

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

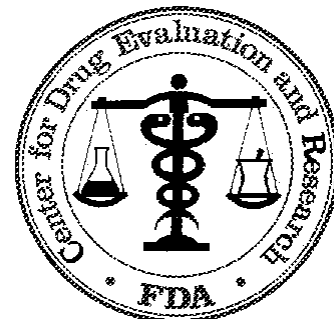
APPLICATION NUMBER:

214697Orig1s000

PRODUCT QUALITY REVIEW(S)

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

DATE: 19-APR-2024
TO: NDA 214697 File
FROM: Craig M. Bertha
Chemistry Reviewer
OPQA I, DPQAVIII
THROUGH: Nina Ni, Ph.D.
Supervisor
OPQA II, DPQAVII



SUBJECT: NDA 214697 Resubmission Evaluation for Epinephrine Nasal Spray – Nitrosamine Impurities

ACTION RECOMMENDATION: Approval¹

BACKGROUND/SUMMARY:

The following product quality deficiency comment was included in the Complete Response Letter (CRL) for ARS Pharmaceuticals, Inc. NDA 214697 dated 09/19/2023:

PRODUCT QUALITY

Deficiency

On August 7, 2023, FDA published a guidance for industry, Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) (August 2023) (NDSRI Guidance), available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-acceptable-intake-limits-nitrosamine-drug-substance-related-impurities>. The NDSRI Guidance is a final guidance, to be implemented immediately upon publication. In that guidance, we state that FDA expects manufacturers and applicants to ascertain the presence of nitrosamine impurities, including NDSRIs, using a 3-step mitigation strategy described in the FDA guidance for industry, Control of Nitrosamine Impurities in Human Drugs (Feb. 2021) (Nitrosamine Guidance) (b) (4). The 3-steps are: 1) conduct risk assessments for nitrosamines in APIs and drug products; 2) conduct confirmatory testing if risks are identified; and 3) report changes implemented to prevent or reduce the presence of nitrosamine impurities in APIs and drug products in approved and pending NDAs and ANDAs. With respect to applications pending before

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¹ The labeling review decision is pending for the NDA. Labeling negotiations with the applicant are pending. However, there are only minor labeling deficiencies from the CMC perspective and we expect the applicant will accept our recommendations (see Labeling chapter of the IQA dated May 11, 2023). In the future, refer to the CMC sections of the final approved labeling.

the Agency, the NDSRI Guidance states that “[a]pplicants with pending applications should conduct a risk assessment for NDSRIs expeditiously and inform FDA if confirmatory testing finds NDSRI levels above the [acceptable intake] [AI] limits recommended in this guidance.” (b) (4) If an NDSRI is detected above the recommended AI limit, the applicant should amend the application as appropriate.

(b) (4) there is a potential for the formation of an NDSRI ((b) (4) in your drug product considering the potential presence of nitrosating agents. Table 1 of the NDSRI guidance identifies the hypothetical formation of (b) (4) in epinephrine and the corresponding recommended AI limit based on the predicted carcinogenic potency categorization approach (see <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/updated-information-recommended-acceptable-intake-limits-nitrosamine-drug-substance-related#predicted>). This recommended AI limit should be applied to (b) (4) (b) (4) to the extent that it forms in your drug product (b) (4)

Your NDA is not adequate because we have not received information concerning a risk assessment or confirmatory data for (b) (4)

To resolve the deficiency:

Provide information to FDA regarding potential NDSRIs in your application as recommended in the NDSRI Guidance, specifically with respect to (b) (4) (b) (4)

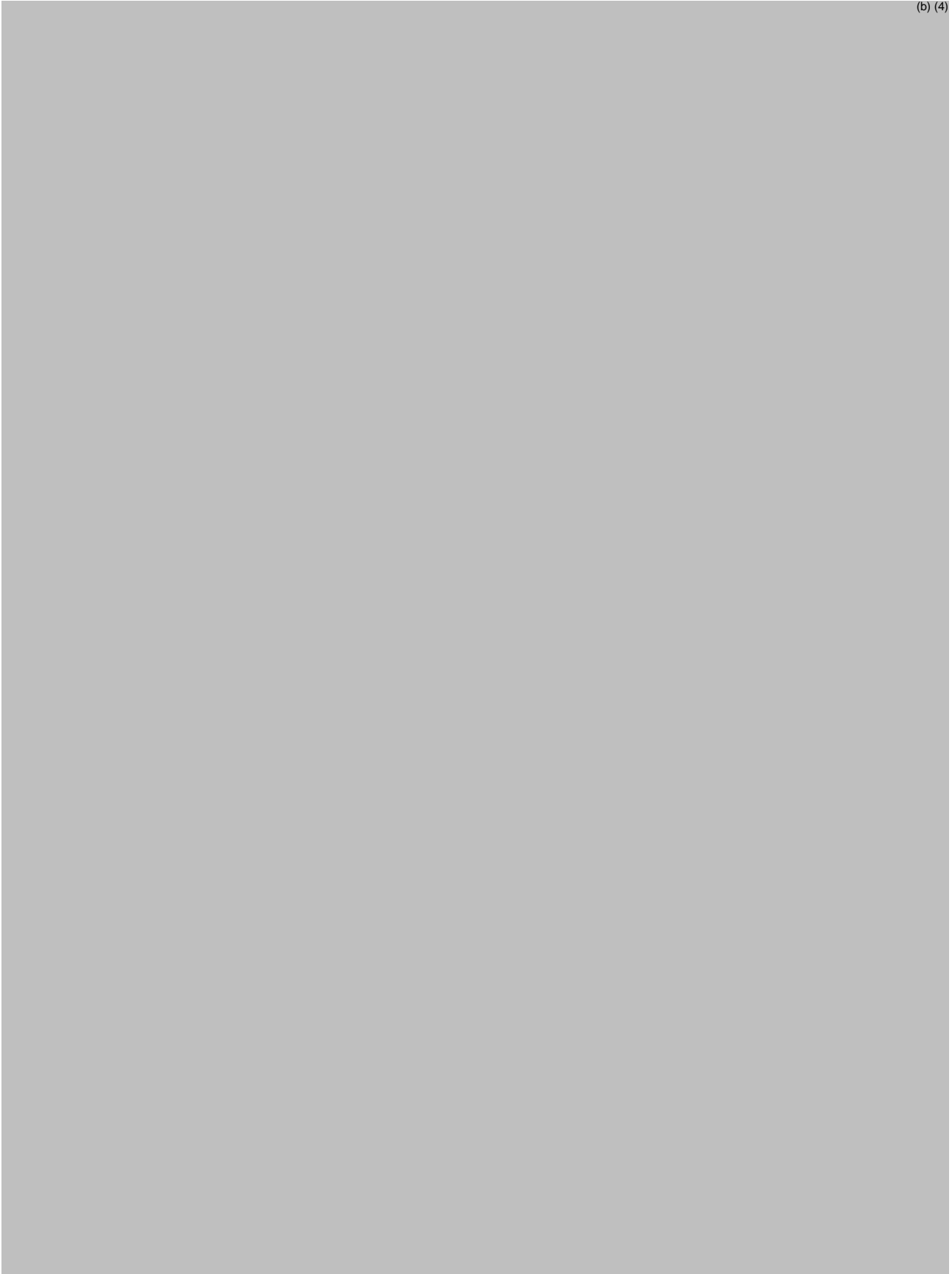
If the (b) (4) impurity is detected in your drug product, submit confirmatory testing data using sensitive and appropriately validated analytical method(s), from three primary batches to demonstrate that (b) (4) in your drug product is at or below the level corresponding recommended AI limit ((b) (4) ng/day) based on the approved maximum daily dose (MDD) at release and throughout the shelf-life. FDA recommends that applicants develop an appropriate control strategy to ensure that the nitrosamine level is reliably at or below the recommended AI limit in your submission (b) (4)

If the level of (b) (4) is above the corresponding recommended AI limit ((b) (4) ng/day) based on the approved (MDD at release and throughout the shelf-life, investigate the root cause and implement changes in the manufacturing process or product formulation to eliminate, mitigate, or reduce nitrosamine impurity consistent with the recommendations in the NDSRI Guidance referenced above if applicable (b) (4) (b) (4) Alternatively, you may provide a scientifically justified rationale to pursue an AI limit different than the FDA recommended AI limit associated with (b) (4)

Summary and Evaluation of Resubmission dated 04/02/2024

(b) (4)

(b) (4)



In conclusion, from a CMC/Quality perspective, the application is **recommended to be approved.**

ATL: Craig M. Bertha, 19-APR-2024

cc:

OND/ORO/DROII/JLarose

OND/OII/DPACC/JLan

OPQ/ONDP/DNDAPI/NDB2/SKelly

OPQ/ONDP/DNDAPI/NDB2/DChristner

OPQ/OPQA II/DPQAVIII/CBertha

OPQ/OPQA I/DPQAVII/NNi

OPQ/OPRO/DRBPMI/RBPMB1/EGimose

OPQ/OPMA/DPMAl/PMB3/QMajumder

OPQ/OPMA/DPMAl/PMB3/CFalabella

OPQ/OPMA/DMAII/MAB4/CGilbert

OPQ/OPMA/DMAII/MAB4/YZheng

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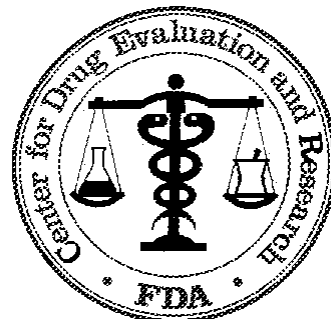
/s/

CRAIG M BERTHA
04/19/2024 12:09:36 PM

NINA NI
04/19/2024 12:31:47 PM

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

DATE: 15-SEP-2023
TO: NDA 214697 File
FROM: Craig M. Bertha
Chemistry Reviewer
ONDP, Division II, Branch 4
THROUGH: Nina Ni
Branch Chief
ONDP, Division II, Branch 4
AND: Hong Cai
Division Director
ONDP, Division II



SUBJECT: NDA 214697 Second Addendum Review for Integrated Quality Assessment (IQA) for Epinephrine Nasal Spray – Nitrosamine Impurities

BACKGROUND/SUMMARY:

(b) (4)

During the course of the review of the NDA, the team sent the following information request (IR in *italics*) to the applicant on 01-FEB-2023:

(b) (4)

PRODUCT QUALITY – Complete Response Letter Deficiency Comment

Deficiency

On August 7, 2023, FDA published a guidance for industry, Recommended Acceptable Intake Limits for Nitrosamine Drug Substance-Related Impurities (NDSRIs) (August

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² *Control of Nitrosamine Impurities in Human Drugs* (February 2021) available at <https://www.fda.gov/media/141720/download>

2023) (NDSRI Guidance), available at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents/recommended-acceptable-intake-limits-nitrosamine-drug-substance-related-impurities>. The NDSRI Guidance is a final guidance, to be implemented immediately upon publication. In that guidance, we state that FDA expects manufacturers and applicants to ascertain the presence of nitrosamine impurities, including NDSRIs, using a 3-step mitigation strategy described in the FDA guidance for industry, Control of Nitrosamine Impurities in Human Drugs (Feb. 2021) (Nitrosamine Guidance) (b) (4). The 3-steps are: 1) conduct risk assessments for nitrosamines in APIs and drug products; 2) conduct confirmatory testing if risks are identified; and 3) report changes implemented to prevent or reduce the presence of nitrosamine impurities in APIs and drug products in approved and pending NDAs and ANDAs. With respect to applications pending before the Agency, the NDSRI Guidance states that “[a]pplicants with pending applications should conduct a risk assessment for NDSRIs expeditiously and inform FDA if confirmatory testing finds NDSRI levels above the [acceptable intake] [AI] limits recommended in this guidance.” (b) (4) If an NDSRI is detected above the recommended AI limit, the applicant should amend the application as appropriate.

(b) (4)

Your NDA is not adequate because we have not received information concerning a risk assessment or confirmatory data for (b) (4)

To resolve the deficiency:

Provide information to FDA regarding potential NDSRIs in your application as recommended in the NDSRI Guidance, specifically with respect to (b) (4)

(b) (4)

If the (b) (4) impurity is detected in your drug product, submit confirmatory testing data using sensitive and appropriately validated analytical method(s), from three primary batches to demonstrate that (b) (4) in your drug product is at or below the level corresponding recommended AI limit ((b) (4) ng/day) based on the approved maximum daily dose (MDD) at release and throughout the shelf-life. FDA recommends that applicants develop an appropriate control strategy to ensure that the nitrosamine level is reliably at or below the recommended AI limit in your submission (b) (4)

If the level of (b) (4) is above the corresponding recommended AI limit ((b) (4) ng/day) based on the approved (MDD at release and throughout the shelf-life, investigate the root cause and implement changes in the manufacturing process or product formulation to eliminate, mitigate, or reduce nitrosamine impurity consistent with the recommendations in the NDSRI Guidance referenced above if applicable (see also NDSRI Guidance at pages 12-14). Alternatively, you may provide a scientifically justified rationale to pursue an AI limit different than the FDA recommended AI limit associated with (b) (4)

RECOMMENDATION: The deficiency comment highlighted in blue above has been included in the current draft CR letter.

ATL: Craig M. Bertha, 15-SEP-2023

cc:

OND/ORO/DROII/JLarose
OND/OII/DPACC/JLan
OPQ/ONDP/DNDAPI/NDB2/SKelly
OPQ/ONDP/DNDAPI/NDB2/DChristner
OPQ/ONDP/DNDPII/Branch IV/CBertha
OPQ/OPRO/DRBPMI/RBPMB1/EGimose
OPQ/OPMA/DPMAI/PMB3/QMajumder
OPQ/OPMA/DPMAI/PMB3/CFalabella
OPQ/OPMA/DMAII/MAB4/CGilbert
OPQ/OPMA/DMAII/MAB4/YZheng

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/s/

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NINA NI
09/19/2023 07:59:29 AM



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Office of Pharmaceutical Quality

New Drug Application (NDA) 214697 Integrated Quality Assessment - Addendum



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RECOMMENDATION

☒ Approval
☐ Approval with Post-Marketing Commitment
☐ Complete Response

NDA 214697 Assessment #1 - Addendum

Drug Product Name	L-Epinephrine Nasal Spray
Dosage Form	Nasal spray
Strength	2 mg/100 mcL per spray (as free base)
Route of Administration	Nasal inhalation
Rx/OTC Dispensed	Rx
Applicant	ARS Pharmaceuticals, Inc.
US agent, if applicable	Richard E. Lowenthal, MS, MSEL (ARS Pharma)

Submission(s) Assessed Review #1	Document Date	Discipline(s) Affected
SD 1 (original)	19-AUG-2022	All
SD 8 (amendment)	30-SEP-2022	Drug Product
SD 14 (amendment)	25-OCT-2022	Manufacturing
SD 20 (amendment)	13-JAN-2023	Drug Product
SD 21 (amendment)	07-FEB-2023	Microbiology
SD 22 (amendment)	10-FEB-2023	Drug Product
SD 25 (amendment)	21-FEB-2023	Microbiology
SD 26 (amendment)	16-MAR-2023	Manufacturing
SD 28 (amendment)	22-MAR-2023	CDRH (consult device review)
SD 30 (amendment)	28-MAR-2023	CDRH (consult device review)
SD 31 (amendment)	03-APR-2023	Drug Product
SD 36 (amendment)	21-APR-2023	CDRH (consult device review)
SD 39 (amendment)	26-APR-2023	Follow-up information for 16-MAR-2023 amendment for Manufacturing
Submission(s) Assessed Review #1 Addendum	Document Date	Discipline(s) Affected
SD 42 (amendment)	29-MAY-2023	Drug Product
SD 43 (amendment)	30-MAY-2023	Drug Product



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QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sharon Kelly	Lawrence Perez
Product	Xin Feng	Craig M. Bertha
Manufacturing	Quamrul Majumder	Christine Falabella
Microbiology	Catherine Gilbert	Yan Zheng
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	N/A	



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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	3	(b) (4)	(b) (4)	Adequate	2/27/2023	Alternate source from DMF (b) (4)
	4			Adequate	11/5/2019	To support a nasal spray product
	4			N/A		For non-clinical review
	2			Adequate	5/21/2020	For injection drug product
	4			Adequate	9/4/2019	To support a nasal spray product
	3			Adequate	8/14/2015	Same actuator and container holder used for other approved nasal spray products
	3					Supporting DMF for DMF (b) (4)
	3			Adequate	1/13/2022	
	3			Adequate	3/7/2017	
	3			N/A		Sufficient information in NDA; Vial used for another approved nasal spray with the (b) (4)

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description



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IND	139091	ARS Pharmaceutical's IND supporting NDA 214697
NDA	204200	Reference drug from Par Sterile Products (Adrenalin Injection)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH – device consult	Pending			Porsche Bennett
Clinical	N/A			
Other	N/A			



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NDA Executive Summary

1. Application/Product Information

NDA Number.	214697
Applicant Name	ARS Pharmaceuticals, Inc.
Drug Product Name	L-Epinephrine Nasal Spray
Dosage Form.	Nasal spray
Proposed Strength(s)	2 mg (as base) per spray
Route of Administration	Nasal inhalation
Maximum Daily Dose	4 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Immediate and emergency first-line treatment of allergic reactions (Type I) including anaphylaxis in Adults and Children ≥ 30 kg (66 lbs.)
Drug Product Description	L-Epinephrine is formulated as a nasal spray (solution), which includes a non-compendial (b) (4) (Aegis' Intravail A3® which is a water soluble nonionic detergent n-dodecyl-β-D-maltoside or DDM), (b) (4) (sodium metabisulfite), (b) (4) (disodium edetate), and other common excipients used in nasal sprays. All excipients, with the exception of DDM, are of USP/NF grade. The drug is not an NME and it is chiral, (b) (4). Note that the concentration of sodium metabisulfite in the formulation is (b) (4) than is typical for epinephrine injection products, and comparative accelerated stability data for the formulation as compared to two approved injection products shows that the nasal spray formulation shows significantly (b) (4).



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	(b) (4) (b) (4) the applicant has agreed to test stability samples for particulates and apply the requirements for injections as per USP <788>. The product is indicated for the treatment of allergic reactions and the dose is 2 or 4 mg. Each spray delivered from the device is targeted to contain 2 mg of epinephrine in 100 mcL of formulation. Epinephrine (b) (4) obtained from (b) (4) (DMF (b) (4) has been found to be adequate for an injection drug product. Manufacturing is done (b) (4) (b) (4) The formulation uses a (b) (4) of epinephrine and the product has a 25 mcL overflow to assure 100 mcL can be delivered (note that (b) (4) (b) (4) for approved epinephrine injection products



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	range from (b) (4) %). The formulation is aqueous-based, (b) (4). There is a (b) (4). The applicant includes information and data for three registration batches (210928, 210929, and 210930), the first of which was also a clinical batch. Note that executed batch records have been provided for the registration batches. A key issue for solutions of epinephrine is chemical stability and shelf-life. Twelve months of long term (25°C/60%RH) stability data were provided in the original application for all parameters and 18 month stability data for (b) (4) particulates was provided in the 5/29/2023 amendment. These data support a 24 month shelf-life. There are also 24 months of long term supportive stability data provided for three batches of a 1 mg strength product (b) (4).		
Co-packaged product information	N/A		
Device information:	Refer to P.7 and DMFs (b) (4)		
Storage Temperature/ Conditions	Store below 77°F (25°C). Excursions permitted up to 122°F (50°C). Do not freeze.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Sharon Kelly	Lawrence Perez
	<i>Drug Product/ Labeling</i>	Xin Feng	Craig M. Bertha
	<i>Manufacturing</i>	Quamrul Majumder	Christine Falabella
	<i>Biopharmaceutics</i>	N/A	N/A
	<i>Microbiology</i>	Catherine Gilbert	Yan Zheng



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	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Anika Lalmansingh	
	<i>ATL</i>	Craig M. Bertha	
Consults	CDRH was consulted to assess the nasal spray device as the product indication is for treatment of an emergent medical condition.		

2. Final Overall Recommendation - Adequate

3. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

All CMC deficiencies have been resolved,¹ thus the application is recommended for approval.

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes

Recommendation by Subdiscipline:

- Drug Substance - Adequate**
- Drug Product - Adequate**
- Quality Labeling - Adequate¹**
- Manufacturing - Adequate**
- Biopharmaceutics - N/A**
- Microbiology - Adequate**

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

4. Life-Cycle Considerations

Established Conditions per ICH Q12: No
Comments: N/A

¹ The labeling review decision is pending for this IQA. Labeling negotiations with the applicant are pending. There are only minor labeling deficiencies from the CMC perspective and we expect the applicant will accept our recommendations. Refer to the CMC sections of the final approved labeling.



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Comparability Protocols (PACMP): Yes

Comments: Applicant has withdrawn the comparability protocol as per the 13-JAN-2023 amendment.

Additional Lifecycle Comments:

N/A



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5. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (*Deficiencies that affect multiple sub-disciplines*)

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

N/A

4. Labeling Deficiencies

Labeling comments have been conveyed to the team via the IQA dated 5/11/2023.

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (*Specify discipline, such as Environmental*)

CDRH device review is pending.

**Application Technical Lead Name and Date:
Craig M. Bertha, 5/31/2023**



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DP attribute/ CQA	Factors that may impact the CQA	O ²	S ^{1,3}	D ¹	Final RA FMECA RPN #	Comment & considerations for risk assessment	Lifecycle considerations
Appearance	Defects in the device constituent part components	1	3	1	3	(b) (4)	
pH	- buffer capacity of formulation - formulation component degradation	4	3	2	24		
Assay & Related Substances	- purity of API - degradation of API as formulated - compatibility of API with formulation and device components	2	3	2	12		
Sodium metabisulfite assay	- incorrect amount of sodium metabisulfite (SMB) formulated (b) (4)	2	3	1	6		
Uniformity of dosage units & dose delivered	- assay variability - assay drop on stability - pump delivery variability due to device defect - lower than target fill and/or leakage	2	3	3	18		

² O = Probability of Occurrence; S = Severity of Effect; D = Detectability

³ Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of “3” will be used throughout)



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Final Risk Assessment for *L*-Epinephrine Nasal Spray

Droplet Size Distribution (DSD)	spray unit variability or defects	2	3	2	12	(b) (4)
Pump delivery	- pump delivery variability due to device defect - lower than target fill and/or leakage	1	3	1	3	
Spray Pattern	- spray unit defect - particulate matter alteration of spray pattern	2	3	4	24	
Particulate matter	- particulate matter sourced from formulation components - particulate matter introduced from manufacturing equipment - particulate matter introduced via the vial or stopper - particulate matter formed by degradation of API	4	3	2	24	
Microbial limits test (refer to microbiology review in	(b) (4)	2	3	2	12	

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/s/

CRAIG M BERTHA
06/02/2023 07:19:12 AM

NINA NI
06/02/2023 01:53:34 PM



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Office of Pharmaceutical Quality

New Drug Application (NDA) 214697 Integrated Quality Assessment



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RECOMMENDATION

☐ Approval
☐ Approval with Post-Marketing Commitment
☒ Complete Response

NDA 214697 Assessment #1

Drug Product Name	L-Epinephrine Nasal Spray
Dosage Form	Nasal spray
Strength	2 mg/100 mL per spray (as free base)
Route of Administration	Nasal inhalation
Rx/OTC Dispensed	Rx
Applicant	ARS Pharmaceuticals, Inc.
US agent, if applicable	Richard E. Lowenthal, MS, MSEL (ARS Pharma)

Submission(s) Assessed	Document Date	Discipline(s) Affected
SD 1 (original)	19-AUG-2022	All
SD 8 (amendment)	30-SEP-2022	Drug Product
SD 14 (amendment)	25-OCT-2022	Manufacturing
SD 20 (amendment)	13-JAN-2023	Drug Product
SD 21 (amendment)	07-FEB-2023	Microbiology
SD 22 (amendment)	10-FEB-2023	Drug Product
SD 25 (amendment)	21-FEB-2023	Microbiology
SD 26 (amendment)	16-MAR-2023	Manufacturing
SD 28 (amendment)	22-MAR-2023	CDRH (consult device review)
SD 30 (amendment)	28-MAR-2023	CDRH (consult device review)
SD 31 (amendment)	03-APR-2023	Drug Product
SD 36 (amendment)	21-APR-2023	CDRH (consult device review)
SD 39 (amendment)	26-APR-2023	Follow-up information for 16-MAR-2023 amendment for Manufacturing

QUALITY ASSESSMENT TEAM

Discipline	Primary Assessment	Secondary Assessment
Drug Substance	Sharon Kelly	Lawrence Perez



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Product	Xin Feng	Craig M. Bertha
Manufacturing	Quamrul Majumder	Christine Falabella
Microbiology	Catherine Gilbert	Yan Zheng
Biopharmaceutics	N/A	
Regulatory Business Process Manager	Anika Lalmansingh	
Application Technical Lead	Craig M. Bertha	
Laboratory (OTR)	N/A	
Environmental	N/A	



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Drug Product

Labeling

Manufacturing

Microbiology



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QUALITY ASSESSMENT DATA SHEET

1. RELATED/SUPPORTING DOCUMENTS

A. DMFs:

DMF #	Type	Holder	Item Referenced	Status	Date Review Completed	Comments
(b) (4)	3	(b) (4)	(b) (4)	Adequate	2/27/2023	Alternate source from DMF (b) (4)
	4			Adequate	11/5/2019	To support a nasal spray product
	4			N/A		For non-clinical review
	2			Adequate	5/21/2020	For injection drug product
	4			Adequate	9/4/2019	To support a nasal spray product
	3			Adequate	8/14/2015	Same actuator and container holder used for other approved nasal spray products
	3					Supporting DMF for DMF (b) (4)
	3			Adequate	1/13/2022	
	3			Adequate	3/7/2017	
	3			N/A		Sufficient information in NDA; Vial used for another approved nasal spray with the (b) (4)

B. OTHER DOCUMENTS: IND, RLD, RS, Approved NDA

Document	Application Number	Description



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IND	139091	ARS Pharmaceutical's IND supporting NDA 214697
NDA	204200	Reference drug from Par Sterile Products (Adrenalin Injection)

2. CONSULTS

Discipline	Status	Recommendation	Date	Assessor
Biostatistics	N/A			
Pharmacology/Toxicology	N/A			
CDRH – device consult	Final	Inadequate	5/11/2023	Porsche Bennett
Clinical	N/A			
Other	N/A			



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NDA Executive Summary

1. Application/Product Information

NDA Number.	214697
Applicant Name	ARS Pharmaceuticals, Inc.
Drug Product Name	L-Epinephrine Nasal Spray
Dosage Form.	Nasal spray
Proposed Strength(s)	2 mg (as base) per spray
Route of Administration	Nasal inhalation
Maximum Daily Dose	4 mg
Rx/OTC Dispensed	Rx
Proposed Indication	Immediate and emergency first-line treatment of allergic reactions (Type I) including anaphylaxis in Adults and Children ≥30 kg (66 lbs.)
Drug Product Description	L-Epinephrine is formulated as a nasal spray (solution), which includes a non-compendial (b) (4) (Aegis' Intravail A3® which is a water soluble nonionic detergent n-dodecyl-β-D-maltoside or DDM), (b) (4) (sodium metabisulfite), (b) (4) (disodium edetate), and other common excipients used in nasal sprays. All excipients, with the exception of DDM, are of USP/NF grade. The drug is not an NME and it is chiral, (b) (4). Note that the concentration of sodium metabisulfite in the formulation is (b) (4) than is typical for epinephrine injection products, and comparative accelerated stability data for the formulation as compared to two approved injection products shows that the nasal spray formulation shows significantly (b) (4)



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	(b) (4) The product is indicated for the treatment of allergic reactions and the dose is 2 or 4 mg. Each spray delivered from the device is targeted to contain 2 mg of epinephrine in 100 mcL of formulation. Epinephrine (b) (4) obtained from (b) (4) (DMF (b) (4)) has been found to be adequate for an injection drug product. Manufacturing is done (b) (4) (b) (4) The formulation uses a (b) (4) of epinephrine and the product has a 25 mcL overfill to assure 100 mcL can be delivered (note that (b) (4) (b) (4) for approved epinephrine injection products range from (b) (4) %). The formulation is aqueous-based, (b) (4) There is a



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	(b) (4) The applicant includes information and data for three registration batches (210928, 210929, and 210930), the first of which was also a clinical batch. Note that executed batch records have been provided for the registration batches. A key issue for solutions of epinephrine is chemical stability and shelf-life. Twelve months of long term (25°C/60%RH) stability data are provided and the applicant indicates these support a 24 month shelf-life. There are also 24 months of long term stability data provided for three batches of a 1 mg strength product (b) (4) (b) (4) (b) (4) (b) (4) However, as (b) (4) noted above, stability data also show (b) (4) (b) (4)		
Co-packaged product information	N/A		
Device information:	Refer to P.7 and DMFs (b) (4) (b) (4)		
Storage Temperature/ Conditions	Store below 77°F (25°C). Excursions permitted up to 122°F (50°C). Do not freeze.		
Review Team	Discipline	Primary	Secondary
	<i>Drug Substance</i>	Sharon Kelly	Lawrence Perez
	<i>Drug Product/ Labeling</i>	Xin Feng	Craig M. Bertha
	<i>Manufacturing</i>	Quamrul Majumder	Christine Falabella
	<i>Biopharmaceutics</i>	N/A	N/A



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	<i>Microbiology</i>	Catherine Gilbert	Yan Zheng
	<i>Other (specify):</i>	N/A	
	<i>RBPM</i>	Anika Lalmansingh	
	<i>ATL</i>	Craig M. Bertha	
Consults	CDRH was consulted to assess the nasal spray device as the product indication is for treatment of an emergent medical condition.		

2. Final Overall Recommendation - Inadequate

3. Basis for Recommendation:

a. Summary of Rationale for Recommendation:

The drug substance, manufacturing, and microbiology review teams are recommending that the application be approved. However, the drug product team recommends a complete response as the evaluation of the product stability data revealed that there were (b) (4) (b) (4) particulates in some of the stability samples. The presence of this particulate matter is thought to be due to the (b) (4)

(b) (4)

Although the applicant has claimed that the particulate matter does not interfere or negatively impact the product performance, they have not addressed the potential impact on the spray pattern, plume geometry of the spray, nor have they addressed the potential of these particulates to clog the cannula of the device. (b) (4)

(b) (4)

(b) (4) in some of the stability samples, the formulation/device combination is not optimal and the applicant should take adequate corrective measures to address this quality deficiency.

Also of note, the initial application included a comparability protocol to change the (b) (4) (b) (4). The applicant claimed that (b) (4)

1 (b) (4)



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(b) (4)
However, the biopharmaceutics team has indicated that such a change would result in a product that was **not** pharmaceutically equivalent to the clinical product. Thus, upon Agency request, the applicant removed the protocol from the application.

CDRH was consulted for evaluation of the nasal spray device and the review team concluded that there are both major and minor deficiencies that the applicant should address prior to approval (refer to separate consult review).

b. Is the overall recommendation in agreement with the individual discipline recommendations? Yes and No²

Recommendation by Subdiscipline:

- Drug Substance** - Adequate
- Drug Product** - Inadequate
- Quality Labeling** - Inadequate
- Manufacturing** - Adequate
- Biopharmaceutics** - N/A
- Microbiology** - Adequate

Environmental Assessment: Categorical Exclusion - Adequate
QPA for EA(s): No

4. Life-Cycle Considerations

Established Conditions per ICH Q12: No

Comments: N/A

Comparability Protocols (PACMP): Yes

Comments: Applicant has withdrawn the comparability protocol as per the 01-JAN-2023 amendment.

Additional Lifecycle Comments:

N/A

² The drug substance, microbiology, manufacturing/facilities sub-disciplines have concluded that these sections of the application are adequate, although the drug product section is inadequate in terms of quality. All aspects (with the possible exception of minor labeling issues) are required to be adequate in order to deem the whole quality section of the application to be adequate and recommend approval action.



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5. List of Deficiencies for Complete Response

1. Overall Quality Deficiencies (*Deficiencies that affect multiple sub-disciplines*)

N/A

2. Drug Substance Deficiencies

N/A

3. Drug Product Deficiencies

Your amendment dated 05-April-2023 provided an explanation for the (b) (4) and (b) (4) of particulate matter observed in stability samples over time, (b) (4). However, you did not address the impact of the (b) (4) of particulate matter on the drug delivery characteristics (e.g., spray pattern, plume geometry) and the potential for the particulates to clog the cannula.

In your composition table in P.1. you indicate that the (b) (4) (b) (4)

Take corrective action(s) to mitigate the particulate formation (b) (4)

Subsequently, provide stability data (as per ICH Q1A) for the modified product demonstrating that the corrective action(s) have improved the product stability. In addition, revisit your product specification parameters for stability testing and the associated acceptance criteria and revise these appropriately to reflect realized improvements in the stability profile.



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4. Labeling Deficiencies

To be address in the next review cycle

5. Manufacturing Deficiencies

N/A

6. Biopharmaceutics Deficiencies

N/A

7. Microbiology Deficiencies

N/A

8. Other Deficiencies (*Specify discipline, such as Environmental*)

Refer to consult review from CDRH for additional CR deficiencies.

Application Technical Lead Name and Date:
Craig M. Bertha, 5/11/2023



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Final Risk Assessment for L-Epinephrine Nasal Spray

DP attribute/ CQA	Factors that may impact the CQA	O ³	S ^{1,4}	D ¹	Initial RA FMECA RPN #	Comment & considerations for risk assessment	Final RA	Lifecycle considerations
Appearance	Defects in the device constituent part components	1	3	1	3	(b) (4)		
pH	- buffer capacity of formulation - formulation component degradation	4	3	2	24			
Assay & Related Substances	- purity of API - degradation of API as formulated - compatibility of API with formulation and device components	2	3	2	12			
Sodium metabisulfite assay	- incorrect amount of sodium metabisulfite (SMB) formulated (b) (4)	2	3	1	6			
Uniformity of dosage units & dose delivered	- assay variability - assay drop on stability - pump delivery variability due to device defect	2	3	3	18			

³ O = Probability of Occurrence; S = Severity of Effect; D = Detectability

⁴ Severity of effect can only be estimated; input from clinical, clinical pharmacology, and pharmacology/toxicology team would be necessary for more accurate assessment of clinical impact of failures of product CQAs (thus a median value of “3” will be used throughout)



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Final Risk Assessment for *L*-Epinephrine Nasal Spray

	lower than target fill and/or leakage								
Droplet Size Distribution (DSD)	spray unit variability or defects	2	3	2	12				
Pump delivery	- pump delivery variability due to device defect - lower than target fill and/or leakage	1	3	1	3				
Spray Pattern	- spray unit defect - particulate matter alteration of spray pattern	4	3	4	48			48	The applicant has not provided sufficient information/data to mitigate the risk for this CQA
Particulate matter	- particulate matter sourced from formulation components - particulate matter introduced from manufacturing equipment - particulate matter introduced via the vial or stopper - particulate matter formed by degradation of API	5	3	4	60			60	The applicant has not provided sufficient information/data to mitigate the risk for this CQA
Microbial limits test	(b) (4)	2	3	2	12				

CHAPTER IV: LABELING

For more details about the items in this template, please see [Chapter IV \(Labeling\) of the NDA IQA Guide](#)

1.0 PRESCRIBING INFORMATION

Assessment of Product Quality Related Aspects of the Prescribing Information:

1.1 HIGHLIGHTS OF PRESCRIBING INFORMATION



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Product Title in Highlights		
Established name(s) ¹	Adequate	epinephrine nasal spray The proprietary name should appear in upper case in the highlight limitation information.

¹ Established name = [Drug] [Route of Administration] [Dosage Form]

Route(s) of administration	Adequate	Nasal inhalation
Dosage Forms and Strengths Heading in Highlights		
Summary of the dosage form(s) and strength(s) in metric system	Inadequate	Revise to include the strength on a per actuation basis, i.e., “Nasal spray: 2 mg of epinephrine in 0.1 mL of solution per actuation”
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state “functionally scored”.	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
If the drug product contains an active ingredient that is a salt, clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (e.g., Tablets: 10 mg of drug-x hydrochloride).	N/A	

1.2 FULL PRESCRIBING INFORMATION

1.2.1 Section 2 (DOSAGE AND ADMINISTRATION)

(b) (4)



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE AND ADMINISTRATION section		
Special instructions for product preparation (e.g., reconstitution and resulting concentration, dilution, compatible diluents, storage conditions needed to maintain the stability of	N/A	

the reconstituted or diluted product)		
Important administration instructions supported by product quality information (e.g., do not crush or chew extended-release tablets, instructions for mixing with food)	N/A	
For parenteral products: include statement: <i>“Parenteral drug products must be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit”</i>	N/A	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 11).	N/A	
For radioactive products, include radiation dosimetry for the patient and healthcare practitioner(s) who administer the drug	N/A	
For hazardous products, include the statement <i>“DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures.x”</i> with x numerical citation to <i>“OSHA Hazardous Drugs”</i> .	N/A	

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DOSAGE FORMS AND STRENGTHS section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Inadequate	Revise both DOSAGE FORMS AND STRENGTHS sections such that the strength is given in terms of the amount of drug delivered per actuation, i.e., " <i>neffy</i> is supplied as a single-dose nasal spray that delivers 2 mg of epinephrine in 0.1 mL solution per actuation."
If the active ingredient is a salt, apply the USP Salt Policy per FDA Guidance. Clearly state whether the strength is based on the active moiety (e.g., Tablets: 10 mg of drug-x) or active ingredient (Tablets: 10 mg of drug-x hydrochloride).	N/A	
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package type terms include pharmacy bulk package and imaging bulk package.	N/A	

Section 11 (DESCRIPTION)

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
DESCRIPTION section		
Proprietary and established name(s)	Adequate	
Dosage form(s) and route(s) of administration	Adequate	
If the active ingredient is a salt, apply the USP Salt Policy and include the equivalency statement per Salt Guidance and MAPP . For example: "TRADENAME contains 100 mg of drug-x (equivalent to 123.7 mg of drug-x hydrochloride)"	N/A	
List names of all inactive ingredients. Use USP/NF names in alphabetical order. Avoid brand names.	Inadequate	Revise the list of inactive ingredients in the DESCRIPTION section to list the ingredients alphabetically.
For parenteral injectable dosage forms, include the name and quantities of all inactive ingredients. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Sterility statement (if applicable)	N/A	
Pharmacological/Therapeutic class	Adequate	
Chemical name, structural formula, molecular weight	Inadequate	Revise the DESCRIPTION section to include the molecular weight of epinephrine.
If radioactive, statement of important nuclear characteristics.	N/A	
Other important chemical or physical properties (such as pKa or pH)	Adequate	

2. Section 11 (DESCRIPTION) Continued

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
For oral prescription drug products, include gluten statement (if applicable)	N/A	
Remove statements that may be misleading or promotional (e.g., "synthesized and developed by Drug Company X," "structurally unique molecular entity")	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled. Note the labeling requirement may be applicable to another section of the PI (e.g., Section 2).	N/A	

1 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
HOW SUPPLIED/STORAGE AND HANDLING section		
Available dosage form(s)	Adequate	
Strength(s) in metric system	Adequate	
Available units (e.g., bottles of 100 tablets)	Adequate	
Identification of dosage forms (e.g., shape, color, coating, scoring, imprinting, and color and clarity of the solution, when applicable); Include NDC(s)	Adequate	
Assess if the tablet is scored. If product meets guidelines and criteria for a scored tablet, state "functionally scored"	N/A	
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package.	N/A	
Special handling about the supplied product (e.g., protect from light, refrigerate). If there is a statement to "Dispense in original container," provide reason why (e.g., to protect from light or moisture, to maintain stability, etc.). For hazardous drugs, state "DRUG X is a hazardous drug. Follow applicable special handling and disposal procedures. ^x " with x numerical citation to "OSHA Hazardous Drugs."	Adequate	

Section 16 (HOW SUPPLIED/STORAGE AND HANDLING) (Continued)

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Storage conditions. Where applicable, use USP storage range rather than storage at a single temperature.	Inadequate	Revise the storage conditions in the HOW SUPPLIED/STORAGE AND HANDLING section to meet the format requirements of USP <659>, i.e., "Store at 20°C to 25°C (68°F - 77°F), with excursions permitted up to 50°C (122°F) [see USP Controlled Room Temperature]" Revise the storage conditions in the HOW SUPPLIED/STORAGE AND HANDLING section to indicate that freezing will impact drug delivery, i.e., "If <i>neffy</i> freezes, it will not deliver drug." Revise the storage conditions in the HOW SUPPLIED/STORAGE AND HANDLING section to indicate that the product should be stored in its original package prior to use, i.e., "Store <i>neffy</i> in the blister package and cartons provided."
Latex: If product does not contain latex and manufacturing of product and container did not include use of natural rubber latex or synthetic derivatives of	N/A	

natural rubber latex, state: <i>“Not made with natural rubber latex. Avoid statements such as “latex-free.”</i>		
Include information about child-resistant packaging	N/A	

1.2.5 Other Sections of Labeling

There may be other sections of labeling that contain product-quality related information. For example, there are specific required/recommended warnings for certain inactive ingredients [e.g., aspartame, aluminum in large and small volume parenterals, sulfites, FD&C Yellow Number 5 (tartrazine), and benzyl alcohol]. Please notify the prescription drug review division if the product contains any of these inactive ingredients.

Please include your comments about other sections of labeling if they contain product quality information.



Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments (If an item is Inadequate, provide more details on the issues, as appropriate)
Manufacturing Information After Section 17		
Name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer	Inadequate	The section 17 will be edited to include the name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.

2.0 PATIENT LABELING

Assessment of Product Quality Related Aspects of Patient Labeling (e.g., Medication Guides, Instructions for Use, Patient Information):

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ²	Adequate	
Special preparation instructions (if applicable)	N/A	
Storage and handling information (if applicable)	Inadequate	the storage conditions should be edited to meet the requirements of USP <659> (e.g., Store at room temperature (see USP Controlled Room Temperature, between 20°C to 25°C (68 - 77°F, with excursions permitted up to 50°C or 122°F).)
If the product contains a desiccant, ensure the desiccant has a warning (e.g., "Do not eat.") and the size and shape of the desiccant differs from the dosage form.	N/A	
Active ingredient(s) (if applicable)	N/A	
Alphabetical listing of inactive ingredients (if applicable)	N/A	
Name and location of business (street address, city, state, and zip code) of manufacturer, distributor, and/or packer	Inadequate	Revise section 17 to include the name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.

Any deficiencies should be listed at the end in the "ITEMS FOR ADDITIONAL ASSESSMENT."

3.0 CONTAINER AND CARTON LABELING

3.1 Container Labels

Draft Container Label – Blister:

---

² Established name = [Drug] [Route of Administration] [Dosage Form]

Item	Items in Proposed Labeling (choose "Adequate", "Inadequate", or "N/A")	Assessor's Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Established name ³ , (font size and prominence)	Adequate	
Strength(s) in metric system	Adequate	
Route(s) of administration	Adequate	
If the active ingredient is a salt, include the equivalency statement per Salt Guidance and MAPP .	N/A	
Net contents (e.g., tablet count, volume of liquid)	Adequate	
"Rx only" displayed on the principal display	Adequate	
NDC	Adequate	
Lot number and expiration date	Adequate	
Storage conditions. If applicable, include a space on the carton labeling for the user to write the new beyond-use-date (BUD).	Inadequate	Revise the storage conditions in the carton label storage and handling information to be consistent with USP <659>, i.e., "Store at 20°C to 25°C (68°F - 77°F), with excursions permitted up to 50°C (122°F) [see USP Controlled Room Temperature]"
For injectable drug products for parental administration, use appropriate package type term (e.g., single-dose, multiple-dose, single-patient-use). Other package terms include pharmacy bulk package and imaging bulk package, and these products require a "Not for direct infusion" statement.	N/A	
For parenteral injectable dosage forms, include the name and quantities of all active and inactive ingredients in alphabetical order. For ingredients added to adjust the pH or make isotonic, include the name and statement of effect.	N/A	
If alcohol is present, must provide the amount of alcohol in terms of percent volume of absolute alcohol	N/A	
Linear Bar code	Adequate	

Item	Items in Proposed Labeling (choose “Adequate”, “Inadequate”, or “N/A”)	Assessor’s Comments about Carton Labeling (If an item is Inadequate, provide more details on the issues, as appropriate)
Name of manufacturer/distributor /packer	Adequate	
If there is a Medication Guide, must include a statement about dispensing a Medication Guide to each patient.	N/A	
No text on Ferrule and Cap overseal, unless a cautionary statement is required.	Adequate	
If there is a USP monograph for the drug product and it contains a labeling requirement, ensure the labeling requirement is fulfilled.	Adequate	
When a drug product differs from the relevant USP standard of strength, quality, or purity, as determined by the application of the tests, procedures, and acceptance criteria set forth in the relevant compendium, its difference shall be plainly stated on its label.	N/A	
And others, if space is available.	N/A	

Assessment of Carton and Container Labeling: *Inadequate*}

Any deficiencies should be listed at the end in the “ITEMS FOR ADDITIONAL ASSESSMENT.”

3. ITEMS FOR ADDITIONAL ASSESSMENT

Assess consistency of product-quality information in prescription drug labeling (PI, c/c labeling, and FDA-approved patient labeling). See [Carton/Container Labeling Specific Resources](#) for a presentation about inappropriate inconsistencies of product quality information between labeling. If there are inappropriate inconsistencies between the labeling (e.g., established name, strength(s), package type term, discard statement, identifying characteristics, storage, reconstitution/dilution instructions), please list these as deficiencies in this section.

³ Established name = [Drug] [Route of Administration] [Dosage Form]

Overall Assessment and Recommendation:

Some sections of the PI need to be edited to meet the appropriate USP and CFR requirements.

1. Revise the proprietary name in the Highlights Limitation Statement (21 CFR 201.57(a)(1)) such that it appears both times in UPPERCASE letters, i.e.,

“These highlights do not include all the information needed to use NEFFY safely and effectively. See full prescribing information for NEFFY.”
2. Revise both DOSAGE FORMS AND STRENGTHS sections such that the strength is given in terms of the amount of drug delivered per actuation, i.e.,

“**neffy** is supplied as a single-dose nasal spray that delivers 2 mg of epinephrine in 0.1 mL solution per actuation.”
3. Revise the list of inactive ingredients in the DESCRIPTION section to list the ingredients alphabetically.
4. Revise the DESCRIPTION section to include the molecular weight of epinephrine.
5. Revise the storage conditions in the HOW SUPPLIED/STORAGE AND HANDLING section to meet the format requirements of USP <659>, i.e.,

“Store at 20°C to 25°C (68°F - 77°F), with excursions permitted up to 50°C (122°F) [see USP Controlled Room Temperature]”
6. Revise the storage conditions in the HOW SUPPLIED/STORAGE AND HANDLING section to indicate that freezing will impact drug delivery, i.e.,

“If **neffy** freezes, it will not deliver drug.”
7. Revise the storage conditions in the HOW SUPPLIED/STORAGE AND HANDLING section to indicate that the product should be stored in its original package prior to use, i.e.,

“Store **neffy** in the blister package and cartons provided.”
8. Revise section 17 to include the name and location of business (street address, city, state, and zip code) of the manufacturer, distributor, and/or packer.
9. Revise the storage conditions in the carton label storage and handling information to be consistent with USP <659>, i.e.,

“Store at 20°C to 25°C (68°F - 77°F), with excursions permitted up to 50°C (122°F) [see USP Controlled Room Temperature]”

Primary Labeling Assessor Name and Date: Xin Feng, 25-April-2023

Secondary Assessor Name and Date (and Secondary Summary, as needed): Craig Bertha, 25-April-2023



Xin
Feng

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Craig
Bertha

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CHAPTER VII: MICROBIOLOGY

[IQA NDA Assessment Guide Reference](#)

Product Information	
NDA Number	214697
Assessment Cycle Number	01
Drug Product Name/ Strength	neffy (Epinephrine nasal spray), (b) (4) mg
Route of Administration	Intranasal
Applicant Name	ARS Pharmaceuticals, Inc.
Therapeutic Classification/ OND Division	Division of Pulmonology, Allergy, and Critical Care (DPACC)
Manufacturing Site	(b) (4)
Method of Sterilization	Non-sterile nasal spray

Assessment Recommendation: Adequate

Assessment Summary:

The drug product is a non-sterile nasal spray. (b) (4)
(b) (4)

List Submissions being assessed (table):

Document(s) Assessed	Date Received
Original (0001)	08/19/2022
Labeling IR (0003)	09/09/2022
Expiry amendment (0008)	09/30/2022
Quality IR Response (0014)	10/25/2022
Quality IR Response (0020)	01/13/2023
IR Response (0021)	02/07/2023
IR Response (0025)	02/21/2023

Highlight Key Issues from Last Cycle and Their Resolution: N/A

Remarks: This 505(b)(2) is an eCTD submission. The applicant requested fast track status based on unmet medical need, however on 10/21/2022 it was given a standard review clock.

Concise Description of Outstanding Issues

(List bullet points with key information and update as needed): N/A

Supporting Documents: N/A

P.1 DESCRIPTION OF THE COMPOSITION OF THE DRUG PRODUCT

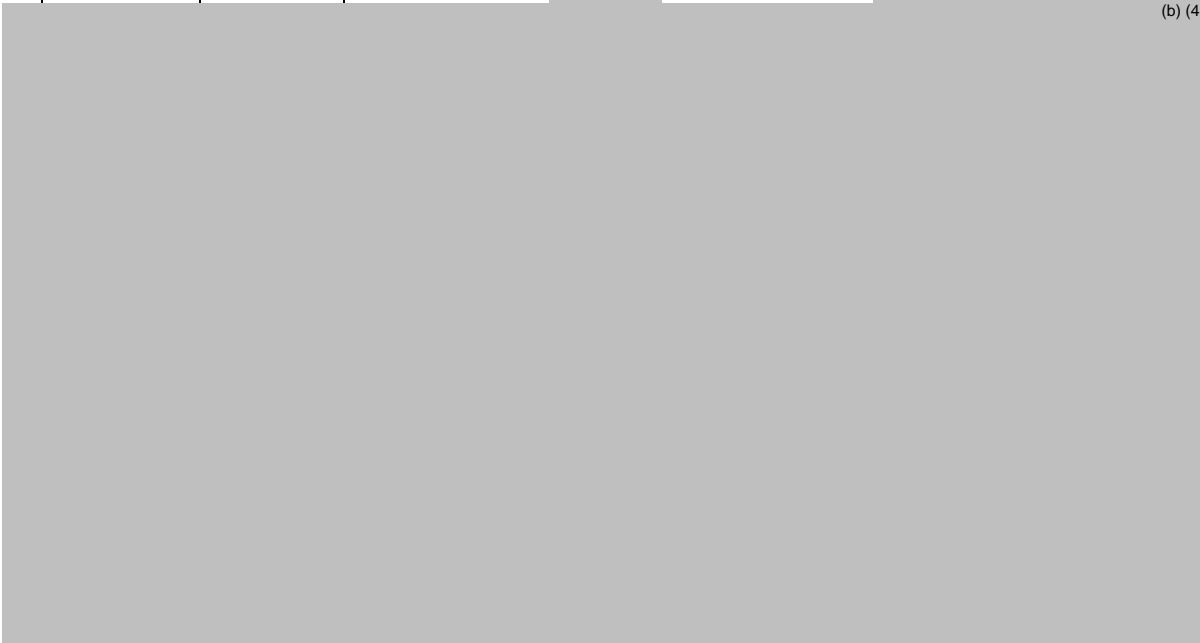
- **Description of drug product** – neffy (Epinephrine nasal spray), ^(b)₍₄₎ mg, is a non-sterile, ^(b)₍₄₎ solution indicated for the immediate and emergency treatment of Type I allergic reactions. It is administered via intranasal spray.

- **Drug product composition** –

Ingredient	Content per mL	Function
L-epinephrine, USP/Ph Eur	^(b) ₍₄₎	API
Dodecyl maltoside (DDM), in house standard	2.75 mg	^(b) ₍₄₎
Benzalkonium Chloride, USP/NF/Ph Eur	^(b) ₍₄₎	^(b) ₍₄₎
Sodium Chloride, USP/Ph Eur		^(b) ₍₄₎
Disodium Edetate, USP/Ph Eur		^(b) ₍₄₎
Sodium metabisulfite, USP/NF/Ph Eur		^(b) ₍₄₎
WFI, USP/Ph Eur		^(b) ₍₄₎
HCl, USP/NF/Ph Eur		pH adjustment
NaOH, USP/NF/Ph Eur		pH adjustment

- **Description of container closure system** –

Component	Packaging	Description (Gland material code)	Manufacturer
Vial	Primary	400 µL Type ^(b) ₍₄₎ clear glass vial	^(b) ₍₄₎
Stopper	Primary	^(b) ₍₄₎ rubber stopper	^(b) ₍₄₎
Vial holder	Secondary	Unit Dose Sprayer (UDS)	^(b) ₍₄₎
Spray pump	Secondary	Single use blister pack consisting of ^(b) ₍₄₎	^(b) ₍₄₎



not applicable to the quality microbiology review. As the product is single-dose, the presence or lack of a preservative in the formulation does not impact the microbiological quality, therefore the (b) (4) (b) (4) will not be assessed in this review.

Assessment: The applicant has adequately described the drug product composition and the container closure system designed to maintain product microbiological quality.

Adequate

P.2 PHARMACEUTICAL DEVELOPMENT

P.2.5 MICROBIOLOGICAL ATTRIBUTES

(b) (4)



Catherine
Gilbert

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Yan
Zheng

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/s/

CRAIG M BERTHA
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