CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212319Orig1s000

PRODUCT QUALITY REVIEW(S)

U.S. FOOD & DRUG ADMINISTRATION

CENTER FOR EVALUATION OF DRUGS

Memorandum

DATE: July 3, 2018

TO: Division of Neurology Products

THROUGH: Thomas F. Oliver, Ph.D., Division Director, Office of New Drug Products

FROM: Wendy Wilson-Lee, Ph.D., Branch Chief, Office of New Drug Products

SUBJECT: OPQ Review Memo

APPLICATION/DRUG: NDA 212319 Atropine Injection, Single Dose Autoinjector

OPQ recommends **APPROVAL** of NDA 212319 for Atropine Injection, Single-Dose Autoinjector, 2 mg/0.7 mL. ANDA 208933 was converted to NDA 212319 as it was determined that Rafa's application (ANDA 20983) was not eligible for approval under the section 505(j) of the FD&C Act and instead it should instead be a 505(b)(2) application. FDA administratively converted the application to a 505(b)(2) NDA and it was transferred to OND for review.

OPQ references the Integrated Quality Assessment completed under ANDA 208933 for reviews from the drug substance, drug product, process, microbiology, and facilities disciplines. Upon administrative closure of the ANDA, several OPQ issues were outstanding. These issues are related to seven main topics:

1. Confirmation of drug product shelf life for the fully assembled autoinjector
2. Establishment of device reliability
3. Requested updates to the submission
4. Validation of Assay and Related Substances Method
5. Process Description
6. Biowaiver Request/Bioequivalence
7. Labeling Review

The analysis and mitigation of associated risks for the open product quality-related issues are described in the Product Quality Benefit-Risk Assessment (see Attachment 1). As a result, there are two post-marketing requirements and a post-marketing commitment for two of the product quality related issues (see Table 1). The OPQ PMC for confirmation of drug product shelf life, developed in collaboration with the Office of Lifecyle Drug Products and Office of Policy for Pharmaceutical Quality, is described

in Attachment 2. All identified product quality related issues from the ANDA review are adequately resolved and are not considered approvability issues for NDA 212319.

Table 1: NDA 212319 Post-Marketing Requirements and Commitments

Responsible Organization	Type	Study Objective
CDRH	PMR	Establishment of Device Reliability Specifications Related to Activation
DMEPA	PMR	Human Factors Evaluation of Critical Task Removing Safety Cap
OPQ	PMC	Confirmation of Drug Product Shelf Life for the Fully Assembled Autoinjector

All facilities listed for NDA 212319 are acceptable based on the overall manufacturing inspection recommendation of APPROVAL on July 2, 2019. The claim for categorical exclusion is granted based on 21 CFR 25.31(c). A statement regarding no extraordinary circumstances is provided in accordance with 21 CFR 25.15(d). The biowaiver request is granted (see Attachment 3). The tentative drug product expiry is 19 months when stored at controlled room temperature. All product quality-related labeling comments, including carton and container labels, were communicated through the Division of Neurology. The revised labeling is acceptable from a product quality perspective.

Attachment 1: Product Quality Benefit-Risk Analysis
Attachment 2: OPQ PMC 3446-3 Confirmation of Drug Product Shelf Life
Attachment 3: Biopharmaceutics Biowaiver Review Memo

NDA 212319 OPQ Review Memo Attachment 1: Product Quality Benefit-Risk Analysis

A. Product Quality Review Context

Atropine Injection, Single-Dose Autoinjector manufactured by Rafa Laboratories is indicated treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides. This is a life-threatening condition. The drug product is currently in drug shortage as the holder of the listed drug product (Meridian Technologies) is not manufacturing or distributing product. The Rafa Atropine Autoinjector is not FDA-approved. The product is approved in Israel for their military use. An Emergency Use Authorization (EUA) was granted to allow the use of the investigational atropine autoinjector manufactured by Rafa to support supplying the National Stockpile.

The drug product is a sterile solution for intramuscular injection via a single-dose autoinjector. The primary container closure system is designed to maintain the sterility of the formulated atropine drug product and protect from light exposure. In addition, the cartridge is designed to be assembled into the secondary container closure system which comprises an autoinjector device. The nose-pressure-activated automatic injector is suitable for intramuscular administration and designed to deliver a volume of (b) (4) mL of atropine drug solution.

(b) (4)

(b) (4)

ANDA 208933 was converted to NDA 212319 as it was determined that Rafa's application (ANDA 20983) was not eligible for approval under the section 505(j) of the

FD&C Act and instead it should instead be a 505(b)(2) application. FDA administratively converted the application to a 505(b)(2) NDA and it was transferred to OND for review.

Supporting submissions for NDA 212319 include ANDA 209833 and EUA 27. Rafa included a cross-reference to previously submitted information in NDA 212319. The Centers for Disease Control provided a Letter of Authorization to NDA 212319 to allow reliance on EUA 27 for product quality information.

B. Final Analysis of Product Quality Review Findings

Upon administrative closure of the ANDA, seven OPQ issues were outstanding. These issues are related to seven main topics:

1. Confirmation of drug product shelf life for the fully assembled autoinjector
2. Establishment of device reliability
3. Requested updates to the submission
4. Validation of Assay and Related Substances Method
5. Process Description
6. Biowaiver Request/Bioequivalence
7. Labeling Review

Each issue is described below along with the final analysis, conclusions, and lifecycle considerations.

Issue #1: Confirmation of Shelf Life for the Fully Assembled Finished Drug Product

The NDA submission does not include drug product stability results for the fully assembled autoinjector at long-term or accelerated testing conditions. The NDA also does not include (b) (4) results.

Analysis

Although stability data is not available on the fully assembled autoinjector, stability data is provided for the filled cartridges through 36 months stored at long-term conditions in the vertical orientation. The long-term condition studied is the same as the recommend storage condition (25°C/60% RH). In addition, stability data on the fully assembled autoinjector stored for two weeks at elevated temperature (65°C) is provided along with a protocol to conduct a (b) (4) study.

Stoppers at both ends of the filled cartridge are made of (b) (4). One stopper also includes a (b) (4) that contacts the drug product solution. Storage in

the horizontal position would be expected to represent worst-case exposure scenarios. Data collected from samples stored vertically is considered supportive data in regards to establishing expiry, as the extractables and leachables study showed no detectable amounts of compounds associated with these product contact materials. The only detectable extractable can be traced back to a cleaning agent used prior to fill.

The combination of the stability data for the filled cartridge at the recommended storage condition, the results from the elevated temperature study, and the results from the extractables/leachables study together is considered representative of the expected shelf life performance for the fully assembled autoinjector.

Conclusions

A tentative expiry of 19 months can be assigned to the fully assembled autoinjector when stored at controlled room temperature irrespective of orientation.

Lifecycle Considerations

Review staff from Office of Lifecyle Products, Office of New Drug Products, and Office of Policy for Pharmaceutical Quality negotiated an agreed upon Post-Marketing Commitment (PMC) with the Applicant to confirm the drug product shelf life for the fully assembled autoinjector. (b) (4)

Issue #2: Establishment of Device Reliability

The proposed functional testing criteria do not include appropriate reliability specifications for attributes associated with activation of the autoinjector (i.e. activation force, extended needle length, delivered volume, and injection time).

Analysis

The reliability of the product is defined to be (b) (4)% for activation force, deliverable volume, delivery time, and needle extended length. However, the acceptable quality limit (AQL) established at lot release did not match this level of reliability. The verification testing completed on the subject device does not meet an acceptable level of reliability for the subject device's intended use. The expected reliability criterion for the device should be successful activation for at least 99.999% of activation events with a 95% level of confidence. The Applicant did provide a risk analysis per the appropriate ISO standard. In this risk analysis, the Applicant adequately addressed the delivery error hazards identified.

Conclusions

The Applicant's risk analysis clearly identifies activation as a critical characteristic and includes risk mitigation strategies to address the delivery errors identified. Although the reliability criterion does not meet the expected criterion, the criterion applied ensures that (b) (4)% of activation events will result in a successful activation. The risk associated with failure to activate is further mitigated by the fact that soldiers usually carry three autoinjectors. If a failure to activate is experienced, two additional autoinjectors are available to provide treatment. Considering the (b) (4)% probability of failure, although not improbable, the chance of all three autoinjectors failing to activate is assumed to be very low.

Lifecycle Considerations

A PMR to conduct the requested device reliability with respect to successful actuation is instituted. The Applicant agreed to this PMR on July 2, 2018.

Issue #3: Requested Updates to the Submission

Certificates of analysis were not provided for three reference standards – 1) (b) (4) a degradant; 2) (b) (4) a degradant; and 3) (b) (4) The specification provided for the (b) (4) did not appear to comply with current USP monograph requirements. A consolidated drug product specification was also not provided.

Analysis

Although a consolidated drug product specification is not included, tabular listings of tests with applicable acceptance criteria were provided for both the drug product release and stability testing. A specification for USP-grade (b) (4) was provided via cross-reference to the EUA. The (b) (4) specification can be confirmed on inspection. Method validation reports indicate that reference standards were used for the (b) (4) degradants along with the (b) (4) The quality of these reference standards can be confirmed on inspection.

Conclusions

The absence of this information in the preferred format in the submission presents a low risk to both patient safety and product quality.

Lifecycle Considerations

The OPQ PMC includes recommendations to provide certificates of analysis for the identified reference standards, a revised (b) (4) specification, and a consolidated drug product specification in the final report.

Issue #4: Assay and Related Substances Analytical Method Validation

Validation results for the assay and related substances analytical procedure showed a discrepancy in the results reported for the (b) (4) related substances compared to the defined limit of detection for the method. These results do not support use of the assay and related substances analytical method as a quantitative measure of (b) (4) related substances.

Analysis

(b) (4) However, based on the single dose acute treatment of a life-threatening condition and intramuscular administration, risks associated with complications from infection (b) (4) in the product are considered low. As such, a quantitative determination of (b) (4) content or the content of (b) (4) related substances is not considered a critical. Validation of other method parameters support the use of the method as a limit test.

Conclusions

The test for (b) (4) related substances can be considered a limit test instead of a quantitative test. A comment will be added to action letter indicating that the method validation supports use of the (b) (4) related substances analytical method as a limit test.

Lifecycle Considerations

If the Applicant should seek to use the (b) (4) related substances test as a quantitative measure, a supplement could be filed post-action providing results from validation of the method using samples spiked with (b) (4) related substances to support the switch from limit test to quantitative test method.

Issue #5: Process Description

(b) (4)

(b) (4)

(b) (4)

Issue #6: Biowaiver Request/Bioequivalence

OGD closed the bioequivalence review without recommending an action, and transferred the review information to OND.

Analysis

Although no action was recommended, the Division of Bioequivalence review identified the drug product as Q1/Q2 equivalent. The Division of Biopharmaceutics concurred with this assessment (see Attachment 3).

Conclusions

The biowaiver is granted.

Lifecycle Considerations

None.

Issue #7: Labeling Review

OGD closed the labeling review without recommending an action, and transferred the review information to OND.

Analysis

Both the proposed product and the reference drug (Atropen®) contain 1.67 mg/0.7 mL atropine base in a citrate buffer. Thus, the established name should be "Atropine Injection" and the USP "Atropine Sulfate Injection" monograph is not applicable. When the Atropen was approved, Atropine Sulfate Injection was a marketed unapproved drug and the Atropen labeled potency was based on the equivalent amount of atropine sulfate.

Due to potential medication errors that could result from correction of the label for an emergency use product, and consistent with labeling developed for the CDC emergency use authorization (EUA-027), the label potency will continue to be 2 mg/0.7 mL and a statement that the product contains 1.67 mg atropine equivalent to 2 mg atropine sulfate will be added to all product labeling.

Conclusions

The revised labeling, including the carton and container labels, is acceptable from a product quality perspective.

Lifecycle Considerations

Conversion of the labeling to PLR/PLLR is deferred for six months after action. A labeling supplement will be submitted to affect this conversion. A product quality review of the labeling supplement will be needed.

C. Summary Basis for Product Quality Review Recommendation

The identified product quality-related issues transferred from the ANDA review are not considered approvability issues for the NDA. The potential risks associated with these issues are mitigated mostly by post-marketing strategies. Specifically, risks associated with assigning a provisional drug product expiry, validation of key analytical procedures, and submission of supporting information are mitigated either via cross-reference to the EUA or via the OPQ PMC. Risks associated with device reliability during activation are mitigated by the CDRH PMR. Risks associated with (b) (4) process descriptions for (b) (4) and reliance on end product testing to ensure quality are mitigated by either assumption of acceptable risk by OPQ or the Applicant. The biowaiver request is granted and acceptable labeling, including carton and container labels, has been negotiated.

Residual risks are further mitigated by the unmet medical need, target population, and intended use scenario. While these issues may preclude approval of a product intended for general use in the general population, emergency use by military personnel exposed to nerve agents presents a unique case with a higher threshold for risk tolerance due to the severity of exposure to the nerve agent. As such, OPQ considers the information provided and the risk mitigation strategies employed acceptable to support approval of NDA 212319.

NDA 212319 OPQ Review Memo Attachment 2: OPQ PMC 3446-3 Confirmation of Drug Product Shelf Life

NDA 212319 **Atropine Injection Single-Doe Autoinjector**

PMC#: 3446-3

PMC Title: *Confirmation of Drug Product Shelf-Life*

PMC Milestone Dates:		
	Final Protocol Submission	August 9, 2018
	Interim Report Submission	March 9, 2019
	(b) (4)	
	Study Completion Date	January 9, 2021
	Final Report Submission	April 9, 2021

PMC Overview

Due to the absence of stability data provided for the fully assembled autoinjector, a post-marketing commitment to conduct additional stability testing on the fully assembled autoinjector is necessary. Please provide a final protocol submission by August 9, 2018 detailing how results for the following test conditions will be generated to confirm drug product shelf life for:

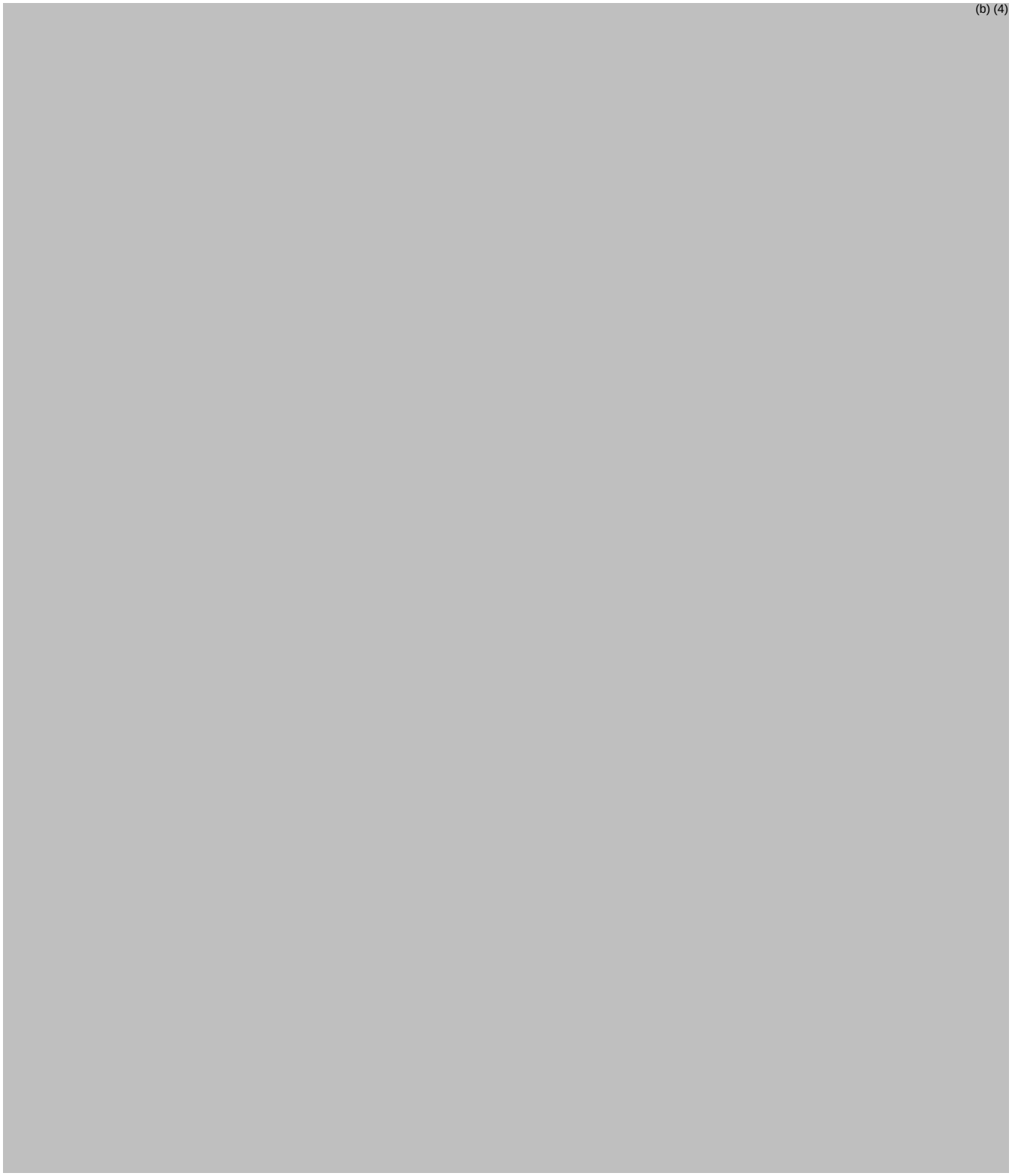
(b) (4)

Please submit the PMC protocol as a Prior Approval Supplement with a request for expedited review by August 9, 2018.

Please submit an interim report that includes the results of the retained sample testing (b) (4) study along (b) (4)

After agreement is reached on the protocol, please complete the requested studies by January 9, 2021 with submission of the final report by April 9, 2021 via a Prior Approval supplement to the NDA.

(b) (4)



This information can be provided via cross-reference to previously submitted information if it is representative.

Office of Pharmaceutical Quality/Office of New Drug Products
BIOPHARMACEUTICS REVIEW

Application No.:	NDA 212319	**Primary Reviewer:** Angelica Dorantes, Ph.D.	
Submission Date:	June 27, 2018	**Secondary Reviewer:** Paul Seo, Ph.D.	
Division:	Division of Neurology Products	**Date of Review:**	July 3, 2018
Applicant:	Rafa Laboratories, Ltd.		
Trade Name:	Atropine Sulfate Injection, Single-Dose Autoinjector	**Type of Submission:** 505 (b)(2) NDA	
Generic Name:	Atropine Sulfate Injection, USP		
Indication:	Atropine Sulfate Injection is indicated for the treatment of poisoning by susceptible organophosphorus nerve agents having cholinesterase activity as well as organophosphorus or carbamate insecticides		
Dosage Form/ Route of Administration/ strengths	Intramuscular Injection, 2mg/0.7 ml		
Type of Review:	**BIOWAIVER REQUEST**		

BIOPHARMACEUTICS REVIEW SUMMARY:

Background: On December 2, 2016, Rafa Laboratories, Ltd. submitted Original ANDA 209833 for Atropine Sulfate Injection USP, 2 mg/0.7 mL, in accordance with Section 505(j) of the Federal Food, Drug, and Cosmetics Act (FD&C Act). Atropine Sulfate Injection USP, 2 mg/0.7 mL is a single strength, supplied in a single-use prefilled auto-injector syringe. The reference listed drug, AtroPen® Auto-Injector (atropine injection), approved under NDA 17016 on May 15, 1973. The Applicant, Meridian Medical Technologies Inc., has not manufactured this product since 2013 and therefore is not available in the USA commercial market.

Upon review and consultation with various CDER subject matter experts, FDA determined that ANDA 209833 should be administratively converted to a 505(b)(2) NDA. The new NDA 212319 submission for Atropine Sulfate Injection USP, 2 mg/0.7 mL is dated June 27, 2018, and is under the Office of New Drugs/Division of Neurology Products.

Biowaiver Request: In the current submission, the Applicant, Rafa Laboratories, Ltd., is requesting a waiver for the CFR requirement of the submission of *in vivo* bioequivalence (BE) data for their proposed product, Atropine Injection USP, 2 mg sulfate/0.7 mL, under Section 21 CFR § 320.22 (b)(1).

Review: The Biopharmaceutics review is focused on the evaluation of the information supporting the Bioequivalence waiver request for the proposed drug product.

Formulation: The composition of the formulations for the proposed and Listed Drug products and the function of each component in the formulations are listed below. The table below shows that the composition of the formulations of the proposed and Listed drug products, are equivalent.

Comparative Formulations of Proposed and Listed Atropine Sulfate for Injection Products			
		Proposed Atropine Injection	**Listed Atropine Injection**
Ingredients	**Function**	**Quantity Per Unit (mg/ml)**	**Quantity Per Unit (mg/ml)**
Atropine*	Active	(b) (4)	
Glycerin			
Citric acid (b) (4)	Buffer		
Sodium citrate (b) (4)	Buffer		
Phenol (b) (4)			(b) (4)

*Atropine free base

Physicochemical Information: The appearance and pH range of the proposed drug product ((b) (4)) are comparable to those of the Listed drug product ((b) (4))

Route of Administration, Dosage Form and Strength: The route of administration, dosage form and strength of the test product are the same as those of the Listed drug product. The product's labeling is comparable to that of the Listed drug product. It is noted that the labeling provided by the applicant was compared to the Listed drug product under NDA 017106/S-032, and approved on September 17, 2004.

***Auto-Injector Device Features*:** The features of the Atropine Sulfate Injection USP device, 2 mg/0.7 mL are the same as those of the Listed drug product with few minor differences, which do not alter product performance or operating principles.

In Vitro Performance Tests: Because the proposed Atropine Sulfate Injection, Single-Dose Autoinjector product is a drug-device combination product, the comparison between the proposed and Listed drug products with respect to the following in vitro performance tests is in general needed to support the BE waiver request;

- Delivered volume,
- Ejection time,
- Trigger force,
- Extended needle length

It is noted that the Applicant was not able to conduct the side-by-side comparison *in vitro* performance testing between the proposed and Listed drug products because the Listed drug product is not commercially available.

Although no direct comparative testing was performed, it is noted that functional testing of Atropine Sulfate Injection USP, 2 mg/0.7 mL is performed at both initial qualification and full production lot release testing of the auto-injectors and includes activation force, dispensed volume, dispensing time, and needle extended length after dispensing.

Taking in consideration that in vitro performance testing is conducted for the proposed drug product at initial qualification & full production, the acceptance criteria limits for the performance test are the same as those of the Listed drug product, and the medical need for this product, Biopharmaceutics believes that the lack of direct comparison information for the in vitro performance tests is a low risk, and therefore the biowaiver's evaluation is not impacted.

RECOMMENDATION:

The Division of Biopharmaceutics considers that the overall information provided to support the biowaiver request meets the requirements of Section 21 CFR § 320.22 (b)(1). Therefore, the Applicant's request for a waiver of the CFR's requirement of in vivo bioequivalence testing for Atropine Injection USP, 2 mg sulfate/0.7 mL, is granted.

From the Biopharmaceutics viewpoint, 505(b)(2) NDA 212319 for Atropine Injection USP, 2 mg sulfate/0.7 mL is recommended for APPROVAL.

Primary Reviewer

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Branch Chief
Division of Biopharmaceutics-Branch 1
Office of New Drug Products
Office of Pharmaceutical Quality

Secondary Reviewer

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cc : NDA 212319/DARRTS

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/s/

ANGELICA DORANTES
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PAUL R SEO
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