CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

209260Orig1s000

PRODUCT QUALITY REVIEW(S)

MEMORANDUM

U.S. FOOD & DRUG ADMINISTRATION

DATE: 26 January, 2018

TO: File: NDA 209260

FROM: Mohan Sapru, Ph.D.
Application Technical Lead (ATL)
Office of New Drug Products (ONDP)
Office of Product Quality (OPQ)/CDER

SUBJECT: Integrated Quality Review Update Memo: NDA 209260; Atropine Sulfate Injection, USP

Introduction: The Integrated Quality Review for NDA 209260, with approval recommendation from quality /CMC perspective, was uploaded to Panorama on January 3, 2018. Subsequently, updated information was received from the Applicant to address emerging issues related to NDA 505(b)(2) designation (Biopharmaceutics aspects) and bioburden acceptance limits (Microbiology Aspects), which are briefly discussed below.

Biopharmaceutics Aspects: This 505(b)(2) NDA for Atropine Sulfate Injection (0.4 mg/mL) multi-dose vial has relied for approval, in part, on Agency's findings of efficacy and safety for the Listed Drug, Ansyr (Atropine Sulfate) Injection (0.1 mg/mL; NDA 21146). The Biopharmaceutics review team focused on the evaluation of the Applicant's biowaiver request and supporting justification. The review team concluded that the Applicant has provided adequate scientific justification to establish the bridge between its proposed product and Ansyr, thereby, permitting reliance on FDA's findings for that Listed Drug, as per 21 CFR 320.24(b)(6). In response to Agency's information request (dated January 23, 2018), the Applicant on January 24, 2018 submitted a statement of reliance on two additional listed drugs (Bacteriostatic Sodium Chloride 0.9% in Plastic Container ([NDA 018800) and Bacteriostatic Water for Injection in Plastic Container (NDA 018802), which also contain 9 mg/mL benzyl alcohol. The Agency concluded that reliance on the findings of safety for these two listed drugs is appropriate and adequate to support the safety of the proposed benzyl alcohol content of Atropine Sulfate Injection (0.4 mg/mL) in adults. From a Biopharmaceutics perspective, NDA 209260 for Atropine Sulfate Injection (0.4 mg/mL) has been recommended for approval (for details, please refer to revised Biopharmaceutics review by Drs. G. Geiser and T. Wu, dated January 25, 2018).

Microbiology Aspects: Due to the high doses of drug product needed to treat organophosphate, carbamate or muscarinic mushroom poisoning, there was concern regarding the exposure of patients to high levels of endotoxins that could exceed (b) (4) times the USP chapter < 85 > limit of 5 EU/kg of body weight. Based on an amendment (dated January 9, 2018), the Applicant proposed to reduce the endotoxins acceptance limits from (b) (4) EU/mg to (b) (4) EU/mg. The microbiology review team concluded that the endotoxin level-related risk associated with extraordinarily large doses of drug product is acceptable given the severity of the medical condition necessitating that dose. USP chapter <85> limits on endotoxins exposure are compliant as long as the total maximum dose does not exceed 1.65 mg/kg/hr. (for details, please refer to Microbiology memo by Drs. V. Huse and S. Langille, dated January 26, 2018).

Revised Drug Product Specification:

Test	Acceptance Criteria	Test Method [1]
Visual Inspection		USP <1>
1. Description	1. Clear and colorless solution	10-08-05-6005
2. Clarity	2. Clear	
3. Degree of coloration	(b) (4)	
4. Visible particles	4. Essentially free from visible particles	
pH	3.0 to 3.8	USP <791>
Osmolality	(b) (4)	USP <785>
Extractable volume	(b) (4)	USP <1>
Identification		FRD127
1. Retention time	1. The retention time of the major peak in the chromatogram of the assay preparation corresponds to the chromatogram of the standard preparation as obtained in the assay and ratio (R) of the retention times is: (b) (4)	
2. UV	2. Corresponds to UV spectrum of reference solution	
Assay		
Atropine sulfate monohydrate Label claim 0.4 mg/mL	(b) (4)% to (b) (4)% of label claim	FRD127
Benzyl alcohol Label claim 9 mg/mL	(b) (4)% to (b) (4)% of label claim	FRD127

Revised Drug Product Specification Evaluation: The revised drug product specification, which includes reduction of the endotoxins acceptance limits from (b) (4) EU/mg to (b) (4) EU/mg, is acceptable.

Conclusion: Consistent with the quality assessment as per Integrated Quality Review (dated January 3, 2018), NDA 209260 Atropine Sulfate Injection, USP, is recommended for approval from quality/CMC perspective.

Mohan K. Sapru -S

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NDA 209260; Atropine Sulfate Injection, USP

Integrated Quality Review

Recommendation: Approval

Drug Name/Dosage Form	Atropine Sulfate Injection, USP
Strength	0.4 mg/mL
Route of Administration	Intravenous (IV), intramuscular (IM), subcutaneous (SC) or endotracheal
Rx/OTC Dispensed	Rx
Applicant	Fresenius Kabi, USA, LLC.
Submissions (s) Reviewed	NDA 209260, all the submitted CMC amendments, and Type II DMF # (b) (4)

Quality Review Team

DISCIPLINE	REVIEWER	BRANCH/DIVISION
Drug Substance	Ramsharan Mittal	ONDP/DNDPI/NDBII
Drug Product/Environmental Assessment (EA)	Thomas Wong	ONDP/DNDPI/NDPBI
Process	Ziyang Su	OPQ/OPF/DPAI/PABI
Facility	Rose Xu	OPF/DIA/IABI
Biopharmaceutics	Gerlie Gieser	ONDP/DB/BBI
Microbiology	Valerie A. Huse	OPQ/OPF/DMA/MABII
Regulatory Business Process Manager	Grafton Adams	OPRO DRBPMI/RBPMBI
Application Technical Lead	Mohan Sapru	ONDP/DNDPI/NDPBI

RELATED/SUPPORTING DOCUMENTS

Document	Application Number	Description
Type II DMF	# (b) (4)	The DMF was reviewed in the context of the current submission and found adequate.

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 209260 (Atropine Sulfate Injection, USP) is recommended for approval.

B. Recommendation on Post-Marketing Commitments (PMCs), Agreements, and/or Risk Management Steps, if Applicable

Not applicable.

II. Summary

The applicant, Fresenius Kabi USA LLC, has sought U.S. marketing approval for Atropine Sulfate Injection 0.4 mg/mL (20 mL multi-dose vial) for intramuscular (IM), intravenous (IV), subcutaneous (SC) or endotracheal administration; utilizing the 505(b)(2) regulatory pathway. The application relies for approval on FDA's findings of efficacy and safety for the Listed Drug, Ansyr® (Atropine Sulfate) Injection (0.1 mg/mL) in a single-use syringe [NDA 21146 held by Hospira]. In addition to strength, and presentation configuration, the proposed multi-dose injectable formulation is also different from the Listed Drug (LD), in terms of the presence of a preservative (benzyl alcohol, 9 mg/mL).The proposed Atropine Sulfate Injection is a muscarinic antagonist indicated for temporary blockade of severe or life threatening muscarinic effects. The product is manufactured using a (b) (4) process. The proposed control strategies for the drug substance and drug product, which include release specifications, and in-process controls are adequate to ensure product quality, including product sterility.

A. Drug Substance (Atropine Sulfate, USP) Quality Summary

The drug substance Atropine Sulfate, USP is chemically designated lα H, 5α H-Tropan-3-α-ol (±)-tropate (ester), sulfate (2:1) (salt) monohydrate, {(C17H23N03)2•H2S04•H20}, and is very soluble in water. Atropine, a naturally occurring belladonna alkaloid, is a racemic mixture of equal parts of d- and 1-hyocyamine, whose activity is due almost entirely to the levo isomer of the drug. The drug substance has been briefly described in the current NDA submission. The CMC details concerning the drug substance such as structural characterization, impurity profile, manufacturing, analytical method validations, container closure system and stability have been cross-referenced to Type II DMF # (b) (4), which was been reviewed in the context of this NDA submission and found to be adequate (for details, refer to DMF (b) (4) review by R. Mittal in Panorama). Based on information provided in this NDA, all critical quality attributes of Atropine Sulfate, USP drug substance are tested as per proposed release specification. The proposed specifications meet the current USP requirements and are adequate to control the identity, strength, quality, physical and chemical purity, and potency. Briefly, in accordance with the USP monograph, the assay limit is set at 98.0 % to 102.0 %. Assay is determined by the USP method. The limits for organic impurities such as tropic acid, 7-hydroxyhyoscyamine, scopolamine, 6-hydroxyhyoscyamine, hyoscyamine-related compound A, littorine, apoatropine, any individual unspecified impurity, and total impurities are in

compliance with the USP monograph. In order to control the total amount of tropic acid (a process impurity and a degradation product) in the finished product and ensure that the impurity does not exceed the finished product specification of NMT 0.2 % at release and NMT (b) (4) % over shelf life, the proposed acceptance criterion for tropic acid in the drug substance of NMT (b) (4) % is acceptable. Microbial bioburden and bacterial endotoxins are tested on release in accordance with USP <61> and USP <85>, respectively. The proposed a retest period of (b) (4) months is supported by stability data.

B. Drug Product Quality Summary

Atropine Sulfate Injection, USP is a sterile, nonpyrogenic isotonic solution of atropine sulfate in water for injection with sodium chloride sufficient to render the solution isotonic. Each mL contains atropine sulfate, 0.4 mg (equivalent to 0.33 mg of atropine); benzyl alcohol, 9 mg; sodium chloride 9 mg. All excipients used in the proposed product meet the requirements of the current USP/NF including the current USP<(b) (4)> for (b) (4). The inactive ingredients of the proposed drug product are the same as that of the listed drug with the exception of the addition of the preservative benzyl alcohol and sulfuric acid as the only pH adjuster to the proposed product formulation. These differences are considered irrelevant in the context of having a potential effect on the therapeutic equivalence or stability of the product. The excipient active compatibility studies have not revealed any incompatibilities. The preservative benzyl alcohol has been associated with serious adverse events and death ("gasping syndrome") in neonates. Although normal therapeutic doses of this product deliver amounts of benzyl alcohol that are substantially lower than those reported in association with the "gasping syndrome", the minimum amount of benzyl alcohol at which toxicity may occur is not known. The product labeling alerts that the practitioners administering this and other medications containing benzyl alcohol should consider the combined daily metabolic load of benzyl alcohol from all sources. Regarding product development, the applicant defined quality target product profile (QTPP) based on the USP monographs. The critical quality attributes (CQAs) have been identified based on QTPP, compendial requirements, physicochemical properties of the drug substance, and applicant's developmental studies. The identified QTPP and CQAs have been used as a basis for establishing the finished product specifications. Formulation studies have determined that the drug product is acceptable for (b) (4). The drug product specification includes testing all the identified CQAs. Given the the proposed product is a USP monograph product, the acceptance criteria for assay, pH and bacterial endotoxins test either conform to or are tighter than the USP monograph limits. All the analytical methods have been adequately validated. The justification for related substances specification is based on ICH guidelines Q3B(R2), 12-month ICH stability data from three exhibit batches and toxicology assessments. Antimicrobial effectiveness per USP <51> has been validated down to (b) (4) % of the benzyl alcohol label claim. Hence, a (b) (4) % label claim is justified to assure preservative effectiveness for release and during the shelf life of the product. Per amendment Seq. #008, the applicant indicated that that due to (b) (4); the revised extractable volume has been revised to NLT (b) (4) mL and NMT (b) (4) mL. Although the proposed upper limit of the extractable volume (b) (4) the USP <1151> recommended limit of 20.6 mL (for 20 ML vial), the (b) (4) amount of solution in the vial is not expected to have any meaningful effect on the stability of the drug product or the patient safety. Based on patient safety-relevant risk assessment, the proposed upper limit of NMT (b) (4) mL for the extractable volume is acceptable.

Manufacturing: The manufacturing process involves (b) (4) . In-process controls are adequate. Elemental impurity analysis results suggested no impurity reached a level higher than the permitted daily exposure (PDE). All tested elements have been found to be below (b) (4) of the PDE. (b) (4) The proposed control strategy that includes environmental controls, and in-process controls and specifications are adequate to ensure product quality .

Microbiological Aspects: Details concerning the manufacturing process and process controls, including building and facilities, overall manufacturing operations, (b) (4) and microbiological monitoring of the environment have been cross-referenced to Type V DMF (b) (4), which has been previously reviewed and found adequate. The applicant has adequately demonstrated the antimicrobial effectiveness for the proposed multiple dose drug product. Furthermore, the drug product release specification includes sterility (USP <71>), and bacterial endotoxins (USP <85>) testing. The stability data support the drug product's microbiological quality throughout the shelf life period.

Biopharmaceutics Aspects: The original submission included a request for biowaiver of *in vivo* bioavailability/bioequivalence (BA/BE) study for the proposed product under the provision of 21 CFR 320.22(b)(1)(I). However, the Agency notified the applicant that their biowaiver request per 21 CFR § 320.22(b)(1) is not applicable because the formulation of the proposed to-be-marketed drug product is not qualitatively and quantitatively the same as that of the Listed Drug. In addition to strength, and presentation/packaging configuration, the formulation of the proposed multi-dose injectable solution is different from the Listed Drug (LD) in terms of the presence of a preservative (benzyl alcohol, 9 mg/mL). Based on applicant's data and information available in the labeling of Ansyr®, it is evident that the test and the reference products are sterile, non-pyrogenic and clear/colorless solutions with comparable pH and osmolality. Thus, based on 21 CFR 320.24(b)(6), the applicant's request to waive the requirement to conduct an *in vivo* bioavailability or bioequivalence (BE) study, to bridge the proposed drug product to the Listed Drug, is granted. Specifically, proposal to market 0.4 mg/mL is unlikely to pose any safety and efficacy concerns because such strength falls between two strengths of already approved products, i.e., 0.1 mg/ml (e.g., Ansyr®) and 2 mg/0.7 ml (e.g., Abbvie's discontinued product; ANDA 71295). The higher strength drug product permits administration of reduced volumes of the injectable solution, which is an advantage over the Listed Drug, especially when administered via the intramuscular or subcutaneous routes. Because the drug product is introduced directly into systemic circulation, the addition of benzyl alcohol as preservative to the proposed product is not anticipated to alter the systemic bioavailability of atropine sulfate. The typical maximum cumulative amount (135 mg) of benzyl alcohol received from using the proposed drug product, as indicated in the labeling, is comparable to that received when Mesna [ANDA 90913] is administered as three intravenous bolus injections over an 8-hour period per day, i.e., 129.5 mg benzyl alcohol per day (388.6 mg to 647.7 mg for 3 to 5 days).

Container Closure System: Atropine Sulfate Injection will be filled into (b) (4) 20 mL glass vials, which are closed with (b) (4) rubber stoppers and capped with aluminum crimped flip-off seals. FK USA's proposed specification is consistent with the requirements to confirm that the vial and closure provide a complete seal to maintain sterility.

The results of physicochemical (USP <381>), extractables, biological/toxicity testing and stability studies adequately support the suitability of the commercial container closure system for its intended use. Since the pH of the solution is well below 7.0 and there is no complexing agent (EDTA) or no alkaline salt in the formulation, the risk of glass delamination is very low. Furthermore, (b) (4) vials are less susceptible to delamination as compared to (b) (4) vials. The results of extraction study on stoppers, performed per USP <1663>, are acceptable. The migration/leachable study, performed per USP <1664>, shows that there is no concern on leachable substances that could migrate into the drug product for the duration of the shelf-life of the product.

Expiration Date & Storage Conditions: The stability data support a shelf-life of 24 months when stored at controlled room temperature (20°C – 25°C; 68°F – 77°F). In addition, the in-use stability data support 24-hour use period after the initial puncture with storage at 20°C to 25°C. The container label includes the statement "after initial use, store between 20° to 25°C (68° to 77°F) and discard within 24 hours." The revised Sections 2.1 of Full Prescribing Information also includes the statement for discarding the unused portion within 24 hours.

C. Assessment of Manufacturing Facilities: The office of Process and Facilities has recommended overall approval for all the currently listed manufacturing facilities concerning this NDA.

III. Summary of Drug Product and Intended Use

Proprietary Name of the Drug Product	N/A
Non Proprietary Name of the Drug Product	Atropine Sulfate Injection, USP
Route of Administration	For intravenous administration, but may also be administered via subcutaneous, intramuscular or via an endotracheal tube
Strength(s)	0.4 mg/mL in 20 mL vial
Proposed Indication(s)	Atropine Sulfate Injection, USP is a muscarinic antagonist indicated for temporary blockade of severe or life threatening muscarinic effects

Maximum Daily Dose/ Duration of Treatment	For dosage and administration: • • (b) (4) . • • Adult dosage: - Antisialagogue or for antivagal effects: Initial single dose of 0.5 mg to 1 mg (b) (4) - Antidote for organophosphorus or muscarinic mushroom poisoning: Initial single dose of (b) (4) mg to (b) (4) mg (b) (4), repeated every (b) (4) to (b) (4) minutes. - (b) (4): 1 mg (b) (4), repeated every 3 to 5 minutes (b) (4) • Patients with (b) (4) • Disease: Limit the total dose to 0.03 mg/kg to 0.04 mg/kg. (2.4)
Alternative Methods of Administration	Intramuscular, subcutaneous or endotracheal

D. Biopharmaceutics Considerations

1. BCS Designation: The proposed drug product is an injectable solution, and the applicant has not request an official BCS designation,

2. Biowaivers/Biostudies: The applicant's biowaiver request was granted based on evaluation under 21 CFR 320.24(b)(6),

3. IVIVC: N/A.

E. Any Special Product Quality Labeling Recommendations: The expression of the proposed USP monograph product strength is in sulfate salt form. This is acceptable per the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances published in June 2015. Upon request, the applicant incorporated an atropine equivalence statement in the container labels and Prescribing Information sheet.

F. Environmental Assessment: Pursuant to 21 CFR § 25.31(a), the applicant has claimed a categorical exclusion from from the requirements of an environmental impact analysis statement. The applicant's claim for categorical exclusion is adequately justified.

G. Life Cycle Knowledge Information

Final Risk Assessment-

NDA 209260 (Atropine Sulfate Injection, USP)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Sterility	Formulation Container Closure Process Parameters Scale/Equipment/ Site	**H (High)**	Drug product release specification includes sterility (USP <71>) and bacterial endotoxin (USP <85>) testing. Container closure integrity studies indicate that the container closure system remains integral and therefore can maintain the sterility of the product.	Acceptable	Given that the product sterility is the high risk attribute, any proposed changes in (b) (4) manufacturing process or microbiological testing-related product specification may need to be carefully evaluated.
Endotoxin Pyrogen	Formulation Container Closure Process Parameters Scale/equipment/ Site	**M (Moderate)**	Bacterial endotoxin levels, with acceptance limits of NMT (b) (4) EU/mg, are tested on release	Acceptable	Any proposed changes concerning acceptance limits for endotoxin levels will need to be evaluated based on the maximum total daily dose.
Assay (API), Stability	Formulation Container Closure Raw Materials Process Parameters Scale/Equipment/ Site	L (Low)	Stability of the API and the drug product, and suitability of commercial container closure system have been well demonstrated. Manufacturing process is reasonably well-controlled.	Acceptable	
Uniformity of Dose – Fill/ deliverable Volume	Formulation Container Closure Process Parameters Scale/equipment/ site	L (Low))	Extractable volume is tested on release. Based on patient safety-relevant product risk assessment, the proposed upper limit of NMT (b) (4) mL for the extractable volume is acceptable.	Acceptable	

Final Risk Assessment (continued)

From Initial Risk Identification			Review Assessment		
Attribute/ CQA	**Factors Affecting CQA**	**Initial Risk Ranking**	**Risk Mitigation**	**Final Risk Evaluation**	**Comments**
Osmolality	Formulation Raw materials Process parameters Scale/equipment/ site	L (Low)	Osmolality is monitored per USP <785> on release	Acceptable	
pH (High)	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	pH is monitored per USP <791> on release with acceptance limits 3.0 to 3.8	Acceptable	
Particulate Matter	Formulation Container Closure Process Parameters Scale/equipment/ site	**M (Moderate)**	Particulate matter (A. ≥ 10 µm; B ≥ 25 µm) is monitored on release per USP <788>.	Acceptable	
Leachable Extracts	Formulation Container Closure Raw materials Process parameters Scale/equipment/ site	L (Low)	The maximum daily doses of all leachables are far below the relevant permitted daily exposure values (PDE). Therefore, the packaging system can be regarded as toxicologically safe for the use	Acceptable	There is some low risk of glass delamination on storage beyond the currently granted expiration period Therefore, during the lifecycle management of this product; the vials/product may need to be monitored for delamination and fine particles formation.
Appearance	Formulation Raw materials Process Parameters Scale/equipment/ site	L (Low)	The product appearance is routinely monitored on release.	Acceptable	

OVERALL ASSESSMENT AND SIGNATURES: EXECUTIVE SUMMARY

Application Technical Lead (ATL) Assessment and Signature:

From the chemistry, manufacturing, and controls (CMC)/quality perspective, NDA 209260 (Atropine Sulfate Injection, USP) is recommended for approval.

Mohan Sapru, M.S., Ph.D.
Application Technical Lead (ATL)
CMC Lead for Cardiovascular and Renal Products (Actg)
ONDP/DNDPI/NDPBI

Mohan K. Sapru -S

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LABELING

I. Package Insert (Seq. #0006)

1. *Highlights of Prescribing Information*

ATROPINE SULFATE injection, for intravenous, intramuscular, subcutaneous or endotracheal use
Initial U.S. Approval: 1960

---------- **DOSAGE FORMS AND STRENGTHS** ----------
8 mg per 20 mL (0.4 mg per mL) multiple dose glass vial (3)

Item	Information Provided in NDA
Product Title (Labeling Review Tool and 21 CFR 201.57(a)(2))	
Proprietary name and established name	There is no proprietary name. Established name is atropine sulfate.
Dosage form, route of administration	For intravenous injection but may be administered via subcutaneous, intramuscular or via an endotracheal tube.
Controlled drug substance symbol (if applicable)	N/A. Not a controlled substance.
Dosage Forms and Strengths (Labeling Review Tool and 21 CFR 201.57(a)(8))	
Summary of the dosage form and strength	Atropine Sulfate Injection, USP, 0.4 mg/mL

2. *Section 2 Dosage and Administration*

2.1 General Administration

(b) (4)

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12))	
Special instructions for product preparation (e.g., reconstitution, mixing with food, diluting with compatible diluents)	Discard unused portion within 24 hours.

3. *Section 3 Dosage Forms and Strengths*

3 DOSAGE FORMS AND STRENGTHS

Atropine Sulfate Injection, USP, 8 mg per 20 mL (0.4 mg per mL) multiple dose glass vial.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(4))	
Available dosage forms	Injection
Strengths: in metric system	0.4 mg/mL
Active moiety expression of strength with equivalence statement (if applicable)	Expressed in sulfate salt form. This is acceptable per the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances published in June 2015. Atropine equivalence statement is included in the container labels and Prescribing Information sheet.
A description of the identifying characteristics of the dosage forms, including shape, color, coating, scoring, and imprinting, when applicable.	There is no mention of appearance of the injection for identification purposes.

4. *Section 11 Description*

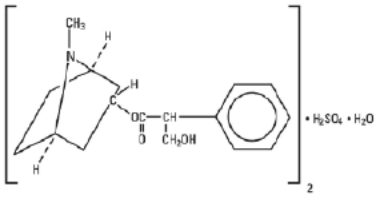
11 DESCRIPTION

Atropine Sulfate Injection, USP is a sterile, nonpyrogenic isotonic solution of atropine sulfate in water for injection with sodium chloride sufficient to render the solution isotonic. It is administered parenterally by subcutaneous, intramuscular or intravenous injection.

Each mL contains atropine sulfate, 0.4 mg [redacted] (b) (4) benzyl alcohol, 9 mg; sodium chloride 9 mg. May contain sulfuric acid for pH adjustment. pH 3.5 (3.0 to 3.8).

Sodium chloride added to render the solution isotonic for injection of the active ingredient is present in amounts insufficient to affect serum electrolyte balance of sodium (Na^+) and chloride (Cl^-) ions.

Atropine Sulfate, USP is chemically designated 1α H, 5α H-Tropan-3-α-ol (±)-tropate (ester), sulfate (2:1) (salt) monohydrate, $(C_{17}H_{23}NO_3)_2 \cdot H_2SO_4 \cdot H_2O$, colorless crystals or white crystalline powder very soluble in water. It has the following structural formula:



Atropine, a naturally occurring belladonna alkaloid, is a racemic mixture of equal parts of d- and l-hyocyamine, whose activity is due almost entirely to the levo isomer of the drug.

Sodium Chloride, USP is chemically designated NaCl, a white crystalline powder freely soluble in water.

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(12), 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv))	
Proprietary name and established name	There is no proprietary name. Established name is atropine sulfate.
Dosage form and route of administration	It is administered parenterally by subcutaneous, intramuscular or intravenous injection. The administer route via an endotracheal tube is not mentioned.
Active moiety expression of strength with equivalence statement (if applicable)	Expressed in sulfate salt form. This is acceptable per the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances published in June 2015. Atropine equivalence statement is included in the container labels and Prescribing Information sheet.
For parenteral, otic, and ophthalmic dosage forms, include the quantities of all inactive ingredients [see 21 CFR 201.100(b)(5)(iii), 21 CFR 314.94(a)(9)(iii), and 21 CFR 314.94(a)(9)(iv)], listed by USP/NF names (if any) in alphabetical order (USP <1091>)	Inactive ingredients with quantities are provided.
Statement of being sterile (if applicable)	Yes, it is stated.
Pharmacological/ therapeutic class	Muscarinic antagonist
Chemical name, structural formula, molecular weight	Provided.
If radioactive, statement of important nuclear characteristics.	Not applicable
Other important chemical or physical properties (such as pKa or pH)	See photocopy above

Section 16 How Supplied/Storage and Handling

16 HOW SUPPLIED/STORAGE AND HANDLING

Atropine Sulfate Injection, USP is supplied as follows:

(b) (4)	NDC No.	Strength	
	63323-580-20	8 mg per 20 mL (0.4 mg per mL)	20 mL multiple dose vial, packaged in 10.

Store at 20° to 25°C (68° to 77°F) [see USP Controlled Room Temperature]. After initial use, discard within 24 hours.

FRESENIUS KABI
Lake Zurich, IL 60047

www.fresenius-kabi.com/us

Item	Information Provided in NDA
(Refer to Labeling Review Tool and 21 CFR 201.57(c)(17))	
Strength of dosage form	Expressed in sulfate salt form. This is acceptable per the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances published in June 2015. Atropine equivalence statement is included in the container labels and Prescribing Information sheet.
Available units (e.g., bottles of 100 tablets)	20 mL multiple dose vial, packaged in 10
Identification of dosage forms, e.g., shape, color, coating, scoring, imprinting, NDC number	Seq. #000 and 006 - The visual description of the tablets should be provided in the How Supply section. The same NDC number for the carton container (contains 10 vials) is used. Need a separate NDC number. Seq.# 009 – A different NDC number has been assigned to the single vial container label but no revision has been made to the How Supply section.
Special handling (e.g., protect from light)	Not applicable
Storage conditions	Provided.
Manufacturer/distributor name (21 CFR 201.1(h)(5))	Provided.

Reviewer's Initial Assessment of Package: Inadequate.

- Need injection identification characteristics in both description and how supplied sections.
- Need NDC number for the individual vial.
- The (b) (4) in the How Supplied section should be removed to avoid confusion.

Reviewer's Final Assessment of Package: Inadequate.

- A separate NDC number, 63323-580-03, has been assigned to the single vial container label.

Deficiencies:

- The administer route via an endotracheal tube is not mentioned in the Dosage Form and Route of Administration section.
- Need injection identification characteristics in both Description and How Supplied sections.
- The (b) (4) in the How Supplied section should be removed to avoid confusion.
- The How Supply section needs to be revised to replace the old NDC number for the single vial container with the new NDC number.
- The NDC number, 63323-580-20, needs to be added to the multiple dose vial pack carton/tray container column.

All deficiencies will be resolved in the Labeling review meetings with the full multidisciplinary team.

II. Labels:

1. ***Container and Carton Labels*** (Seq. #0009)

   Vial label

(b) (4)

2. ***Carton Label*** (Seq. #0009)

Carton Label

1 Page(s) of Draft Labeling has been Withheld in Full as B4 (CCI/TS) immediately following this page

Item	Information provided in the container label	Information provided in the carton label(s)
Proprietary name, established name (font size and prominence (21 CFR 201.10(g)(2))	There is no proprietary name. Established name is atropine sulfate.	There is no proprietary name. Established name is atropine sulfate.
Dosage strength	Expressed in sulfate salt form. This is acceptable per the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances published in June 2015. Atropine equivalence statement is included in the container labels and Prescribing Information sheet.	Expressed in sulfate salt form. This is acceptable per the CDER Guidance for Industry – Naming of Drug Products Containing Salt Drug Substances published in June 2015. Atropine equivalence statement is included in the container labels and Prescribing Information sheet.
Net contents	Provided	Provided
"Rx only" displayed prominently on the main panel	Yes	Yes
NDC number (21 CFR 207.35(b)(3)(i))	Seq. #000 and 006 - The same NDC number for the carton container (contains 10 vials) is used. Need a separate NDC number. Seq.# 009 – A different NDC number has been assigned to the single vial container label.	Yes
Lot number and expiration date (21 CFR 201.17)	Yes	Seq. #000 and 006 - No space holder for lot number and expiration date. Seq.# 009 – Space holder for lot number and expiration date has been identified.
Storage conditions	Provided.	Provided.
Bar code (21CFR 201.25)	Yes	Yes
Name of manufacturer/distributor	Yes	Yes
And others, if space is available	After initial use, discard within 24 hours.	After initial use, discard within 24 hours.

Reviewer's Initial Assessment of Labels: Inadequate.

- Endotracheal administration is not mentioned in the container labels.
- There are no lot # and expiration date in the carton/tray container label.
- The individual container and the carton container cannot have the same NDC number. There should be a separate NDC number for the individual container.

Reviewer's Final Assessment of Labels: Adequate.

DEMPA has the same concerns and IR was sent to the applicant by DMEPA. The applicant revised the container labels via Amendment Seq. #0009 by revising the container labels to include endotracheal administration route, identified a place holder for the lot # and expiration date in the carton/tray container label, and assigned a new NDC number, 63323-580-03, to the single vial container label.

Overall Assessment and Recommendation: Inadequate.

It is adequate in containers labeling but is inadequate in Prescribing Information sheet. All deficiencies will be resolved in the Labeling review meetings with the full multidisciplinary team.

Thomas Wong

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Wendy Wilson- Lee

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BIOPHARMACEUTICS

Product Background:

NDA: 209260; 505(b)(2)

Drug Product Name / Strength: Atropine Sulfate Injection USP
Each mL solution contains 0.4 mg atropine sulfate (equivalent to 0.33 mg atropine free base).
Each multi-dose vial contains 20 mL solution.

Route of Administration: For intravenous injection; alternatively, via intramuscular or subcutaneous injection, or via endotracheal tube administration

Applicant Name: Fresenius Kabi USA LLC

Review Summary:

This 505(b)(2) NDA for Atropine Sulfate Injection (0.4 mg/mL) multi-dose vial relies for approval on FDA's findings of efficacy and safety for the Listed Drug, Ansyr® (atropine sulfate) Injection (0.1 mg/mL) in a single-use syringe [NDA 21146 held by Hospira]. In addition to strength, and presentation/packaging configuration, the formulation of the proposed multi-dose injectable solution is also different from the Listed Drug (LD), i.e., in terms of the presence of a preservative (benzyl alcohol, 9 mg/mL).

The Biopharmaceutics Review focused on the evaluation of the Applicant's biowaiver request and supporting justification. In an Information Request dated 6/6/2017, FDA notified the Applicant that their biowaiver request per 21 CFR § 320.22(b)(1) is not feasible because the formulation of the proposed to-be-marketed parenteral drug product is not qualitatitvely and quantitatively (Q1/Q2) the same as that of the Listed Drug. Based on the data provided by the Applicant and information available in the labeling of Ansyr®, FDA concludes that the test and the reference products are sterile, non-pyrogenic and clear/colorless solutions with comparable pH and osmolarity.

Thus, based on 21 CFR 320.24(b)(6), the Applicant's request to waive the requirement to conduct an *in vivo* bioavailability or bioequivalence (BE) study to bridge the proposed drug product to the Listed Drug is granted; see the FDA recommended edits to the proposed labeling to ensure safe and effective use of the proposed drug product.

From a Biopharmaceutics perspective, NDA 209260 for Atropine Sulfate Injection (0.4 mg/mL) is recommended for APPROVAL.

List Submissions reviewed:

SDN-1, 3/28/2017 (Original)
SDN-4, 7/06/2017 (Response to Biopharmaceutics Information Request)

Biowaiver Request

Reviewer's Assessment: *BIOWAIVER REQUEST GRANTED; see FDA recommended labeling edits to ensure safe and effective use of the proposed to-be-marketed drug product*

This 505(b)(2) NDA references the literature-based PK, efficacy and safety findings for NDA 21146 Ansyr® (atropine sulfate) Injection, USP Plastic Syringes.

Unlike the Listed Drug (Ansyr®; LD), the proposed drug product has a higher drug concentration (0.4 mg/mL vs. 0.1 mg/mL), is packaged in a multiple-dose vial (instead of in a single-use syringe) and thus, is formulated to contain a preservative (i.e., benzyl alcohol, 9 mg/mL). The proposed indications and dosage (on a mg basis) are the same as those approved for Ansyr®. However, since the proposed drug product has a 4-fold higher strength than the LD, in the proposed labeling the recommended injection volumes are 75% lower than those required to deliver the same drug amounts as the LD.

Proposed Strength (0.4 mg/mL)

The Applicant believes that the proposal to market 0.4 mg/mL poses no safety and efficacy concerns because such strength falls between two strengths of already approved products, i.e., 0.1 mg/ml (e.g., Ansyr®) and 2 mg/0.7 ml (e.g., Abbvie's discontinued product; ANDA 71295). The higher strength drug product permits administration of reduced volumes of the injectable solution which is an advantage over the Listed Drug especially when administered via the intramuscular or subcutaneous routes. If all other things are the same/equal, this Reviewer anticipates the efficacy and safety of a 0.4 mg/mL strength of atropine sulfate solution to be comparable to 0.1 mg/mL strength, i.e., when considering that the same drug amount (on a mg basis) is introduced into the injection site.

Presence of Benzyl Alcohol as Preservative

- Because the intravenously (IV) administered drug product is introduced directly into systemic circulation, the addition of benzyl alcohol as preservative to the Applicant's product is not anticipated to alter the systemic *bioavailability* of atropine sulfate.
- The Applicant claims that the "proposed drug product is currently marketed as unapproved drug products by several manufacturers in the US". Note that in this Reviewer's search of DailyMed, only one of six such drug products were identified to contain benzyl alcohol as preservative. Specifically, only West-Ward's product is qualitatively and quantitatively (Q1/Q2) the same as the proposed drug product.
- Per Section 2.2 (Dosage and Administration) of the proposed labeling, the maximum single-time use of this drug product in adults typically requires approximately 15 mL which contains 6 mg atropine sulfate and 135 mg benzyl alcohol. Of note, Section 5 (Warnings and Precautions) describes the deaths and other serious adverse events associated with the use of >99 mg/kg/day benzyl alcohol in neonates and low birth weight infants, and that the minimum amount of benzyl alcohol at which toxicity may occur is not known.
- Based on this Reviewer's search of the Inactive Ingredients Database, the typical maximum cumulative amount (135 mg) of benzyl alcohol received from using the proposed drug product as indicated in the labeling is comparable to that received when Mesna [ANDA

90913] is administered as three intravenous bolus injections over an 8-hour period per day, i.e., 129.5 mg benzyl alcohol per day (388.6 mg to 647.7 mg for 3 to 5 days). Note however that Mesna's approved labeling includes the following statement: "Safety and effectiveness of Mesna Tablets in pediatric patients have not been established. Because of the benzyl alcohol content in Mesna Injection, the multidose vial should not be used in neonates or infants and should be used with caution in older pediatric patients." Thus, this Reviewer believes that the the presence of 9 mg/mL of benzyl alcohol in the Applicant's 0.4 mg/mL Atropine Sulfate for Injection is expected to be safe for use by adults.

- In view of reports linking benzyl alcohol use to toxicity in neonates and low birth weight infants (likely attributed to immature metabolizing capacity for benzyl alcohol), this Reviewer supports the labeling team's decision to include a warning about the use of the proposed (preservative-containing) drug product by neonates, infants, pregnant women and lactating mothers.
- (b) (4) Thus, the systemic concentrations (and any systemic side effects) of benzyl alcohol are not anticipated to be any higher from IM and SC injections than following IV administration of the proposed drug product. Additionally, based on available literature information, this Reviewer does not anticipate the added preservative to contribute significantly to the drug product's local adverse event potential. For example, in human pain studies, intramuscularly administered benzyl alcohol was reported to possess local anesthetic effect (Int J Tox, 20(Suppl. 3):23–50, 2001). However, it may be prudent to mention in the labeling the potential of benzyl alcohol to cause rare cases of hypersensitivity, and contact dermatitis following injection (see Section 2.7.4 Summary of Clinical Safety of this NDA).
- Note however that it is not clear to this Reviewer how the presence of benzyl alcohol as preservative in the proposed multi-dose atropine sulfate injectable drug product could potentially impact the reported rapid absorption rate of atropine (plasmaTmax within 30 min) following intramuscular administration, as well as following subcutaneous administration. The Ansyr® labeling indicates that exercise increases the absorption of IM-administered atropine. Some online sources suggest the possible muscle relaxing effect of ethyl alcohol. Also, this Reviewer was not able to find in the Inactive Ingredients Database products approved for intramuscular or subcutaneous administrations which contain levels of benzyl alcohol as high as that deliverable from the proposed drug product when used via these alternative routes.[1,2,3] Therefore, the Applicant's proposal to adopt the language from the Ansyr® labeling stating preference for IV (over IM, SC, or endotracheal) administration of atropine sulfate injection appears to be justified.

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[1] Progesterone Injection 50 mg/mL [NDA 17362] contains 10% (b) (4) benzyl alcohol. Each mL of the solution contains (b) (4) benzyl alcohol. When administered as recommended in the approved labeling, a 0.1 to 0.2 mL intramuscular injection of this product per dose or per day delivers (b) (4) to (b) (4) benzyl alcohol per day; (b) (4) to (b) (4) for 6 to 8 days. The approved labeling states: "Safety/Efficacy in pediatric patients not established."

[2] Leuprolide acetate injection [ANDA 78885] contains 9 mg/mL benzyl alcohol. When administered by subcutaneous injection per the recommended dosage, each dose and each 14-day kit delivers 1.8 mg and 25.2 mg benzyl alcohol, respectively. Per the approved labeling, this product is administered chronically via the subcutaneous route.

[3] Propyliodone Intratracheal Suspension [NDA 009309] contains benzyl alcohol but the quantitative information is not available in the FDA databases.

Comparative Physico-Chemical Properties

Based on the 7/6/2017 and the 11/29/2017 follow-up email Responses to the Biopharmaceutics Information Request dated 6/6/2017, the measured pH (~3.6) and osmolarity (~371 mOsmol/L [calculated]) of the three registration batches of the proposed drug proposed drug product (produced by the proposed commercial manufacturer) are comparable to those reported in the approved Ansyr® labeling (pH 3.0 to 6.5, and 308 mOsmol/L [calculated]). Per the Applicant, the osmolarity values for their product are "lower than 600 mOsm/L where potential vein damage might become a reason of concern." During 12 months of long-term storage, the proposed drug product's pH remained within the 3.5 and 3.7 range, suggesting physico-chemical stability. Note that per the respective package inserts, the storage condition [USP Controlled Room Temperature] for the proposed product and the Listed Drug is the same. Note also that the Applicant reported that Ansyr® cannot be procured for comparative *in vitro* analytical testing because it is currently in the FDA Drug Shortage List.

The approved Final Product QC Specifications include controls for (1) pH [3.0 to 3.8], (2) osmolality [(b) (4) mOsm/kg to (b) (4) mOsm/kg], (3) appearance [clear and colorless solution], and (4) extractable volume [Not less than nominal volume of (b) (4) mL], in addition to identification tests and limits for atropine sulfate and benzyl alcohol assays [(b) (4) – (b) (4)% and (b) (4) - (b) (4)% of label claim, respectively], impurities/degradants/(b) (4) sterility, non-pyrogenicity, antimicrobial effectiveness, container-closure integrity, and particulates. Per the Drug Product Reviewer (Dr. Thomas Wong), the approved tests and acceptance criteria comprising the Final Product QC Specifications either conform to or are more stringent than those specified in the USP Monograph of Atropine Sulfate Injection. Additionally, based on the results of studies conducted by the Applicant, there are no incompatibility (e.g., leaching, glass delamination) concerns with the drug product in its proposed packaging configuration.

List of Deficiencies:

None

Primary Biopharmaceutics Reviewer Name and Date:
Gerlie Gieser, Ph.D. (12/12/2017)

Secondary Reviewer Name and Date (and Secondary Summary, as needed):
Ta-Chen Wu, Ph.D. (12/12/2017)

Gerlie Gieser

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Ta-Chen Wu

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MICROBIOLOGY

IQA Review Guide Reference

Product Background

NDA: 209260

Drug Product Name / Strength: Atropine Sulfate Injection, USP, (0.4 mg/mL)

Route of Administration: Intravenous, intramuscular, subcutaneous, endotracheal

Applicant Name: Fresenius Kabi USA, LLC

Manufacturing Site: (b) (4)

Method of Sterilization: (b) (4)

Review Recommendation: **Recommended for Approval**

Review Summary: The drug product is (b) (4) in a 20 mL glass vial with (b) (4) fill and then (b) (4) .

List Submissions Being Reviewed: 28 Mar 2017 (eCTD 0000)

Highlight Key Outstanding Issues from Last Cycle: None.

Remarks: The drug substance used in Atropine Sulfate, USP is the same as that of the RLD Atropine Sulfate Ansyr™ Plastic Syringe. The addition of a preservative (benzyl alcohol) and pH adjuster are the only differences made to the drug product solution.

Concise Description Outstanding Issues Remaining: Not applicable.

Supporting Documents:

- Fresenius Kabi USA, LLC DMF (b) (4) for manufacturing facility and accompanying LOA dated 23 Jan 2017
- Review #6 of DMF (b) (4) (Adequate) dated 25 Sep 2015
- Review #13 of DMF (b) (4) (Adequate) dated 25 Feb 2017
- Review # 14 of DMF (b) (4) (Adequate) dated 10 Jul 2017

List Number of Comparability Protocols (ANDA only): None.

S Drug Substance

The drug substance has a microbial limit of NMT (b) (4) CFU/g (total aerobic) and NMT (b) (4) CFU/g (total yeasts and molds) with NMT (b) (4) EU/mg. Tests are performed as per USP <61> and USP <85>.

P.1 Description of the Composition of the Drug Product

- **Description of drug product –** The drug product is a sterile and preserved multi-dose clear liquid injectable at 0.4 mg/mL (8 mg/vial) in a 20 mL (b) (4) glass vial with stopper and a 20 mL fill.

- **Drug product composition –**

Table 1 – Drug Product Composition (3.2.P.1 Description and Composition of the Drug Product, page 1, table 3.2.P.1-1)

Strength	0.4 mg/mL			
Packaging Configuration	(b) (4) mL fill in a 20 mL vial			
Vial	20 mL, (b) (4) glass vial			
Stopper	20 mm , (b) (4) stopper			
Seal	20 mm, Flip-cap Aluminum crimp seal			
Component	**Content (per mL)**	**Content (per vial)**	**Function**	**Quality of Ingredient**
Atropine sulfate monohydrate[1]	0.4 mg	8 mg	Active Ingredient	USP
Sodium Chloride	9 mg	180 mg	Tonicity adjuster	USP
Benzyl Alcohol	9 mg	180 mg	Preservative	NF
Sulfuric Acid[2]	QS	QS	pH adjuster	NF
Water for Injection	QS to mL	QS to 20 mL	(b) (4)	USP

1 Equivalent to 0.33 mg/mL Atropine free base

2 (b) (4)

- **Description of container closure system –**

Table 2 – Container Closure System (3.2.P.7 Container Closure System, page 4, table 3.2.P.7-2)

Product Code	Part #	Packaging Component	DMF Holder(s)	DMF #
(b) (4)				

Adequate

Reviewer's Assessment: The description of the drug product and container/closure system are acceptable for a multiple-dose injectable.

P.2 Pharmaceutical Development

P.2.5 Microbiological Attributes

(b) (4)

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