item Form FDA 483 at the conclusion of the inspection. In addition, they also discussed six verbal items with the site's management at the inspection closeout. My evaluation of the Form FDA 483 observation (**Attachment 1**), the Discussion Items, and the firm's response dated April 5, 2023 (**Attachment 2**) are presented below.

Observation #1: For a clinical investigation involving children, conducted under 21 CFR 50.53, the investigator did not always obtain the permission of both parents where feasible. Specifically, the IRB stated in its initial approval that both parent signatures are required when obtaining assent. However, we observed that the informed consent or assent forms did not have the second parent signature for all 24 enrolled pediatric clinical subjects.

Site's Response:

The CI, Dr. Huamin Henry Li, acknowledged the observation and explained that both parents were unable to provide signatures on the informed consent form due to restrictions implemented during the COVID-19 pandemic that allowed only one parent accompany the subject. Dr. Li mentioned that corrective actions have been implemented, including notifying the IRB, sponsor and CRA of the Form FDA 483 observation; updating the site's SOP on ICF

procedures; and re-training staff. Dr. Li also proposed additional corrective actions, including improving communication between the site study personnel and the IRB regarding the ICF signature requirements for future studies. The complete response can be found in **Attachment 2**.

OSIS Evaluation:

The clinical site should have followed the IRB approved ICF for enrolling the subjects regarding the parental signatures. The IRB-approved ICFs (version 1.1 dated Jun 8, 2020 (for Study Protocol Version 2.0), ICF version 1.1 dated July 16, 2020 (for Study Protocol Version 3.0), and ICF version 5.0 dated Oct 5, 2021 (for Study Protocol Version 5.0) required signatures from both parents, but the site obtained the signature from a single parent for all subjects (Subjects (b) (6)) audited during the inspection by the ORA Investigators. Subjects (b) (6) (b) (4) were enrolled from July to November 2020 and Subjects (b) (4) were enrolled from November 2021 to June 2022.

Thus, based on the evidence collected, adequate informed consent was not obtained for 24 pediatric subjects as required by the IRB for **Study EPI 10** prior to enrolling the pediatric subjects into the study. Based on the lack of informed consent for all pediatrics subjects at the Clinical Inspections of Institute for Asthma and Allergy, the review division should determine the impact of this finding on the reliability of the study data from the site.

Discussion Item #1: IP accountability related issues.

Specifically,

- a. The investigators found an undated picture which showed inadequate packaging of the test article.
- b. The IP storage and supply room door was propped open and was not securely locked.
- c. The test cartridge inhaler did not include the required FDA label statement, "Caution New Drug - Limited by Federal (or United States) law to investigational use" on any accompanying labeling or packaging; Instead, only "INV USE" was printed on the cartridges.
- d. The lot number, date of receipt, and dosage were written on the plastic bags containing the remaining IPs using a marker instead of using appropriate labeling.

Site's Response: The CI and the site's management acknowledged the above findings. During the inspection, they stated that the cartridges shown in the picture were for training purpose and did not contain any active ingredients. The site's management promised corrective actions to address the findings.

OSIS Evaluation:

- a. This finding is true in fact and is a documentation issue. However, it does not impact study data as the test cartridge was not used in the study and was for training purposes only.
- b. No evidence was provided for this observation. However, FDA investigators acknowledged in the EIR that the IPs of Study EPI 10 and other studies were securely stored in the locked refrigerators at 4°C and the -80°C freezer in the IP storage room per their respective labeling requirements. This observation has no impact on study data.
- c. No supporting evidence was provided for this observation. The ORA investigators acknowledged this was a sponsor responsibility. This observation has no impact on study data.
- d. No supporting evidence was provided for this observation. This observation is true in fact, but the EIR did not provide any evidence that the labeling was faded or smudged. Thus, the observation is not objectionable and has no impact on study data.

Discussion Item #2: Minor protocol deviations including:

- a. Subject (b) (6) took OTC ibuprofen within 2 days prior to the Baseline visit and the sponsor provided an exemption to protocol restriction #2. However, this was not reported as a planned protocol deviation.
- b. Subject (b) (6) fasted and was 7 minutes short of the 8-hour requirement per the protocol and inclusion/exclusion criteria prior to the screening visit
- c. Subject (b) (6) source record Electronic Medical Record (EMR) had a BMI value of 26.26 at the screening visit and was recorded as 26 in the CRF in the source records. The Inclusion Criteria #2 listed the expected BMI should be ≤26. The ORA Investigators found no sponsor permission for the subject to be enrolled.
- d. Subject (b) (6) had previously taken medications (Bactrim DS and Tacrolimus external ointment) and were documented in the EMR. However, these medications were not reported in the Electronic Data Capture (EDC) system.

Site's Response: The CI and the site's management acknowledged the findings and promised corrective actions.

OSIS Evaluation:

- a. This finding is true in fact. Subject (b) (6) took ibuprofen the night before and was approved by the medical monitor for dosing per the study protocol (v 3.0) Restriction #2, which specified that enrolled subjects are restricted to "take over-the-counter (OTC) products for the two days prior to dosing on Day 0 and during the study unless approved by the medical monitor." Therefore, this is not a protocol deviation. Therefore, this finding is unlikely to impact the screening results and the subject welfare and safety.
- b. This finding is true in fact. For Subject (b) (6) fasting for 7 hours and 53 minutes instead of 8 hours fasting prior to the screening visit. Although this was a protocol deviation, Subject (b) (6) had screening results within the normal range. I recommend the review division assess discussion item #2b on screening results and subject safety.
- c. This finding is true in fact. The study protocol was silent on the rules of rounding clinical values. It appears that the Subject (b) (6) BMI value of 26.26 was rounded to 26 in the CRF. ORA did not collect evidence that this was done intentionally to enroll the subject into the study. The EIR also does not provide information if this was the only time rounding was done, or it was being done for other subjects too. This finding appears to be a documentation issue. The review division should evaluate the impact of this finding on whether the subject met the inclusion criteria.
- d. ORA did not provide any supporting documentation. Although Bactrim and Tacrolimus used by Subject (b) (6) were not considered as prohibited drugs per the study protocol, the review division should determine if this finding has any impact on subject safety and data reliability.

Discussion Item #3: No SOPs were implemented regarding quality management, a process for training, a process for data management, and a process for certifying copies of the source EMR.

Site's Response: The CI and the site's management acknowledged the finding and promised corrective and preventative actions.

OSIS Evaluation: This finding is true in fact. However, there is no regulatory requirement for the SOPs mentioned above. During

the inspection, the ORA Investigators did not observe any objectionable conditions regarding quality management, training, data management and certifying copies of the source EMR. Therefore, this finding is unlikely to impact study data reliability. No corrective actions are necessary.

Discussion Item #4: Good Documentation Practice related issues, including:

- a. Non-contemporaneous signatures by the CI in the AE Logs.
- b. Subject (b) (6) ICF was not signed by the parent at the time of IC process (b) (6). The missing ICF signature was identified during a monitoring visit on (b) (6). The parent subsequently signed the ICF but appeared to backdate on the form as (b) (6) instead of the actual signing date, which was unknown.
- c. The PK samples' shipping labels to the bioanalytical laboratory for subjects (b) (6) were not documented with the actual shipment date, subject identifiers and primary/backup sample type.
- d. In the signed Form FDA-1572, Dr. Li was listed both the PI and sub-investigator, and Dr. Mark Scaropa was omitted as a Sub-investigator.
- e. For Subject (b) (6) the five concomitant medications (Epinephrine 0.3 mg auto-injector, Albuterol sulfate HFA 108 mcg, Qvar RediHaler 80 mcg, Zyrtec 10 mg, and Naproxen 600 mg) in the Concomitant Medication Log had no stop date and were not marked whether the medication was ongoing.

Site's Response: The CI and the site's management acknowledged these findings and promised corrective actions. They stated that they initially documented AEs in the source records, but in the middle of the study the CRO requested that AEs should be documented in the AE Logs, which caused the late signature of the CI. They confirmed that there was an oversight in the Form FDA-1572 and Dr. Scaropa should have been listed as the sub-investigator.

OSIS Evaluation: Although the findings in discussion item 4 are true in fact,

- a. This appears to be a documentation issue.
- b. The missing signature of Subject (b) (6) parent in the ICF was reported as a protocol deviation on 12/14/2021 in the Clinical Study Report. The clinical site also completed a Note-to-File (NTF) (**Attachment 3**). The clinical site should have verified that the parent used the current date while

signing the ICF. Subject (b) (6) did not experience any AEs during the study.

- c. This appears to be a documentation issue. However, the EIR does not provide adequate information to evaluate the finding. The actual shipping dates, subject IDs and sample types should be available to retrieve and reconstruct based on the attached clinical manifest and the relevant courier tracking records. Therefore, this finding is unlikely to have an impact on sample integrity.
- d. Although Form FDA-1572 omitted Dr. Scaropa as a Sub-Investigator, he signed the Site Signature/Delegation of Authority Log on 11/09/2020 and performed all the responsibilities as a Sub-Investigator and ORA investigators did not find any issues. This is a documentation issue and unlikely to impact the study outcome.
- e. Although the finding is true in fact, the protocol did not require recording the start or stop dates of concomitant medications. The start dates recorded in concomitant medications form are well before the start of study initiation. The protocol states that the asthma and other medications to manage chronic conditions will not be discontinued unless they pose a risk to the study outcomes or safety of the subject. The EIR does not provide any information about how the concomitant medications were used during the study. There is insufficient information to evaluate the impact of this finding and determine whether the concomitant medications were considered a risk to the study outcome or subject safety.

Discussion Item #5: Facility and equipment related issues. Specifically,

- a. (b) (4)
 - b. (b) (4)
 - c. (b) (4)
- (b) (4) All IPs are stored in either the -80°C freezer, 4°C refrigerators, or storage equipment set at ambient temperature. The ORA Investigators acknowledged not observing any IP stored outside of the storage equipment.

Site's Response: The site's management acknowledged the findings. They stated that the (b) (4)

(b) (4)

The site management promised corrective actions.

OSIS Evaluation: The findings are not objectionable, and no supporting evidence was provided to support the findings in discussion item #5.

- a. The ORA Investigators acknowledged in the EIR that they did not find any concerns related to the study due to the

(b) (4)

of Study EPI 10.

- b. The ORA Investigators did not find evidence of any impact on sample processing due to the

(b) (4)

(b) (4)

- c. The ORA investigators acknowledged in the EIR that

(b) (4)

(b) (4)

did not appear to have any impact because all IPs were stored in the temperature-controlled storage equipment according to their respective storage requirements and did not have any temperature excursions.

The above indicated facility and equipment related issues did not appear to have impact on subject dosing, sample processing and integrity of the IPs. Therefore, these findings are unlikely to impact study data reliability.

Discussion Item #6: The study records were kept in the

(b) (4)

(b) (4)

The investigators noticed that the office door was left open on first two days of the inspection when no authorized personnel was in the room. We acknowledge that we did not observe any personnel or patients enter the

(b) (4)

Site's Response: The CI and the site's management acknowledged the finding and promised corrective actions.

OSIS Evaluation: No supporting evidence was provided for the observation in discussion item #6. The ORA investigators acknowledge that they did not observe any unauthorized personnel or patients accessing the room during the inspection. There is no evidence showing that the integrity of the study records was compromised. Therefore, this finding is unlikely to impact study data reliability.

Clinical Site #2: University of South Florida (Study Site #03)

Asthma, Allergy & Immunology Clinical Research Unit

13801 Bruce B. Downs Blvd., Suite 505
Tampa, FL 33613

Clinical Investigator: Richard F. Lockey, M.D.

Scope of Inspection

ORA Investigator Héctor J. Colón Torres audited the clinical portion of **Study EPI 10** at University of South Florida, Tampa, FL from April 3 to 6, 2023.

This was the first FDA BIMO BA/BE inspection of the clinical site. The current inspection included a review of the following items: IRB approvals, monitoring reports, responsibilities and delegation logs, subject records including CRFs, informed consent process, protocol adherence and deviations, inclusion/exclusion criteria, concomitant medications, study drug administration and accountability, and adverse events reporting.

Inspectional Findings

At the conclusion of the inspection, Investigator Colón did not observe any objectionable findings. Form FDA 483 was not issued and no verbal items were discussed with the clinical site's management.

Please note that as mentioned above, a single-parent signature on the ICF was obtained for 2 out of 28 subjects enrolled at University of South Florida, Tampa. These were reported as protocol deviations in Table 14 of the CSR. No exhibits were collected for this deviation during the inspection.

Yiyue Zhang, Ph.D.
Senior Staff Fellow

ATTACHMENTS:

Attachment 1. Form FDA 483 issued to IAA

Attachment 2. IAA's written response to Form FDA 483

Attachment 3. IAA's Note-to-File dated Jun 24, 2022

FEI Numbers:

- Institute for Asthma and Allergy, P.C.: 3024213423 (Site) and 3012725427 (CI)
- University of South Florida: 3005568382 (Site) and 1031534 (CI)

Email cc:

OSIS/Kassim/Folian/Fenty-Stewart/Johnson/
OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Zhang
OSIS/DGDSI/Cho/Benson/Skelly/Au/Ou
ORA/OBIMO/ORA_BIMO_Inspection_POC@fda.hhs.gov/Chon/Facchin/Colón

Draft: YZ 05/09/2023, 05/12/2023, 05/15/2023, 05/18/2023,
05/22/2023, 05/23/2023

Edit: GB 05/11/2023, 05/12/2023, 05/15/2023, 05/17/2023,
05/18/2023, 05/22/2023; AD 05/17/2023, 05/18/2023,
05/19/2023, 05/22/2023, 05/23/2023; CB 5/23/2023

ECMS:

Cabinets/CDER OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/Institute for Asthma
and Allergy, P.C., Chevy Chase, MD, USA

Cabinets/CDER OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/University of South
Florida, Tampa, FL, USA

OSIS File#: BE 9615

eNSpect Assignment ID: 207028

eNSpect Op IDs:

- 233960 (Institute for Asthma and Allergy, P.C., Chevy Chase, MD)
- 233961 (University of South Florida, Tampa, FL)

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/s/

YIYUE ZHANG
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05/23/2023 08:53:03 PM

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)

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

Date of This Review:	May 15, 2023
Requesting Office or Division:	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Application Type and Number:	NDA 214697
Product Name, Dosage Form, and Strength:	Neffy (epinephrine) nasal spray, 2 mg
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	ARS Pharmaceuticals Inc.
FDA Received Date:	August 19, 2022, September 9, 2022, and October 11, 2022
TTT ID #:	2022-1022
DMEPA 1 Safety Evaluator:	Lissa C. Owens, PharmD
DMEPA 1 Team Leader:	Idalia E. Rychlik, PharmD

1 REASON FOR REVIEW

As part of the approval process for Neffy (epinephrine) nasal spray, the Division of Pulmonology, Allergy, and Critical Care (DPACC) requested that we review the proposed Neffy prescribing information (PI), container labels, and carton labeling for areas of vulnerability that may lead to medication errors.

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-N/A
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) and carton labeling 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 ARS Pharmaceuticals Inc..

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 RECOMMENDATIONS FOR DIVISION OF PULMONOLOGY, ALLERGY, AND CRITICAL CARE (DPACC)

Table 2. Identified Issues and Recommendations for Division of Pulmonology, Allergy, and Critical Care (DPACC)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Full Prescribing Information – Section 2 Dosage and Administration			
1.	The strength is presented with a trailing zero.	Trailing zeros or the absence of a leading zero] can lead to tenfold dosing errors when the decimal point goes unnoticed.	We recommend revising the strength to remove the trailing zero.

5 RECOMMENDATIONS FOR ARS PHARMACEUTICALS INC.

Table 3. Identified Issues and Recommendations for ARS Pharmaceuticals Inc. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Carton Labeling			
1.	The carton does not have a statement “dispense in this sealed carton”.	The lack of this statement may result in dispensing and administration errors. Dispensing the device without the carton circumvents the safety features of the carton labeling and may lead to medication errors and safety concerns.	We recommend adding the statement “Dispense in this sealed carton” on the principal display panel of the carton.
2.	The strength expression is not in a prominent location on the PDP.	As presented the strength may be overlooked.	We recommend relocating the product strength to a more prominent location on the PDP, directly below the product established name.
3.	The Recommended Dosage statement is missing from carton.	This is a requirement per 21 CFR 201.55 that labels for prescription drugs bear a statement of the recommended dosage.	Add the recommended dosage statement: “Recommended Dosage: see Prescribing Information.” to

Table 3. Identified Issues and Recommendations for ARS Pharmaceuticals Inc. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
			the side panel in accordance with 21 CFR 201.55.
4.	Repetitive statement “(b) (4)”	There is potential for the user to overlook the word (b) (4) and use in this situation. It is stated prior to this (b) (4)	Delete the repetitive statement (b) (4) from the side panel.
5.	The route of administration on the PDP lacks clarity and prominence.	The route may be overlooked. and misunderstood.	Revise the route of administration statement on the PDP to read: “Use in the Nose only (Single-Use)” and increase the prominence of the statement.
6.	Nonrequired and the duplicate statement (b) (4) s located on the PDP.	This statement is already located on the side panel. Overcrowding the PDP and repetitive labeling statements draw the readers’ attention away from other more important product info.	Delete the repetitive statement (b) (4) on the PDP.
7.	On the top and side panel the strength is located between the proprietary name and the established name.	There should not be an interruption between the proprietary name and the established name.	You may: 1. Revise the strength presentation so that there is no interruption between the proprietary name and the established name. -or- 2. The name and strength may be deleted from the side and top panel as it displayed as required on the PDP.

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED
APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Neffy that ARS Pharmaceuticals Inc. submitted on August 19, 2022.

Initial Approval Date	N/A
Active Ingredient	epinephrine
Indication	Immediate and emergency first-line treatment of allergic reactions (Type I) including anaphylaxis in Adults and Children ≥ 30 kg (66 lbs.)
Route of Administration	Intranasal
Dosage Form	Nasal spray
Strength	2 mg
Dose and Frequency	(b) (4) If symptoms continue to progress after approximately (b) (4) minutes (b) (4) (b) (4) <i>neffy</i>, give a second dose using a new <i>neffy</i> device into one nostril
How Supplied	a carton containing two (2) blister packages each with a single spray device.
Storage	Store below 77°F (25°C). Excursions permitted up to 122°F (50°C). Do not freeze. <i>neffy</i> freezes below 5°F (-15°C). (b) (4)

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 data, we reviewed the following Neffy labels and labeling submitted by ARS Pharmaceuticals Inc..

- Container label(s) received on August 19, 2022
- Carton labeling received on August 19, 2022
- Instructions for Use received on August 19, 2022, available from <\\CDSESUB1\EVSPROD\nda214697\0001\m1\us\draft-labeling-text-ifu.pdf>
- Prescribing Information (Image not shown) received on August 19, 2022, available from <\\CDSESUB1\EVSPROD\nda214697\0001\m1\us\prescribing-information-neffy.pdf>

F.2 Label and Labeling Images

Container label(s)



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

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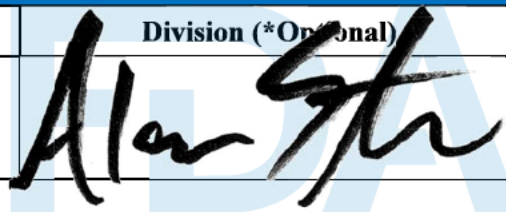
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DIVISION OF DRUG DELIVERY, GENERAL HOSPITAL & HUMAN FACTORS
INTERCENTER CONSULT MEMORANDUM

Date	5/9/2023		
To:	ANIKA LALMANSINGH (CDER- OPQ) and JI HYUN LAROSE (CDER- OND)		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From	Porsche Bennett OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA214697, Epinephrine nasal spray ICC2200794_ICC2200768 ICCR00868571 ICCR00870331		
Recommendation	Filing Recommendation Date: 9/20/2022 ☐ 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: 1/9/2023 ☒ 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: 4/14/2023 ☐ 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)
Porsche P. Bennett -S Digitally signed by Porsche P. Bennett -S Date: 2023.05.10 14:21:59 -04'00'		

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA214697
Sponsor	ARS PHARMACEUTICALS INC
Drug/Biologic	Epinephrine nasal spray
Indications for Use	Immediate and emergency treatment of allergic reactions (Type I), including anaphylaxis
Device Constituent	Nasal Spray
Related Files	IND139091

Review Team		
Lead Device Reviewer		
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
Biocompatibility	Papatya Kaner	CON233322

Important Dates	
Discipline-Specific Review Memos Due	04/07/23
Final Lead Device Review Memo Due	04/14/23
Interim Due Dates	Meeting/Due Date
Filing	09/21/2022
74-Day Letter	11/01/22
Mid-Cycle	01/09/2023
Primary Review	04/14/2023
Internal Meeting(s)	N/A
Sponsor Meeting(s)	N/A

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 <u>Notes</u>
	Yes	No	NA	
Device Description	X			
Labeling	X			
Design Controls	X			
Risk Analysis		X		Firm did not provide a fault tree analysis nor adequate risk management documentation
Design Verification		X		Firm provided inadequate design verifications and shelf life data
Reliability		X		Firm provided an inadequate reliability assessment and data
Consultant Discipline Reviews		X		Biocompatibility data for the (b) (4) device inadequate, referenced DMF does not include irritation testing
Clinical Validation	X			
Human Factors Validation			X	Deferred to DMEPA
Facilities & Quality Systems		X		Firm provided inadequate quality systems documentation

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:

Drug Product Comment #1: The firm did not test spray content uniformity post transportation simulation with rationale provided that the drug product is aqueous and spray content uniformity testing is also covered by delivered dose testing. CDRH defers the requirement of spray content uniformity testing to the CDER DP reviewer.

Clinical Comment #1: The firm appears to have included the 2mg combination product using the Aptar device in clinical PK studies; however, it does not appear that the (b) (4) device was used in clinical studies. The decision for validation of the device through clinical studies using the (b) (4) device constituent part is deferred to CDER.

Labeling Comment #1: It appears that the instructions for use, container label, and carton label do not have the intended users stated on the labels. For example, the patient information leaflet includes the intended users as adults and children 66lbs and greater. However, the other labeling does not include a weight minimum or age. CDRH defers the requirement for the labeling to include the intended users to CDER.

Labeling Comment 2: The labeling does not appear to include an Rx Only statement, the use period once the device is removed from the blister packaging, and instructions regarding shaking of the combination product in alignment with labeling recommendations per FDA's guidance, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, section V- labeling considerations, pages 37-45.

CDRH defers the requirement for the labeling to include the Rx statement, the use period once removed from packaging, and instructions regarding shaking of the device to CDER.

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:

CDRH is providing the following 'letter-ready' Major Deficiencies written so they can be directly communicated to the Sponsor:

Device Major Deficiencies:

Device CR Deficiency 1: In your submission you included 1mg Aptar device pilot study data, 1mg Aptar definitive reliability study data, 1mg Aptar shipping study data, 2mg Aptar aging reliability study data, 2mg (b) (4) shipping reliability study data, and 2mg Aptar stability data; however, it does not appear any of the data provided includes device performance testing of essential performance requirements post transportation simulation of the Aptar device. As a result, FDA sent device comment 4 dated 04/18/23. Your response does not specifically address submission of performance testing post shipping of the Aptar device nor rationale for how leveraged data of the 1mg Aptar device performance or 2mg (b) (4) device performance data are applicable. Therefore, safety and efficacy of the proposed combination product using the Aptar device constituent part remains unclear. Given your device is proposed for emergency use, testing should be provided to ensure the device performs according to specification post preconditioning. Provide device performance testing of essential performance requirements post transportation simulation of the Aptar device.

Device CR Deficiency 2: You indicate that your firm intends to utilize the nasal actuator and container holder components manufactured by (b) (4) and therefore you have referenced Device Master File (DMF) (b) (4) however, the referenced DMF did not include biocompatibility test reports. In response to the biocompatibility information request sent to your firm April 20, 2023, you provided the summary biocompatibility reports for the (b) (4) device, and you also indicated that the full biocompatibility reports were subsequently included in DMF (b) (4). However, the provided biocompatibility reports did not include irritation testing. As your device is intended to be a mucosal membrane contacting nasal spray, per FDA's Guidance "Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" (<https://www.fda.gov/media/85865/download>) irritation testing should be conducted given the contact type and duration. Irritation testing is needed to determine the safety of the proposed combination product. Therefore, provide an irritation test report for the (b) (4) device.

CR Deficiency 3:

In your submission you included reliability testing of the proposed combination product using the Aptar and (b) (4) devices; however, you did not include a fault tree analysis (FTA), design or process risk analysis, nor a trace matrix in your submission and therefore, we are unable to trace how design and process risks were adequately mitigated by controls and thereby determine if the proposed combination product is able to meet the reliability target for emergency use devices of 99.999% with (b) (4). Based on ISO 14971:2019, *Application of risk management to medical devices*, FDA believes the detection of failure to successfully inject in 1/100,000 injection attempts is an appropriate risk management target for ensuring successful injection and treatment when there is only one opportunity to inject. Therefore, provide the following:

- a. Provide a fault tree analysis with a top-level failure mode of "failure to successfully deliver complete intended dose" as the primary endpoint, followed by a second level that consist of all essential performance requirements

(EPRs), and subsequent levels that consist of events that can occur independently or dependently, stemming from basic events. For an example of how to structure a fault tree analysis, refer to the example flow diagram included in FDA's guidance titled "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" (<https://www.fda.gov/media/137158/download>).

- b. Provide a risk analysis associated with the final finished combination product that is inclusive of risks associated with the device constituent parts of the combination product. Your risk analysis should include all identified risks, potential hazards that are apparent to your device, risk control measures and/or mitigation strategies, verification of risk control and/or mitigation measures, and the clinical acceptability of any residual risk associated with the device. Outline the methods in which you identified the risks of the product within your risk analysis documentation (e.g., DFMEA, UFMEA, Fault Tree Analysis).
- c. Provide a trace matrix that shows traceability between design requirements, risk control measures and verification and validation activities

CR Deficiency 4: In your submission you included document "control-critical-steps" that list in-process controls for each stage of manufacturing of the combination product; however, you do not appear to detail in your submission in-coming inspection activities and testing conducted for lot release for FDA to determine the complete control strategy for the proposed combination product. FDA needs to ensure reliability specifications will be maintained for all essential performance requirements as they can impact the overall reliability of the combination product. Detail the control strategy for the proposed combination product, discussing in-coming inspection, in-process controls, and lot release testing.

Device Minor Deficiencies:

Device Minor Deficiency 1: FDA sent device information requests 3 and information request 4 dated 04/18/23. In response to the information requests you stated, "Samples of neffy 2 mg vials in the Aptar device and the (b) (4) device components stored approximately 24 months at room temperature will be tested for spray pattern and the data will be provided in a subsequent submission to the NDA within 3 weeks of this response" and "further, ARS will perform additional testing of neffy 2 mg vials in both the Aptar and (b) (4) device components stored approximately 24 months at room temperature for each performance characteristic including spray pattern and plume geometry which is a characterization test not typically tested routinely for nasal sprays. These data will be provided in a subsequent submission to the NDA within 3 weeks of this response." As the data has not yet been provided, FDA does not have sufficient information to determine adequacy of spray pattern and plume geometry testing for the Aptar and (b) (4) devices at this time. Provide spray pattern and plume geometry data for the Aptar and (b) (4) devices.

Device Minor Deficiency 2: In your submission for the proposed combination product, you have not provided information on your cGMP compliance approach. Your marketing application should contain a complete summary of your base operating system as described in the FDA guidance titled Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products issued in January 2017 (<https://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM429304.pdf>). Provide detail of your cGMP approach.

Device Minor Deficiency 3: You have not provided a summary of your Corrective and Preventive Action (CAPA) procedure in accordance to 21CFR820.100. CAPA procedures are used to determine the cause of problems and non-conformances, and the appropriate measures used to correct and prevent such problems and non-conformances from recurring. Summarize the procedure(s) for your CAPA System and ensure the following elements are included:

- a. Identification of sources of quality data and analysis of these data to identify existing and potential causes of nonconforming practices and products;
- b. Procedures should include requirements to analyze processes, work operations, concessions, quality audit reports, quality records, service records, complaints, returned product, and other sources of quality data to identify existing and potential causes of nonconforming product, or other quality problems;
- c. Procedures should include review and disposition process of nonconforming product, including documentation of disposition. Documentation shall include the justification for use of nonconforming product and the signature of the individual(s) authorizing the use;
- d. Describes requirements for implementing and recording changes in methods and procedures needed to correct and prevent identified quality problems;
- e. Ensures that information related to quality problems or nonconforming product is disseminated to those directly responsible for assuring the quality of such product or the prevention of such problems;
- f. Investigation of nonconformities and their causes;
- g. Identification and implementation of actions needed to correct and prevent recurrence of nonconformities;
- h. Verification or validation of the corrective and preventive actions taken to ensure that such action is effective and does not adversely affect the finished device; and
- i. Requires all documentation of all CAPA activities.

2.3. Recommended Post-Market Commitments/Requirements

CDRH has Post-Market Commitments or Requirements	☐
CDRH does not have Post-Market Commitments or Requirements	☒

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3. PURPOSE/BACKGROUND

3.1. Scope

ARS PHARMACEUTICALS INC is requesting approval of Epinephrine nasal spray. The device constituent of the combination product is a Nasal Spray.

CDER/OPQ has requested the following [consult](#) for review of the device constituent of the combination product:

Facilities Review: Neffy® (epinephrine nasal spray) is an aqueous solution in a single use container. The solution is a (b) (4) that is filled into unit dose 400 µL Type I glass vials and closed with a (b) (4) (b) (4) rubber stopper and then assembled into a Unit Dose Sprayer (UDS) device. The device is a (b) (4) dispenser delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 100 µL per actuation. Neffy is indicated for the immediate and emergency treatment of allergic reactions (Type I), including anaphylaxis.

Please assign a CDRH reviewer to assess the device-related facilities. The CDER facility reviewer, Suzanne Hudak, has requested a due date of 2 weeks from the submission of this consult request. Please advise if that is feasible.

<https://force-dsc.lightning.force.com/lightning/r/Case/5003d000004qK84AAE/view>

Engineering Review: Requesting CDRH consult of the nasal device for neffy (epinephrine nasal spray) for NDA 214697. This is an original priority review with goal date: 2/17/2023. Advisory Committee is planned for 12/8/2022.
<https://force-dsc.lightning.force.com/lightning/r/Case/5003d000004hgpeAAA/view>

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 Performance and Shelf life
Device Biocompatibility
Device Reliability
Device Facilities Compliance

This review will not cover the following review areas:

Device Human Factors: Deferred to DMEPA
Device Sterility: Deferred to CDER
Drug Product: Deferred to CDER
Drug Substance: Deferred to CDER
Overall Labeling Adequacy: Deferred to CDER

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

- IND139091, ICC2100293, ICCR00071790: CDRH consulted for ARS-1 as it relates to (b) (4) as a comparator for the IND and an increase in concentration of the drug product from 1mg to 2mg.
- IND139091, ICC1900261, ICCR2019-04684: CDRH consulted for ARS-1

Sponsor Question communicated via email: *For planning purposes, we were hoping to get any feedback on the concept below of using (b) (4) in our clinical trial. Since we are comparing the new dose of ARS-1 (Neffy) to EpiPen and Symjepi*

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in the self-administration study (EPI 13) we were hoping to try and use (b) (4) and standard IM injection in the EPI 15 study. This is both to get another autoinjector that we know has lower injection force than EpiPen (highest injection force). So overall 4 injection product comparators to show ARS-1 exposures are within the range of injection products. The concern is that (b) (4) is not approved in the US and is an EU/Canadian approved product. Thus, we will not have detailed manufacturing or CMC data for this product.

FDA Response: Adequacy of pen functionality for a comparator such as the (b) (4) is conducted as part of the IND review. As you have stated the investigational combination product device is not 510k approved, you should ensure the combination product is safe prior to clinical use (e.g., biocompatibility) and ensure design inputs (e.g., essential performance requirements) are verified according to specification. Please refer to the additional comments for device content for IND applications.

Sponsor Question #8: *Other studies completed with the Neffy Aptar UDS device (e.g., Human Factors Validation, Reliability) are unaffected by the change in dose, given the device is identical, and thus should be suitable for submission without repeating these studies. Does the Agency have any other suggestions or requirements necessary for the (b) (4) (b) (4) of Neffy prior to filing the planned 505(b)(2) NDA?*

FDA Response: You stated that you intend to increase the (b) (4) of the drug product. Changes in the manufacturing process and (b) (4) can impact the device performance. After completing the initial reliability report, future design changes and manufacturing process changes may occur that necessitate re-evaluation of reliability to ensure emergency-use device reliability. To determine when the reliability data may need to be updated, the impact of the change should be evaluated based on the existing reliability model. You should consider if the change impacts the design output specifications of the emergency-use nasal spray or the basic events of the fault tree analysis. If it is determined that the change does impact these aspects, creates new design outputs, or creates new risks, then the emergency-use device reliability testing should be re-evaluated for all design inputs that may potentially be impacted (e.g., essential performance requirements) and included within your premarket submission. Such potential changes in performance should be reevaluated as reliability verification testing should be conducted on the final finished combination product after considering the appropriate preconditioning and use conditions over shelf life. In summary, your firm should consider the following approach:

1. Define all changes in the drug product and process
2. Determine changes in risks impacted by the change(s) in drug product and the manufacturing process
3. Determine how reliability testing is impacted by the change in design input, process, risk, or specification
4. Re-evaluate any performance impacted by the change

The sponsor provided a summary of FDA interactions with the firm (located in module 1.2., note to reviewer) which are as follows:

- **12 February 2019:** The United States (US) Food and Drug Administration (FDA) completed its review of IND 139091 and declared the study may proceed.
- **13 February 2019:** The US FDA agreed that the study met the criteria for its “fast track designation”
- **22 May 2019:** ARS requested a Type C Written Response Only meeting between Division of Pulmonary, Allergy, and Rheumatology Products and the Sponsor to obtain written Agency feedback on the results of the recently completed clinical study investigating the pharmacokinetics of ARS-1 in patients with allergic rhinitis (Protocol EPI 04).
- **20 June 2019:** ARS provided The purpose of the submission is to provide meeting background materials for WRO meeting requested by Sponsor (SN 0013, 22 May 2019) and granted by Division (3 June 2019). The

purpose of the meeting is to receive feedback on the results of the recently completed clinical study investigating the pharmacokinetics of ARS-1 in patients with allergic rhinitis (Protocol EPI 04). The submission contained:

- Section 1.6.2 Meeting Background Material
- Section 2.5 Updated Clinical Overview
- Section 2.7.1 Updated Summary of Biopharmaceutic Studies
- Section 2.7.4 Updated Summary of Clinical Safety
- Draft Pharmacokinetic Report for Clinical Study Protocol EPI 04
- **30 July 2019:** ARS requested a designation of Breakthrough Therapy for ARS-1 for the treatment of anaphylaxis.
- **29 August 2019:** ARS requested a Face-to-Face Type B Pre-NDA meeting between the Division of Pulmonary, Allergy, and Rheumatology Products and the Sponsor to:
 - Obtain Agency input on the completed clinical studies with 1 mg ARS-1 and analyses conducted; and
 - Confirm that the data available for the 1 mg ARS-1 dose is adequate for filing an NDA for the emergency treatment of allergic reactions (Type 1) including anaphylaxis based on the RLD epinephrine IM injection (needle and syringe)
- **30 September 2019:** Pre-NDA Meeting Package submitted. The purpose of this submission was to provide the Pre-NDA Meeting Package to support filing of an NDA for ARS-1. The meeting package included:
 - Section 1.6.2 Meeting Background Material
 - Section 2.5 Updated Clinical Overview
 - Section 2.7.1 Updated Summary of Biopharmaceutic Studies
 - Section 2.7.2 Updated Summary of Clinical Pharmacology
 - Section 2.7.4 Updated Summary of Clinical Safety
 - Section 3.2.P.5.1 Updated Release and Shelf-life Specifications
 - Section 3.2.P.8.1-Stability Summary and Conclusion
 - Section 3.2.P.8.3-Updated Stability Data (including 2 months on registration lots)
- **08 October 2019:** The initial Pediatric Study Plan (iPSP) for ARS-1 was provided to the FDA
- **09 January 2020:** FDA informed ARS that **neffy** was accepted as the conditional proprietary name

Based on FDA feedback the sponsor conducted the following:

ARS has considered all advice of the FDA and believes that the current NDA complies with all advice of the Agency.

- **neffy** was evaluated in a series of PK and PD studies with both a 1 mg and 2 mg dose to assess the following:
 - Single dose administration versus injection products
 - Repeat dose (twice) administration versus injection products
 - Effects of worse case nasal dosing situations that include Rhinitis and sitting position
 - Self-administration studies
 - Pediatric studies in children aged 4 to 17, with body weight 15 to <30 kg and 30 kg or greater.
- Primary **neffy** 2 mg studies meet FDA requested criteria

- EPI 15 single dose demonstrated that *neffy* 2 mg is bracketed by IM injection needle and syringe on the lower end of exposures and EpiPen at the upper end of exposures.
- EPI 15 repeat dose administration demonstrated that *neffy* was dose proportional and there was no significant difference in dosing once in each nostril and twice in one nostril. EpiPen was not dose proportional as seen in previous studies with IM injection and EpiPen.
- EPI 16 single dose comparison to 0.3 mg and 0.5 mg IM injection demonstrated similar pharmacokinetics as EPI 15, with overall AUC_{0-t} for *neffy* being within the bracket of 0.3 mg and 0.5 mg IM. The effect of rhinitis was a more rapid absorption but lower maximum exposure compared to normal state, however, the exposure from *neffy* 2 mg was still greater than 0.3 mg IM injection with rhinitis.
- EPI 17 demonstrated that in a ‘real-world’ study that *neffy* 2 mg gave similar exposures to that observed in EPI 15 and EPI 16, with no critical dosing errors and absorption was significantly faster and greater than 0.3 mg IM injection (thus, well bracketed by IM and EpiPen)
- EPI 10 data is provided with an interim analysis on 57 pediatric Type 1 allergy patients dose, including 16 with *neffy* 2 mg and 26 with *neffy* 1 mg doses at the 30 kg or greater body weight. These data support that *neffy* 2 mg gives adequate exposures that are slightly higher than adults in pediatric patients 30 kg or greater body weight.
- A POP PK and Pharmacologically Based Absorption Model (PBAM) was developed and support that *neffy* 2 mg provides adequate exposures in adults and pediatric patients under a variety of conditions.
- Nonclinical studies were executed as agreed with FDA. Several additional studies were also conducted:
 - Ocular tolerability in the rabbit (to ensure no ocular toxicity if accidental exposure)
 - Pilot study in an anaphylaxis dog model.
 - GLP definitive PK study in an anaphylaxis dog model to demonstrate absorption during an anaphylactic reaction with significant hypotension and edema.
- Chemistry, Manufacturing and Control requirements and evaluations were conducted per FDA advice, including three reliability studies for the *neffy* 1 mg concentration and the *neffy* 2 mg concentration with both the Aptar and (b) (4) sourced unit dose sprayer devices (identical devices from two manufacturers).

3.2.1. Related Files

The firm has referenced the following submissions: IND 139091; (b) (4)
(b) (4), and NDA 204200

NDA024200 RLD- Adrenalin (epinephrine injection)

3.3. Indications for Use

Combination Product	Indications for Use
Epinephrine nasal spray	Immediate and emergency treatment of allergic reactions (Type I), including anaphylaxis
Nasal Spray	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed

Sequence	Module(s)
0001	1.1.2 Form FDA 356h
0001	1.2 Cover Letter (note to reviewer)
0001	1.6.3 Correspondence Regarding Meetings
0001	1.4 References
0001	1.14 Labeling
0029	1.11.1 Quality Information Amendment (IR 1 response)
0036	1.11.1 Quality Information Amendment (IRs 2-6 response)
0001	2.3.P Drug Product
0008	2.3.P Drug Product
0001	3.2.P Drug Product
0008	3.2.P Drug Product
0001	5 Clinical Study Reports

4. DEVICE DESCRIPTION

4.1. Device Description

The Neffy development program was initially focused on a 1 mg strength formulation. Subsequently, based on clinical studies, it was determined that a 2 mg strength was optimal for adults and adolescents greater than 30 kg. The combination product is intended to be indicated for patients 4 years and older.

The drug substance is a white to almost white crystalline powder. (Module 2.3.S.7. Stability. Table 2, page 2/3). The drug product is an aqueous solution that is (b) (4) filled into a unit dose 400uL type (b) glass vials and close with a (b) (4) rubber stopper and then assembled into a unit dose sprayer (UDS) (b) (4). The device is a (b) (4) dispenser delivering a spray containing a unit dose of the active ingredient. Each delivered dose contains 100 µL per actuation. After a single actuation, the unit dose system is then considered depleted and discarded. Each UDS consists of an actuator which consist of spray pin, and cannula and a container holder. After assembly, the UDS device is secondary packaged into individual single use blisters composed of (b) (4) (b) (4) and peel open blister lidding. There is a 125 µL overfill. (Module 2.3.P.1).

Anticipated mean peak plasma levels (Cmax) after administration of intranasal *neffy* 2 mg are between approximately 421 pg/mL (self-administration) and 485 pg/mL (HCP-caregiver administration) from primary ARS studies in adults. Pediatric exposures are approximately 540 pg/mL (Cmax) based on data from EPI 10 in children 30 kg or greater.

The container closure system for Neffy® (epinephrine nasal spray) consists of Type (b) (4) glass (b) (4) vials (0.4 mL) supplied by (b) (4) and sealed using a (b) (4) rubber plunger supplied by Aptar Pharma, France. ARS utilizes two suppliers for the unit dose device for Neffy. First, the Aptar device which has been commercially available and used for close to 20 years in other approved products on the US APPEARS THIS WAY ON ORIGINAL market, such as Imitrex (sumatriptan nasal spray), Narcan (naloxone hydrochloride) Nasal Spray, and Valtoco (diazepam nasal spray). Narcan and Valtoco are also similar to Neffy as they are formulations intended for emergency treatment of a life-threatening condition. Second, the (b) (4) device which has been developed specifically as a (b) (4) (b) (4)

The proposed shelf life is 24 months.

The neffy 1 mg formulation is the same as the neffy 2 mg formulation (b) (4) (b) (4)

(b) (4)

4.2. Steps for Using the Device

- Remove the device from (b) (4) packaging
 - (b) (4) thumb on the bottom of the plunger and (b) (4)
 - (b) (4) insert the (b) (4) nozzle into one of the nostrils until (b) (4) fingers touch the nose
 - (b) (4) push the plunger up firmly until it snaps up and sprays into the nostril
 - Dispose of the device (b) (4)
- 1.14.1.1, Draft labeling text- Instructions For Use (Sequence 0012)

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> • Component drawings and specification: The sponsor referenced DMFs from suppliers of the nasal spray device; however, some of the information/DMFs cannot be located within docubridge. Refer to IR1 below, the firm's response is determined to be adequate. • Use of multiple device suppliers for the actuator and vial holder: The firm is intending to obtain approval using two suppliers for the vial holder and spray pump components (i.e., spray pump device). The firm must ensure adequate data and information is provided to support approval of two		

suppliers. The firm must also ensure the devices will be manufactured to the same specifications. Refer to Design verification and reliability section below for determination of adequacy in DV testing and ensuring C/R of (b) (4)/99.999 (b) (4) using both devices.

CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No

	Date Sent: 3/16/2023	Date/Sequence Received: 3/22/2023
Information Request #1		
Sponsor Response		
Reviewer Comments	The firm identified where the specific drawings were located in both the referenced DMFs for the vial and closure components. The firm also included FDA acknowledgement letter for (b) (4)	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

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 (2.3.P.1 basic description of device and packaging)		X		
Device Constituent Labeling (draft carton, device, and instructions for use labeling) 1.14.1		X		
Letters of Authorization (1.4.2 Statement of right to reference): DMFs (b) (4) (1.4.4 Cross reference) to NDA204200 (Adrenalin epinephrine injection)		X		
Essential Performance Requirements defined by the application Sponsor		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.		X		
Risk Analysis supplied in the NDA / BLA by the application Sponsor (Refer to CR deficiency)			X	
Traceability between Design Requirements, Risk Control Measures and V&V Activities (Refer to CR deficiency)			X	
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing	X		
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps) (Refer to IRX)	X		
	Reliability (Refer to IRX)	X		
	Biocompatibility (Refer to IR)		X	
	Sterility			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors			X
	Shelf Life, Aging and Transportation X - Shelf life/aging: Protocol 2.3.P.8- Stability, Data 3.2.P.8.3) - Transportation:	X		
	Clinical Validation	X		
	Human Factors Validation			X
Quality Systems/ Manufacturing Controls Check	Description of Device Manufacturing Process	X		
	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both) - (Refer to CR deficiency)		X	
	CAPA Procedure (Refer to CR deficiency)		X	
	Control Strategy provided for EPRs Incoming: 2.3.P.2 Pharmaceutical-dev, section 4, table 64: Incoming actuator component performance testing, pg 76).	X		

Reviewer Comment

The firm appears to have provided sufficient information to accept the submission.

5.2. Facilities Information

The neffy (epinephrine nasal spray) drug product is manufactured, assembled, tested, labeled, and packaged in accordance with cGMP by (b) (4)

Components of the unit dose sprayer are provided by Aptar Pharma (Le Vaudreuil, France) or (b) (4) (b) (4) (Module 2.2 Introduction, section 6, page 36/43)

Firm Name:	(b) (4)
Address:	
FEI:	
Responsibilities:	Manufacturing, Device Assembly, Release and Stability Testing, Packaging and Labeling
<u>Inspectional History</u> An analysis of the firm's inspection history: ☒ Inspection was conducted (b) (4) The inspection covered drug CGMP and was classified VAI. ☐ An analysis of the firm's inspection history over the past 3 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	
<u>Inspection Recommendation:</u> ☐ 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 Choose an item. ☒ An inspection is not required because A recent medical device inspection of the firm was acceptable. A summary of the inspection conducted (b) (4) is as follows:	

(b) (4)

Reviewer Comment

- In from 356h included in the firm's submission, the FEI for the manufacturing site that conducts device assembly, packaging, and labeling activities is stated to be (b) (4) which does not appear in OSAR. However, the facilities lead from CDER confirmed that appears to be a typo and the FEI is (b) (4)
- A memo was provided to the RPM stating a facilities inspection is not recommended at this time.

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.	
Reviewer Comment	
A full ICCR review is needed as the combination product is indicated for emergency use.	

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:	
<u>Reviewer Comments</u> The submission appears to be fileable as gross information appears to be present in the submission to support review. Information requests will be issued as needed for data/information needed to determine approvability.	
<u>Refuse to File Deficiencies:</u> ☐ Yes ☒ No ☐ N/A	
<u>74-Day Letter Deficiencies:</u> ☐ Yes ☒ No ☐ N/A	

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-Only patient information leaflet includes intended users	

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- 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

Front of nasal spray device and blister pack labeling

(b) (4)

*As a 505(b)(2) NDA application, the labeling for **neffy** 2 mg closely mirrors the Reference Listed Product (RLD), NDA 204200 for Adrenaline (epinephrine) Injection. There are several key labeling changes that are justified based on ARS clinical trials, EpiPen labeling and Literature. While most changes are obvious and*

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referenced to source data or references in the annotated labeling, the following changes are more fully explained.

- Removal of (b) (4)
(b) (4)
- (b) (4)
(b) (4) based on actual dosing studies EPI 12 and EPI 17 (“real world studies”) in allergy patient who self-administer, as well as other experiences during development, it was noted that crossing over from the dominant hand side to the opposite side of the nose was more prone possible dosing errors and made it more difficult for people to keep the sprayer straight into the nose. Given EPI 15 demonstrated that the difference in PK and PD outcomes was minimal (<10% difference in maximum exposures) between dosing twice in one nostril versus two times with once in each nostril, it was decided to simplify the labeling (b) (4) Thus, to avoid dosing errors or confusion, subjects and caregivers are simply told to administer a second dose and it is their choice to dose in the same nostril which appears easier and less prone to errors given the typical dominant hand that would dose **neffy**.
- (b) (4) Recent literature (Casale-2022) and ARS studies demonstrate that recommending that patients get emergency help or go to an emergency room after administration of epinephrine is counterproductive and a major deterrent to patients or caregivers (b) (4) The effectiveness of epinephrine is nearly 100% when dosed within the first 10 minutes after a reaction initiates and literature supports that over 90% of events are resolved with a single dose and it is very rare that a second dose does not resolve the events. The need for a second dose or repeat dosing is not effective is most often associated with delayed treatment. (b) (4)
(b) (4)
- (b) (4)
(b) (4) Patients and caregivers would be educated to contact their physician to get further input on any other actions needed. This is consistent with current medical practice and what allergist are instructing patients on today.
- ARS also will implement educational programs to help instruct patients that if symptoms resolve after a first administration of epinephrine that it is not necessary to go to the emergency room and to instead ‘get medical advice’. If a second dose is needed or symptoms reoccur than it is more appropriate to seek emergency medical assistance. Given only two doses are typically carried and labeling recommends that only a medical professional give more than two doses of epinephrine, this approach is appropriate. (Module 1.2. Note to Reviewer)

Reviewer Comments

Only the PI leaflet includes the patient population (users' minimum weight). Refer to note to CDER.

- **Note to CDER:** It appears that the instructions for use, container label, and carton label do not have the intended users stated on the labels. For example, the patient information leaflet includes the intended users as adults and children 66lbs and greater. However, the other labeling does not include a weight minimum or age.

6.2. Device Specific Labeling Review

Device Specific Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation (Section V- Labeling considerations, pg. 37/45)			
Instructions for Use Label, Blister Label, and PI Label:			
• Product Title	X		
• Established name of the drug product	X		
• Amounts of the drug substance delivered from the pump nasal actuator or mouthpiece (Included in Patient Information Leaflet, not instructions for use or blister label)	X		
Number of medication sprays per container	X		
Net content (fill) weight (Included on blister label, not Instructions for use)	X		
Usual dosage	X		
Excipients (established names)	X		
Route of administration (yes, included in all labeling)	X		
Recommended storage conditions including any warning statements regarding temperature or light exposure	X		
Manufacturer's and/or distributor's name and address	X		
"Rx Only" or "• Only" statement (No, does not appear in any of the labeling)		X	
Lot number (yes, included on blister packaging)	X		
Expiration date (yes, included on blister packaging)	X		
Use period once drug product is removed from protective packaging (if applicable) (No, does not appear in any of the labeling)		X	
Instructions regarding shaking of suspension drug products		X	
Description section of the package insert (yes, as applicable)	X		
How supplied section of the package insert (yes, as applicable)	X		
Patient package insert (yes, as applicable (e.g., priming is not applicable)	X		

Reviewer Comments

The labeling does not include some of the device specific labeling requirements per FDA's nasal spray guidance. Refer to note to CDER

- **Note to CDER:** The labeling does not appear to include a Rx Only statement, the use period once the device is removed from the blister packaging, and instructions regarding shaking of the combination product in alignment with labeling recommendations per FDA's guidance, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, section V- labeling considerations, pages 37-45.

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](#):

The labeling appears to align with that of the other epinephrine combination products. However, the packing label, device label, and instructions for use does not state the intended user and appears to exclude statements that should be included per the nasal spray guidance. Therefore, a note will be provided to CDER. Note: adequacy of labeling is deferred to CDER.

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 <u>Comment to CDER:</u> It appears that the instructions for use, container label, and carton label do not have the intended users stated on the labels. For example, the patient information leaflet includes the intended users as adults and children 66lbs and greater. However, the other labeling does not include a weight minimum or age. Additionally, the labeling does not appear to include a Rx Only statement, the use period once the device is removed from the blister packaging, and instructions regarding shaking of the combination product in alignment with labeling recommendations per FDA's guidance, Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation, section V- labeling considerations, pages 37-45.		
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		
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	

Reviewer Comments

The firm either included design control documentation that is inadequate or did not provide the documentation in their submission for review. All inadequate or missing documentation has been included as a CR deficiency.

7.2. Design Inputs and Outputs

(b) (4)



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
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)	
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)	NA
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	Y
Applying Human Factors and Usability Engineering to Medical Devices	Y

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
Nasal Spray and Inhalation Solution, Suspension, and Spray Drug Products — Chemistry, Manufacturing, and Controls Documentation	Y	Y
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		
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 firm did not provide adequate risk management documentation. Refer to CR deficiency.
--

8.2. Hazard Analysis and Risk Summary Report

[Link to Infusion Pump SAC Reviewer Guide](#)

Reviewer Comments The firm did not provide adequate risk management documentation. Refer to CR deficiency.
--

8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☒ Yes ☐ No ☐ N/A
Reviewer Comments		
The firm did not provide an FTA or adequate risk documentation. Refer to CR deficiency.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

9. DESIGN VERIFICATION REVIEW

9.1. Performance/Engineering Verification

9.1.1. Essential Performance Requirement Evaluation

Essential Performance Requirement (Design Input)	Specification (Design Output)	Verification Method <u>Acceptable</u> (Y/N)	<u>Validation</u> (Y/N)	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)
Uniformity of Dosage Units (Spray Content Uniformity)	Meets requirements of Tier I / II. Per FDA's nasal spray guidance: For acceptance of a batch (1) the amount of active ingredient per determination is not outside of 80 to 120 percent of label claim for more than 2 of 20 determinations (10 from beginning and 10 from end) from 10 containers, (2) none of the determinations is outside of 75 to 125 percent of the label claim, and (3) the mean for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim. If the above acceptance criteria are not met because 3 to 6 of the 20 determinations are outside of 80 to 120 percent of the label claim, but none are outside of 75 to 125 percent of label claim and the means for each of the beginning and end determinations are not	Y	Y	Y-Both devices	N-Aptar device (no data provided) Y- (b) (4) device

	outside of 85 to 115 percent of label claim, an additional 20 containers should be sampled for second-tier testing. For the second tier of testing of a batch, the acceptance criteria are met if (1) the amount of active ingredient per determination is not APPEARS THIS WAY ON ORIGINAL outside of 80 to 120 percent of the label claim for more than 6 of all 60 determinations, (2) none of the 60 determinations is outside of 75 to 125 percent of label claim, and (3) the means for each of the beginning and end determinations are not outside of 85 to 115 percent of label claim.	APPEARS THIS WAY ON ORIGINAL			
Droplet Size Distribution of Spray	^(b) ₍₄₎ cm: D90: < ^(b) ₍₄₎ μm D50: ^(b) ₍₄₎ μm D10: ^(b) ₍₄₎ μm Span: ^(b) ₍₄₎ % < ^(b) ₍₄₎ μm: NMT ^(b) ₍₄₎ % (report mean values)	Y	Y	Y-Both devices	N-Aptar device (no data provided) Y- ^(b) ₍₄₎ device
	^(b) ₍₄₎ cm: D90: < ^(b) ₍₄₎ μm D50: ^(b) ₍₄₎ μm D10: ^(b) ₍₄₎ μm Span: ^(b) ₍₄₎ % < ^(b) ₍₄₎ μm: NMT ^(b) ₍₄₎ % (report mean values)	Y	Y	Y-Both devices	N-Aptar device (no data provided) Y- ^(b) ₍₄₎ device

Pump Delivery	Tier I (10 Actuations): NMT (b) (4) Dose/Shot weight (mg) value may be outside of (b) (4) mg – (b) (4) mg. No Dose/Shot weight (mg) values may be outside of (b) (4) mg – (b) (4) mg. The mean Dose/Shot weight (mg) value must be within (b) (4) mg – (b) (4) mg.	Y	Y	Y-Both devices	N-Aptar device (no data provided) Y- (b) (4) device
	Tier II (10 + 20 Actuations): NMT (b) (4) Dose/Shot weight (mg) values may be outside (b) (4) mg – (b) (4) mg. No Dose/Shot weight (mg) values may be outside (b) (4) mg – (b) (4) mg. The mean Dose/Shot weight (mg) value is not outside (b) (4) mg – (b) (4) mg.	Y	Y	Y-Both devices	N-Aptar device (no data provided) Y- (b) (4) device
Spray Pattern	(b) (4) cm: Dmax (mm): (b) (4) Ovality: (b) (4) (report mean values)	Y	Y	Y-Both devices	N-Aptar device (no data provided) Y- (b) (4) device
	(b) (4) cm: Dmax (mm): (b) (4) Ovality: (b) (4) (report mean values)	Y	Y	Y-Both devices	N-Aptar device (no data provided) Y- (b) (4) device
Actuation Force	(b) (4) N	Y	Y	Y-Both devices	N-Aptar device (no data provided) Y- (b) (4) device

Stability data for Neffy, 2 mg up to 12 months at long term storage conditions (25°C/60% RH) and up to 6 months at the accelerated storage conditions (40°C/75% RH) are provided on the three registration batches (b) (4)
(b) (4) Additionally,

registration stability batches were assessed at 50°C storage condition for up to 3 months to demonstrate stability at extreme temperature excursions (for example accidentally leaving Neffy in a hot car). (2.3.P.8 Stability)

All batches were stored in the inverted orientation which is considered the worst-case storage orientation for the product from a stability perspective.

Table 3: Stability Protocol for Registration Batches (Inverted)

Storage Condition	Interval (Months)									
	T0	1	2	3	6	9	12	18	24	36
25°C / 60%RH	X	X	X	X	X	X	X	X	X	X
40°C / 75%RH		X	X	X	X					
50°C		X	X	X						

X = Appearance, Appearance of Container, Color of Solution, pH, Epinephrine Assay, Related Substances, D-epinephrine (enantiomeric purity), DDM Assay, BZK Assay, EDTA Assay, Delivered Dose, Pump Delivery, Droplet Size Distribution, Actuation Force (Bridge Breaking), Microbial Limits Testing

2.3.P.8, page 6/15, Table 3: Stability Protocol for Registration Batches (Inverted)

In relation to the accelerated and long-term stability studies defined in this NDA, ARS commits to:

1. Conduct and complete the stability studies for Neffy as defined in this NDA.
2. Submit updated stability study results to the NDA at least annually in the format specified by the FDA.
3. Withdraw from the market any batch of Neffy found to fall outside the approved specification. If ARS has evidence that the deviation is a single occurrence that does not affect the safety and efficacy of the dosage form, then ARS will immediately discuss the deviation with the appropriate chemistry team and provide justification for the continued distribution of that batch. The change or deterioration in the batch of Neffy will be reported under 21 CFR 314.81(b)(1)(ii).



Reviewer Comment

- (b) (4) which is common for epinephrine.
- Number of lots tested: 3 lots
- Representativeness of final finished combination product: Firm tested both the Aptar and (b) (4) device constituent parts. Adequacy of testing is discussed below.
- Adequate sample size: Sample sizes for testing was initially unclear. An information request dated 04/18/23 was sent to the firm. The firm's response was determined to be adequate.
- Shipping and stability testing: Refer to summary of data submitted below and the table in section 9.1.1.

Stability testing: Per FDA's nasal spray guidance, page 29, *The stability of nasal and inhalation drug products can be affected by storage under differing orientations. For example, leachable levels, pump appearance, weight loss, assay, particle size distribution, and SCU can be affected by orientation. Primary stability studies should include storage under different orientations (e.g., upright and inverted or upright and horizontal) to characterize any differences in the behavior under storage and to define optimum storage orientation, if any, also, For ANDAs, the long-term and intermediate intervals should be consistent with the ICH guidance, but intervals at 0, 1, 2, and 3 months can be used for accelerated testing. The stability test parameters, with appropriate acceptance criteria, should include those test parameters identified in the drug product specification (refer to section III.F) but can exclude the following: for nasal sprays, identity of the drug substance, spray pattern, osmolality, and net content.*

- The firm tested in the inverted position which is considered to be worst-case. The firm did not test all EPRs on stability such as spray content uniformity. Several discussions were held between CDRH and CDER to determine if "Delivered dose uniformity" and "dose delivered" testing were adequate to demonstrate the intended drug product percentage delivers from the device with a given level of confidence and reliability. Adequacy decision is deferred to CDER. Refer to note to CDER.

Test storage conditions: Per FDA's nasal spray guidance, page 29, *Stability studies should be performed on the drug product with the packaging configuration (i.e., primary, protective) for which approval is sought, using the appropriate test storage conditions. CDER's recommendations on appropriate test storage conditions can be found in the ICH guidance Q1AR Stability Testing of New Drug Substances and Products (November 2000). A summary of these recommendations is provided below.*

Usually, the test storage conditions in the stability protocol for a drug product intended for storage under controlled room temperature conditions should include (1) accelerated (40• 2.C/75• 5%RH), (2) intermediate (30• 2.C/60• 5%RH), if applicable, and (3) long-term (25• 2.C/60• 5%RH) conditions.

The firm tested the following storage condition which are in alignment with the guidance:

Description	Batch No.	DDM Concentration	Use	Storage Configuration	Storage Condition	Table Reference
Clinical and Registration Batch	210928	0.275% DDM	Registration, Clinical Studies EPI 010, EPI 013, EPI 014, EPI 015, EPI 016,	Inverted	25 ± 2 °C/60 ± 5% RH	Table 2
					40 ± 2 °C/75 ± 5% RH	Table 3
					50 ± 2 °C	Table 4
Registration Batch	210929	0.275% DDM	Registration	Inverted	25 ± 2 °C/60 ± 5% RH	Table 5
					40 ± 2 °C/75 ± 5% RH	Table 6
					50 ± 2 °C	Table 7
Registration Batch	210930	0.275% DDM	Registration	Inverted	25 ± 2 °C/60 ± 5% RH	Table 8
					40 ± 2 °C/75 ± 5% RH	Table 9
					50 ± 2 °C	Table 10

Summary of data submitted:

(b) (4)

Summary of approvability concerns and Next steps post CR hold:

- Testing on shipping simulated and aged devices should be conducted on both the (b) (4) and Aptar devices from T=0 to end of shelf life.
 - (b) (4) the firm should conduct testing on the to-be-marketed configuration of the proposed combination product.
 - Next steps for approvability decision of Aptar devices (testing conducted post aging only, not shipping):
 - Test spray content uniformity on aged samples. This can be leveraged from stability data if conducted on the Aptar device. – Completed during IR response dated 04/21/23. Firm confirmed stability testing was conducted on Aptar devices.
 - **Test the Aptar device post shipping for all EPRs including spray content uniformity. – Outstanding**
 - Provide the real time aging equivalent for the aged samples. (b) (4)
(b) (4)
 - **Provide the sample size for stability testing**
 - Next steps for approvability decision of (b) (4) devices (testing conducted post aging and shipping):
 - **Test spray content uniformity on shipped and aged samples. – Outstanding**
 - Provide the real time aging equivalent for the aged samples. (b) (4)
(b) (4)
 - Next steps for determining adequacy of stability data
 - Firm to provide the real time equivalent for accelerated aging- Completed in response to IR dated 04/21/23.
 - Firm to clarify which device was tested on stability, Aptar or (b) (4) device. – Completed during IR response dated 04/21/23. Firm confirmed stability testing was conducted on Aptar devices.
 - **Provide the sample size for stability testing**

Insert Additional Design Verification Table

9.2. 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		
CDRH sent Design Verification Deficiency or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 4/18/2023	Date/Sequence Received: 4/21/2023
Information Request #1	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	The firm clarified that all the data of question (b) (4) and dose delivered met specification but failed the desired confidence and reliability. The passing data in the reliability testing aligns with the passing results for devices tested on stability. The firm also stated none of the values for devices tested for dose delivered were outside of the (b) (4) % to (b) (4) % range.
Response Adequate:	☒ Yes ☐ No, See CR Device Deficiency # Sent on Click or tap to enter a date.

	Date Sent: 4/18/2023	Date/Sequence Received: 4/21/2023	(b) (4)
Information Request #2			
Sponsor Response			

Reviewer Comments	a. Adequacy of the firm's response is deferred to CDER. Refer to note to CDER 1. b. The firm's response is adequate. c. The firm's response is adequate. The samples were manufactured 10 months prior and had been exposed to accelerated stability conditions at 50°C for three months

	which is equivalent to 18 months real time. Therefore, testing provided for the 2mg Aptar reliability study equates to 28 months real time aging. d. The firm's response is adequate as they provided the sample sizes for all testing conducted for design verification. The sample sizes appear to be appropriate to support verification of design outputs to meet the design inputs.
Response Adequate:	☒ Yes ☐ No, See CR Device Deficiency # Sent on Click or tap to enter a date.

	Date Sent: 4/18/2023	Date/Sequence Received: 4/21/2023
Information Request #3	(b) (4)	
Sponsor Response		

	(b) (4)
Reviewer Comments	a. The firm clarified that the stability testing was conducted on the Aptar device. Additionally, in response to IR 2 the firm clarified that the real time aging equivalent for test articles aged for 10 months real time with conditioning to 50°C for 3 months is 28 months real time as 3 months at 50°C equates to 18 months real time. Therefore, additional testing is not needed for device performance over shelf life and determined to be adequate for both the (b) (4) and Aptar devices. b. The firm's response is adequate. c. Testing of the spray pattern on both the Aptar and (b) (4) devices will not be provided in adequate time to review for an approval decision therefore, the firm's response is inadequate. Refer to Minor comment 1.
Response Adequate:	☐ Yes ☒ No, See Minor Deficiency #1 included in CR letter Click or tap to enter a date.

	Date Sent: 4/18/2023	Date/Sequence Received: 4/21/2023
Information Request #4	(b) (4)	

Sponsor Response

	(b) (4)
Reviewer Comments	Testing of each performance attribute using the Aptar and (b) (4) devices will not be provided in adequate time to review for an approval decision therefore, the firm's response is inadequate. Additionally, the firm did not provide testing of the Aptar device post shipping nor rationale for applicability of leveraged data (i.e., 1mg Aptar or 2mg (b) (4) data post shipping).
Response Adequate:	☐ Yes ☒ No, See Major deficiency 1 and Minor deficiency 1 included in CR letter Click or tap to enter a date.

9.3. Discipline Specific Sub-Consulted Review Summary

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

<u>Discipline-Specific Design Verification / Validation adequately addressed</u>						
Discipline	Consult needed			Consultant	Section	Adequately Addressed (Y/N/NA)
	Yes	No	N/A			
Engineering (Materials, Mechanical, General)		X		Note: Conducted by CDRH Lead Reviewer	9.1	N
Biocompatibility	X			Papatya Kaner	9.3	N
Sterility			X	Note: Deferred to CDER		NA
Software / Cybersecurity			X	Note: Device does not include software/cybersecurity		NA
Electrical Safety / EMC			X	Note: Device does not include ES/EMC		NA
Human Factors			X	Note: Deferred to DMEPA	<u>11</u>	<u>NA</u>
Clinical			X	Note: Deferred to CDER		NA

CDRH sent <u>Deficiencies or Interactive Review Questions</u> to the Sponsor	☒ Yes ☐ No
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Discipline:	Date Sent:	Date/Sequence Received:
Consultant:	4/20/2023	4/21/2023
Information Request #1	(b) (4)	

	(b) (4)
Sponsor Response	
Reviewer Comments	The referenced (b) (4) initially did not include biocompatibility data and included a statement that biocompatibility testing of the (b) (4) device was in progress. An IR was sent to the firm requesting the biocompatibility data to be provided for the (b) (4) device. DMF (b) (4) was updated to include the biocompatibility test reports' however, it does not appear that the firm conducted irritation testing. Therefore, the firm's response remains inadequate as cytotoxicity, sensitization, and irritation testing should be conducted for the proposed combination product to enable a safety decision.
Response Adequate:	☐ Yes ☒ No, See Major CR Deficiency 2 included in CR letter

9.3.1. Insert Discipline Review

The following Biocompatibility review was completed by Papatya Kaner. The full memo is located in Appendix B. Below is a summary of the recommendation:
ARS Pharmaceuticals has developed Neffy (epinephrine nasal spray, code name ARS-1) as a needle-free alternative for the emergency treatment of (Type I) allergic reactions, including anaphylaxis. Epinephrine is a non-specific adrenergic agonist that is the drug of choice for the treatment of severe allergic reactions and anaphylaxis. Submission indicated that for dispensing the drug product, Sponsor would use the Aptar UDS device or the (b) (4) device, both of which are single-use, single dose, disposable nasal spray delivery systems. For the Aptar UDS device, all biocompatibility data was incorporated by cross-reference to Device Master File (DMF) (b) (4). The referenced DMF included cytotoxicity, sensitization and irritation testing to demonstrate the biological safety of the actuator and container holder components. Since the drug will be absorbed systematically via nose for the treatment, we also needed acute systemic toxicity endpoint for the biocompatibility assessment of the Aptar device's actuator system. However, the drug will be used as an emergency treatment for allergic reactions, not on a regular basis, hence the nasal spray's actuator will only have limited contact with the nasal mucosa. In addition, Sponsor described the safe use of Aptar device with other drugs such as the following NDAs: Narcan Nasal Spray (NDA# 016636), Tosymra Sumatriptan Spray (NDA #210884), Valtoco (diazepam nasal spray) (NDA #211635), Nayzilam (midazolam) nasal

spray (NDA #211321). Hence, we determined that the biocompatibility assessment of the Aptar UDS device is appropriate for use as the epinephrine nasal spray.

For the (b) (4) device's biocompatibility assessment, Sponsor referenced DMF (b) (4). We were not able to locate this DMF during our search in LORENZ docuBridge database, and the DMF reports emailed by (b) (4) (DMF holder) didn't include any biocompatibility reports. In their 4/21 email, (b) (4) provided the summary biocompatibility reports and indicated that they filed the full biocompatibility reports to the DMF. However, the provided biocompatibility reports didn't include irritation testing, which is required for a mucosal membrane contacting nasal spray per CDRH's 2016 Biocompatibility Guidance "Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process" (<https://www.fda.gov/media/85865/download>). Hence, we decided to include this request as the following CR letter deficiency:

10. CLINICAL VALIDATION REVIEW

10.1. Review of Clinical Studies Clinical Studies

- ☐ There is no device related clinical studies for review
☒ There are clinical studies for review

Clinical PK studies were conducted using the 2mg Aptar nasal spray device. Note that Neffy utilizes a well-known commercial device, the Aptar Unit Dose Sprayer (UDS), to deliver 100 uL volume of solution. The Aptar UDS has been approved as the device constituent part for several combination products, including emergency use products such as Narcan, Naysilam, and Valtoco, using the exact same Aptar device as for Neffy.

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PRIMARY STUDIES									
PK/PD	EPI 10	5.3.4.2	To assess the PK of three doses of ARS-1 in pediatric allergy subjects. To evaluate the comparative PD response in pediatric allergy subjects	Phase 1, single-dose, single treatment study	ARS 0.65 mg ARS 1.0 mg ARS 2.0 mg	57 (at time of interim analysis)	Pediatric subjects with Type I allergies	Single dose (1 day)	Ongoing; Interim CSR
PK/PD	EPI 15	5.3.4.1	To assess the comparative bioavailability of epinephrine after ARS-1 (2.0 mg), EpiPen 0.3 mg, and epinephrine and IM injection 0.3 mg in healthy volunteers. To evaluate the comparative PD response	Phase 1, two-part, six-treatment, six-period, single and repeat dose, crossover study	<u>Part 1</u> Single dose of ARS-1 2.0 mg Single dose of EpiPen 0.3 mg Single dose of IM epinephrine 0.3 mg <u>Part 2</u> Two doses of ARS-1 2.0 mg, both in the right naris, spaced 10 minutes apart Two doses of ARS-1 2.0 mg, one in the left and one in the right nares, spaced	59	Healthy subjects	<u>Part 1</u> 3 days <u>Part 2</u> 12 days	Completed; CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
					10 minutes apart, Two doses of EpiPen 0.3 mg in the left and right anterolateral thigh, 10 minutes apart.				
PK/PD	EPI 16	5.3.4.2	To assess the comparative bioavailability of epinephrine after ARS-1 2.0 mg, EpiPen 0.3 mg, and IM epinephrine 0.3 mg epinephrine in healthy volunteers. To evaluate the comparative PD response	Phase 1, four-treatment, partially randomized, crossover study	ARS-1 2.0 mg IM Epinephrine 0.3 mg IM Epinephrine 0.5 mg ARS-1 2.0 mg after nasal challenge.	36	Subjects with history of allergic rhinitis	4 days	Completed; CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
PK/PD	EPI 17	5.3.4.2	To assess the comparative bioavailability of epinephrine after self-administration of ARS-1 2.0 mg or study staff-administered IM injection in subjects with Type I allergies To evaluate the comparative PD response	Phase 1, single-dose, two-treatment, two-period, randomized crossover study	ARS-1 2.0 mg, self-administered IM epinephrine injection 0.3 mg, study staff-administered	42	Subjects with Type I allergies	3 days	Completed; CSR
SUPPORTIVE STUDIES									
PK/PD	EPI 03	5.3.4.1	To assess the bioavailability of a single dose and repeat dose of IN ARS-1 compared to a single dose and repeat dose of IM epinephrine injection	Phase 1, randomized, single-dose, 5-treatment, 5-period, crossover study	ARS-1 1.0 mg IN ARS-1 1.0 mg IN, twice Epinephrine 0.3 mg IM Epinephrine 0.3 mg IM, Twice Epinephrine 0.5 mg IM	70	Healthy subjects	7 days	Completed; CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the Study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects	Healthy Subjects or Diagnosis of Patients	Duration of Treatment	Study Status; Type of Report
BA	EPI 11	5.3.1.1	To assess the comparative bioavailability of five formulations of ARS-1 with different DDM levels	Phase 1, five-period, five-treatment, randomized crossover study	ARS-1 1.0 mg with 0.20% DDM ARS-1 1.0 mg with 0.25% DDM ARS-1 1.0 mg with 0.30% DDM ARS-1 1.0 mg with 0.50% DDM ARS-1 1.0 mg with 0.30% DDM + (b) (4)	12	Healthy subjects	5 days	Completed CSR
PK/PD	EPI 13	5.3.4.2	To assess the comparative bioavailability of epinephrine after self-administration of ARS-1 (2.0 mg) EpiPen (0.3 mg) Symjepi (0.3 mg) in subjects with Type I allergy conditions. To evaluate the comparative PD response.	Phase 1, single-dose, three-period, three-treatment, six-sequence, randomized crossover study	ARS-1 2.0 mg, EpiPen 0.3 mg Symjepi 0.3 mg	42	Subjects with Type I allergies	4 days	CSR

APPEARS THIS WAY ON ORIGINAL

Reviewer Comments

Due to both ethical and practical limitations, the firm did not conduct randomized, controlled clinical trials to assess the efficacy of epinephrine for the treatment of severe allergic reactions and anaphylaxis. Thus, for the purpose of their submission, efficacy is based on pharmacokinetic comparisons to other approved injection devices and surrogate pharmacodynamic endpoints. To date, no such efficacy study has ever been conducted in patients at risk of serious allergic reactions and anaphylaxis. As such, to further support the efficacy of *neffy* (also called ARS-1), ARS utilized both PK data and PD (hemodynamic) endpoints as surrogate markers for efficacy, with the understanding that these endpoints (blood pressure and heart rate) are indicative of α - and β -adrenergic receptor activation and, consequently, clinical efficacy.

Note to CDER: It does not appear that the (b) (4) device was used in clinical studies. Decision for adequacy of clinical studies using the to-be-marketed configuration is deferred to CDER.

11. HUMAN FACTORS VALIDATION REVIEW

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

12. FACILITIES & QUALITY SYSTEMS

12.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
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CDRH Facilities Inspection Review was not conducted	☒
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12.2. Quality Systems Documentation Review

CDRH Quality Systems Documentation Review conducted	☒
CDRH Quality Systems Documentation Review was not conducted	☐

12.2.1. Description of the Device Manufacturing Process

(b) (4)

What Quality System did the Sponsor choose:

- ☐ Device QSR-based
☐ Drug cGMP-Based Streamline –
☐ Stream-line Both (no streamlined approach)

Reviewer Comments

The firm included document 1.2 note to reviewer; however, the table of contents does not detail where quality system documentation can be located. Additionally, quality system documentation could not be found in the submission. Refer to Minor deficiency 2.

GMP Compliance Summary Conclusion

The Sponsor provided adequate summary information about the GMP compliance activities	☐ Yes	☒ No
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12.2.3. Corrective and Preventive Action Review

The Sponsor provided the following information with regards to corrective and preventive actions:

The firm did not provide CAPA information in their submission.

Reviewer Comments

The firm did not include CAPA information in their submission. Refer to Minor deficiency 3.

CAPA Conclusion

The Sponsor provided adequate information for corrective and preventive actions.	☐ Yes	☒ No
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12.3. Control Strategy Review

(b) (4)

Reviewer Comments

In documents control-critical-steps and 2.3.P.3 manufacture the firm detailed in process controls and the acceptance criteria; however, the firm did not detail incoming inspection or lot release activities to assess the overall control of the combination product, particularly as it pertains to EPRs. Refer to Major CR Deficiency 4.

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

12.4. 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

The firm adequately detailed the manufacturing process for the proposed combination product; however, the firm did not provide information with regard to their cGMP compliance and CAPA procedure. Additionally, the firm solely provided detail with regards to their in-process controls and therefore, adequacy of in-coming inspection and lot release could not be determined to ensure adequate control of the combination product.

CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No

<<END OF REVIEW>>

13. APPENDIX A (INFORMATION REQUESTS)

13.1. Filing/74-Day Information Requests

N/A

13.2. Mid-Cycle Information Requests

N/A

13.3. Interactive Information Requests

(b) (4)



14.APPENDIX B (CONSULTANT MEMOS)

14.1. Biocompatibility Review Memo – Papatya Kaner, CDRH/OPEQ/OHTIII/DHTIIC

APPEARS THIS WAY ON ORIGINAL

Date	5/2/2023		
To:	Porsche Bennett, CDRH Device Reviewer		
Requesting Center/Office	CDER/OND	Clinical Review Division	DROII
From	Papatya Kaner OPEQ/OHT3/DHT3C/THT3C3		
Through (Team)	Courtney Evans Team Lead, Injection Team OPEQ/OHT3/DHT3C/THT3C1		
Through (Division) *Optional	CPT Alan Stevens, Assistant Director OPEQ/OHT3/DHT3C/THT3C1		
Subject	NDA 214697, Neffy (epinephrine nasal spray) for anaphylaxis ICC2200794 ICCR00868517		
Recommendation	Recommendation Date: 12/10/2020 ☐ Device Constituents Parts of the Combination Product <u>are reasonably safe</u> for use in the proposed clinical study ☐ Device Constituents Parts of the Combination Product <u>are reasonably safe</u> for use in the proposed clinical study, CDRH has non-hold comments below ☒ Device Constituents Parts of the Combination Product are <u>not safe</u> for use in the proposed clinical study, CDRH has CLINICAL HOLD comments		

Review Summary:

ARS Pharmaceuticals has developed Neffy (epinephrine nasal spray, code name ARS-1) as a needle-free alternative for the emergency treatment of (Type I) allergic reactions, including anaphylaxis. Epinephrine is a non-specific adrenergic agonist that is the drug of choice for the treatment of severe allergic reactions and anaphylaxis. Submission indicated that for dispensing the drug product, Sponsor would use the Aptar UDS device or the (b) (4) device, both of which are single-use, single dose, disposable nasal spray delivery systems.

For the Aptar UDS device, all biocompatibility data was incorporated by cross-reference to Device Master File (DMF) (b) (4). The referenced DMF included cytotoxicity, sensitization and irritation testing to demonstrate the biological safety of the actuator and container holder components. Since the drug will be absorbed systematically via nose for the treatment, we also needed acute systemic toxicity endpoint for the biocompatibility assessment of the Aptar device's actuator system. However, the drug will be used as an emergency treatment for allergic reactions, not on a regular basis, hence the nasal spray's actuator will only have limited contact with the nasal mucosa. In addition, Sponsor described the safe use of Aptar device with other drugs such as the following NDAs: Narcan Nasal Spray (NDA# 016636), Tosymra Sumatriptan Spray (NDA #210884), Valtoco (diazepam nasal spray) (NDA #211635), Nayzilam (midazolam) nasal spray (NDA #211321). Hence, we determined that the biocompatibility assessment of the Aptar UDS device is appropriate for use as the epinephrine nasal spray.

For the (b) (4) device's biocompatibility assessment, Sponsor referenced DMF (b) (4). We were not able to locate this DMF during our search in LORENZ docuBridge database, and the DMF reports emailed by (b) (4) (DMF holder) didn't include any biocompatibility reports. In their 4/21 email, (b) (4) provided the summary biocompatibility reports and indicated that they filed the full biocompatibility reports to the DMF. However, the provided biocompatibility reports didn't include irritation testing, which is required for a mucosal membrane contacting nasal spray per CDRH's 2016 Biocompatibility Guidance "Use of International Standard ISO 10993-1, *Biological evaluation of medical devices - Part 1: Evaluation and*

testing within a risk management process” (<https://www.fda.gov/media/85865/download>). Hence, we decided to include this request as the following CR letter deficiency:

CR letter deficiency:

In your 4/21/23 email, you provided the summary biocompatibility reports for the (b) (4) device, and you also indicated that the full biocompatibility reports were filed to the DMF (b) (4). However, the provided biocompatibility reports didn’t include irritation testing, which is necessary for a mucosal membrane contacting nasal spray per CDRH’s 2016 Biocompatibility Guidance “Use of International Standard ISO 10993-1, *Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process*” (<https://www.fda.gov/media/85865/download>). Hence, please provide your irritation test report for the (b) (4) device per ISO 10993-23: 2021, *Biological evaluation of medical devices - Part 23: Tests for irritation* for a complete biocompatibility assessment.

Digital Signature Concurrence Table (Doc ID: 04504.03.05)	
For each of the specific issues identified in the recommended requests to the applicant above, I and/or if applicable contributing consulting reviewer(s) (and or supervisors), have provided a statement of basis for the request(s); and either cited as part of it an available, applicable, and relevant final rule, statute, final guidance, or FDA-recognized consensus standard, or confirmed to the best of my ability that there is no final rule, statute, final guidance, or FDA-recognized consensus standard available, applicable, and relevant to the request(s).	
Reviewer Sign-Off	

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/s/

ANIKA A LALMANSINGH
05/12/2023 10:38:37 AM
Uploaded on behalf of CDRH.

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

DATE: 4/21/2023

TO: Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)

FROM: Office of Study Integrity and Surveillance (OSIS)

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

RE: NDA 214697

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

OSIS conducted an Remote Regulatory Assessment (RRA) for the analytical site in Non-responsive

The RRA was conducted under the following submission: NDANon-responsive

OSIS concluded that data from the reviewed studies were reliable.

Site

Facility Type	Facility Name	Facility Address
Analytical	(b) (4)	

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/s/

JOSHUA L PEREZ
04/25/2023 01:24:04 PM

MEMORANDUM

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

DATE: April 3, 2023

TO: Sally Seymour, M.D.
Director
Division of Pulmonology, Allergy, and Critical
Care (DPACC)
Office of Immunology and Inflammation (OII)
Office of New Drugs (OND)

FROM: Yiyue Zhang, Ph.D.
Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Arindam Dasgupta, Ph.D.
Deputy Director
DNDSI/OSIS

SUBJECT: Routine inspection of Children's Hospital Colorado,
Aurora, CO

Inspection Summary

Per the request of OND/OII/DPACC, OSIS arranged an inspection of clinical portion of **Study EPI 10 (NDA 214697, Neffy/Epinephrine nasal spray)** conducted at Children's Hospital Colorado, Aurora, CO.

No significant objectionable conditions were observed and Form FDA 483 was not issued at the inspection close-out. The final inspection classification is No Action Indicated (NAI).

One verbal item was discussion with the site's management at the close-out meeting regarding the inaccurate information of two subjects on the Screening and Enrollment Log. After reviewing the inspectional findings and the site's response, I conclude this finding had no impact on subject safety and welfare and no impact on study data reliability. Thus, the clinical data from **Study EPI 10** conducted at Children's Hospital Colorado are reliable.

Inspected Study

NDA 214697

Study Number: EPI 10

Study Title: A Single-Period, Single-Dose Study of the
Pharmacokinetics and Pharmacodynamics of
Epinephrine After Administration of Intranasal
ARS-1 to Pediatric Subjects with Systemic
Allergies

Dates of Conduct: July 17, 2020 - March 15, 2021

Clinical Investigator (CI): David Fleischer, M.D.

Clinical Site: Children's Hospital Colorado (Study Site #01)

Section of Allergy & Immunology
University of Colorado Denver
13123 East 16th Avenue
Aurora, CO 80045

Inspectional Findings

ORA Investigator Ruth A. Williams (OBIMO) inspected Children's
Hospital Colorado, Aurora, CO from January 23 to 27, 2023.

The previous FDA BIMO Clinical BA/BE inspection of the clinical
site was conducted by ORA from June 17 to 21, 2019 and the final
classification was No Action Indicated (NAI). The previous FDA
BIMO inspection of the CI was conducted by ORA from February 6
to 13, 2020 and the final classification was NAI.

The current inspection included a review of the following items:
Institutional Review Board (IRB) approvals, monitoring reports,
delegation logs and training records. Subject records audited
included case report forms (CRFs), informed consent process,
protocol adherence and deviations, test article accountability
and storage, and adverse events reporting.

At the conclusion of the inspection, Investigator Williams did
not observe significant objectionable findings and did not issue
a Form FDA 483. However, Investigator Williams discussed the
following item with the site's management at the close-out
meeting.

Discussion Item #1: The Screening and Enrollment Log was not
accurate. Specifically, for Subject (b) (6) Subject Initials and
Date of Screening were documented incorrectly. In addition,

Subject (b) (6) was not documented on the Screening and Enrollment log.

Site's Response: The CI acknowledged the finding. The site's management stated it was an oversight and provided a copy of the updated Screening and Enrollment Log with the corrections made during the inspection.

OSIS Evaluation: Although the subject initials and screening date were inaccurate for Subject (b) (6) and missing for Subject (b) (6) on the Screening and Enrollment Log, the EIR stated that the information in the study source records for all subjects were attributable, legible, contemporaneous, original, and accurate. During the inspection, Investigator Williams verified that there was adequate documentation that all study subjects including Subjects (b) (6) met the inclusion/exclusion criteria and all subjects were real and actively participated in the study. The subjects' source records at the clinical site were compared against the study reports submitted to the Agency and no other discrepancies were observed related to Subjects (b) (6).

Therefore, this finding has no impact on subject safety and welfare and no impact on study data reliability.

Yiyue Zhang, Ph.D.
Senior Staff Fellow

FEI Numbers: 1771443 (clinical site); 3016067120 (CI)

cc:

OTS/OSIS/Kassim/Folian/Pham/Mitchell/Fenty-Stewart/CDER-OSIS-BEQ@fda.hhs.gov

OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/Zhang

OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Ou

ORA/OMPTO/OBIMO/ORA_BIMO_Inspection_POC@fda.hhs.gov/Williams

Draft: YZ 03/21/2023, 03/23/2023

Edit: GB 03/22/2023, 03/23/2023; AD 04/03/2023

OSIS File#: BE 9615

eNSpect Assignment ID: 207028; eNSpect Op ID: 234114

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/s/

YIYUE ZHANG
04/03/2023 02:20:08 PM

GOPA BISWAS
04/03/2023 05:10:34 PM

ARINDAM DASGUPTA
04/03/2023 09:39:22 PM

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

DATE: 10/5/2022

TO: Division of Pulmonology, Allergy, and Critical Care (DPACC)
Office of Immunology and Inflammation (OII)

FROM: Division of New Drug Study Integrity (DNDSI)
Office of Study Integrity and Surveillance (OSIS)

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

RE: NDA 214697

The Division of New Drug Study Integrity (DNDSI) within the Office of Study Integrity and Surveillance (OSIS) determined that an inspection is not needed at this time for the site listed below. The rationale for this decision is noted below.

Rationale

The Office of Regulatory Affairs (ORA) inspected the clinical site in **Non-responsive** which falls within the surveillance interval. The inspection was conducted under the following submission: ANDA **Non-responsive**

The final classification for the inspection was No Action Indicated (NAI).

Inspection Site

Facility Type	Facility Name	Facility Address
Clinical	West Coast Clinical Trials (WCCT) Global, Inc.	5630 Cerritos Avenue, Cypress, CA

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/s/

JAMES J LUMALCURI
10/05/2022 01:38:29 PM