CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

212319Orig1s000

OTHER REVIEW(S)

INTERCENTER CONSULT REVIEW MEMORANDUM

Date	July 6, 2018
To	Harold Sano, RPM, CDER/OND/ODEII/DNP
Requesting Division	Division of Neurology Products
From	John McMichael, Combination Products Team Lead CDRH/ODE/DAGRID/GHDB
Through (Team Lead)	John McMichael, ICC Team Lead CDRH/ODE/DAGRID/GHDB
Through (Branch Chief)	CAPT Alan Stevens CDRH/ODE/DAGRID/GHDB
Subject	Consult for NDA 212319 (converted from ANDA 209833) – Rafa Atropine Auto-Injector ICC1700049
Recommendation	**APPROVABLE with 1 Post-Market Requirement – See Section 11**

Digital Signature Concurrence Table	
Reviewer	John C. Mcmichael -S
Team Lead	2018.07.06 13:23:26 -04'00'
Branch Chief	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300189211, cn=Alan M. Stevens -S Date: 2018.07.06 13:56:09 -04'00'

1. Submission Overview

Table 1. Submission Information	
Submission Number	NDA 212319
Sponsor	Rafa Laboratories Ltd.
Drug/Biologic	Atropine
Indications for Use	Treatment of organophosphorus nerve agent and organophosphorus or carbamate insecticide poisoning in an intentional terrorism-related or unintentional event.
Device Constituent	Rafa Auto-Injector
Related Files	ICC1600647 ICC1700853 ICC1800224

Table 3. Important Dates	
Final Lead Device Review Memo Due	07/07/2018

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2. PURPOSE/BACKGROUND

2.1. Scope

Rafa Laboratories submitted an Abbreviated New Drug Application (ANDA) for market approval of their atropine auto-injector that is currently being produced under the issuance of Emergency Use Authorization 27 (EUA 27). This ANDA

was then converted to NDA 212319 in June 3018 in coordination with the Sponsor, OND and OGD. This memo is a represents a review of the converted NDA.

The device constituent of the combination product is a single-use, emergency-use auto-injector.

The consultant was informed on June 19, 2018 (06/19/2018) that ANDA 209833 would be converted to a 505(b)2 NDA application under NDA 212319 and that all ANDA consultant reviews should be completed/closed out by 06/29/2018 with any outstanding review issues clearly identified.

The goal of this memo is to provide a final review of the device constituent parts of the combination product currently under NDA 212319.

2.2. Prior Interactions

CDRH/ODE completed a review of the product under EUA 27 prior to its issuance as well as a closeout review for ANDA 209833 prior to conversion to NDA. Given the context and need of the EUA, certain data requirements typical for market approval (i.e. exhaustive reliability data) were not obtained prior to issuance of the EUA. The Sponsor was made aware that these data requirements would be necessary prior to approval of any future marketing application.

2.2.1. Related Files

ICC1600647
ICC1700853
ICC1800224

2.3. Indications for Use

Combination Product	Indications for Use
Atropine	Treatment of organophosphorus nerve agent and organophosphorus or carbamate insecticide poisoning in an intentional terrorism-related or unintentional event.
Rafa Auto-injector	Delivery of Atropine

3. ADMINISTRATIVE

3.1. Documents Reviewed

Document Title	Location
ICC1600647 – CDRH/ODE Review	N/A
ICC1700853 – CDRH/ODE Review	N/A
ICC1800224 – CDRH/ODE Review	N/A
Specifications	GSR 3.2.P.5

Attachment 3.2.P.5.1-1 Updated DP Specifications	GSR 3.2.P.5
Container Closure System	GSR 3.2.P.7
Attachment 3.2.P.7-32 IDF Surgeon General	GSR 3.2.P.7
Attachment 3.2.P.7-33 MPID AtroPen v2	GSR 3.2.P.7
Attachment 3.2.P.7-27 QA-7300 Design And Development Procedure	GSR 3.2.P.7
Attachment 3.2.P.7-28 QA-7100 Risk Management Procedure - (b) (4)	GSR 3.2.P.7
Attachment 3.2.P.7-29 QA-7302 (b) (4) DHF DMR DHR Procedure	GSR 3.2.P.7
Attachment 3.2.P.7-30 QD-TOC-001 DHF Table of Contents	GSR 3.2.P.7
Attachment 3.2.P.7-38 Force of Injection and Break Loose Extrusion	GSR 3.2.P.7
Attachment 3.2.P.7-37 Penetration and Needle Integrity	GSR 3.2.P.7
Attachment 3.2.P.7-36 SPEC-CRT-001(1)	GSR 3.2.P.7
Attachment 3.2.P.7-40 Activation Force Investigation	GSR 3.2.P.7
Attachment 3.2.P.7-41 VR-0001 Verification report	GSR 3.2.P.7
Attachment 3.2.P.7-56 QA-8521 CAPA	GSR 3.2.P.7
3.2.P.8.1 Stability Summary	GSR 3.2.P.8
Draft Auto Injector Label	GSR 1.14
Quality Information Amendment	GSR 1.11
Comparison	GSR 3.2.P.7
(b) (4)	Email
	Email
	Email
ANDA 209833 1.12.4 Request for Comments_FINAL	Email
meeting-request	GSR 1.6
Request for Comments	GSR 1.6
Quality Information Amendment.05.18.18	Email

4. DEVICE DESCRIPTION AND PERFORMANCE REQUIREMENTS

4.1. Device Description

The following information was provided by the Sponsor in the NDA:

Each prefilled auto-injector provides a single dose of atropine. When activated, the auto-injector dispenses 1.67 mg atropine base (equivalent to 2 mg atropine sulfate) in 0.7 mL of sterile pyrogen-free solution through a single needle for rapid intramuscular (IM) administration.

Rafa Atropine Auto-Injector is not FDA-approved. The product is approved in Israel for their military use.

Figure 1: Rafa Atropine Auto-Injector

(b) (4)

(b) (4)

4.2. Performance Requirements and Specifications

Reviewer Note: Although comparison to the RLD is not a requirement for the newly converted NDA (previously ANDA 209833), the consultnat kept the Sponsor's comparison to the RLD as reference to an approved product's specifications since they are identical in performance.

The following is information that was provided related to the Reference Listed Drug, Atropen, and the subject product, the Rafa Atropine Auto-Injector:

Referenced Listed Drug

Figure 1: Rafa Atropine Auto-Injector

(b) (4)

Feature	Reference Listed Drug	Rafa Atropine Auto-Injector
Number of Components	12	12
Activation	Pressure	Pressure
Drug Cartridge	(b) (4)	
Injection Device Weight (no solution)		
Overall Length		
Maximum Diameter of Unit		

Needle	22 gauge	22 gauge
Needle Construction	(b) (4)	
Needle Extended Length		
Force to Activate		
Injection Time		
Dose Accuracy		
Needle End Cap	Green-colored, smoothly-finished cap having a centered “grey eye”	Green-colored, smoothly-finished cap having a centered “grey eye”
Safety Catch	Yellow safety catch	Yellow safety catch
Arming End	Shall have a safety release protected by a yellow covering cap	Shall have a safety release covered by a yellow covering cap
Yellow Cap Dimension: Overall Length	NMT 14 mm	NMT 19 mm
Yellow Cap Dimension: Diameter	13 to 17.7 mm	12 mm

1 (b) (4) cartridges are used per the original material of construction of the cartridges used in the RLD.

The following component description was provided by the Sponsor of the pre-EUA:

Component	Material Description	Manufacturer/Supplier
Injector Collet; (b) (4)	(b) (4)	
Injector Spring		
Outer Plastic Tube		
Injector Cap (b) (6) (b) (4)		
US Label for Finished Device		

		(b) (4)
Immediate Package Carton, Printed	Printed cardboard boxes, Controlled Document No (b) (4) (b) (4)	(b) (4)

Table 3.2.P.7–2. Primary Packaging Components for Auto-injector Assembly

Component	Material Description	Manufacturer/Supplier
Cartridge Assembly, Filled	See Section 3.2.P.1	Rafa Laboratories, Ltd.
Inner Plastic Tube	(b) (4)	
Firing Seat Ring (Safety Disc)		
Safety Plug		
Injector Collet; (b) (4)		

The following is a direct comparison from the reference listed drug to the subject device's essential perforamnce requirements provided by the Sponsor:

Performance Test	Acceptance Criteria	
	Reference Listed Drug	Atropine Sulfate Injection USP, 2 mg/0.7 mL
Activation Force	(b) (4)	
Dispensed Volume		
Dispensing Time		
Needle Extended Length after Dispensing	19 to 22 mm	19 to 22 mm

The following is a listing of the relevant device characteristics created by the consultant from the various documents supplied to the NDA:

Device Characteristic	Description / Specification
Injector Name	Atropine Auto-Injector
Drug Product Concentration	2 mg / 0.7 mL
Delivered Volume / Dose Accuracy	(b) (4)
Injection Time	
Injection Site	Outer thigh, upper arm
Injection tissue and depth of injection	Intramuscular
Audible / visual feedback	N/A
Cap Removal Force	N/A
Activation Force	(b) (4)
Visibility of medication container	None
Needle Specifications • Length(s) • Gauge(s) • Connection type	22 gauge, 19-22 mm. prestaked (b) (4)
Type of Use (e.g. single use, disposable, reusable, other)	Single-use, Emergency-use
Intended user	EMS, patient, HCP, civilians
Injection mechanism (e.g., manual piston, spring, gas, etc.)	Spring-powered
Method of actuation	Pressure against injection site
Automated Functions	Injection of needle and dispensing of drug
Residual Medication	N/A
Dose Units of Measure (e.g., mL, Units, mg, increments, etc.)	mg/mL
Environments of use	Any environment
Storage conditions and expiry	Storage: 59-86 degrees F Expiration:
Graduation marks / fill lines	N/A
Preparation and administration	1. Remove auto-injector (AI) from plastic sleeve 2. Firmly hold AI with green tip pointed down 3. Pull off yellow safety cap 4. Aim and firmly jab green tip straight down (90 degree angle) again the outer thigh (b) (4) The AI device will give the medicine when you do this. 5. Hold AI firmly in place for at least 10 seconds to allow the injection to finish. 6. After 10 seconds, remove the AI from skin and massage the injection site in a circle motion for several seconds. **Note: If you do not see the needle visible after removal from the skin, it means an injection did not**

	occur. Check to be sure the yellow safety cap has been removed. After yellow safety cap removal has been verified, repeat steps 4 and 5 pressing harder against the thigh to activate the injector. If you still do not see the needle, use a new auto-injector and start over again at step A. 7. After injection, avoid contact with blood or needle by carefully bending needle back against injector using a hard surface. Using the bent needle as a hook, pin the used AI to the patient's clothing. Alternatively, either place the AI back into plastic sleeve and leave it next to patient or write number of AIs used on a triage tag, hand, forehead, chest, etc. Move yourself and the exposed person away from the contaminated area right away. Try to find medical help. **AIs contain only one dose. If you need more than 1 injection,** obtain a fresh AI, go back to step 1, and follow the same instructions for each new AI used.
Safety Features	No needle safety guard after injection – instructions state to bend needle against hard surface after successful injection

Reviewer Comment:
The proposed generic device constituent and RLD device constituent are identical in their performance specifications and mechanism of action. The materials and dimensions of the physical device are nearly identical and the consultant reviewer find these differences to be negligible in the evaluation of the device from a performance standpoint.

5. Design Control Review

Design Control Documentation Check

Design Control Requirement*	**Signed/Dated Document Present**		**Submission Location**
	Yes	**No**	
Design Requirements Specifications	YES		ANDA 209833 / Email
Design Verification Data	YES		ANDA 209833 / Email
Risk Analysis supplied	YES		ANDA 209833 / Email
Validation Data	N/A		RLD approval of Atropen
• Human factors	N/A		

• Clinical data			
Traceability Documentation	YES		ANDA 209833 / Email

6. DESIGN VERIFICATION AND VALIDATION REVIEW

Summary of Design V&V Attributes

Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing			X
To-be-marketed device was used in the pivotal clinical trial			X
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e. emergency use combination product may require separate reliability study)		X	
Traceability demonstrated for specifications to performance data	X		

The following table identifies any standards or relevant FDA guidance documents not listed in the above table that might be referenced by the sponsor or determined to be relevant by the CDRH / ODE reviewer in the course of the design review.

Reference Standard / Guidance	Description / Extent of FDA Recognition	Documentation Adequate	
		Yes	No
ASTM D4169-16	Simulated shipping validation study – Fully Recognized	YES	

Reviewer Comments:

The Sponsor did not provide sufficient reliability data to support approval of the product given its emergency-use indications. It is noted that the Sponsor fully intends to provide the requested reliability information; however, no reliability data had been submitted at the time of this memo.

6.1. Design Validation Review

Design Validation Attributes	Yes	No	N/A
Phase I/II/III Study utilized the to-be-marketed device			X
Bioequivalence Study utilized to-be-marketed device			X
Simulated Actual Use Study utilized to-be-marketed device			X

Reviewer Comments:

- **The Sponsor is utilizing the comparison to the Reference Listed Drug, Atropen, to support the clinical validation of the drug product. The consultant reviewer finds it acceptable that the RLD and the subject device shares all of the same functional performance specifications and basic design principles. The firm supplied a shipping validation study, verification testing after aging/wear, and the results of release testing of a production quality batch to support the validation of the product.**
- **The reliability of the product is defined to be (b) (4) % for activation force, deliverable volume, delivery time, and needle extended length by the MPID procurement requirements document. However, the AQL = (b) (4) at lot release originally defined in ANDA 209833 did not match this level of reliability given the lack of adequate reliability information for the device overall performance.**
    - **The Post-Market Requirement for reliability information should address this review issue for the future. At present, the consultant reviewer finds the listed reliability for the performance requirements of activation force, deliverable volume, delivery time, and extended needle length to be inadequate with a desired level of reliability to be NLT 99.99&/95% confidence. This has been communicated to the firm.**
- **The verification testing completed on the subject device does not meet an acceptable level of reliability for the subject device's intended use.**
- **The Sponsor did not establish or provide data to support that the reliability of the device Successfully Activating is not less than 99.999% with 95% level of confidence. Without this information, the consulting reviewer finds the application Not Approvable for lack of safety information regarding the emergency-use device.**

6.2. Design Verification Review

Essential Performance Requirement	Specification	Verification	Validation	Aging / Stability (Y/N)	Shipping/ Transportation (Y/N)	Lot Release Testing (Y/N)
Injection Time	(b) (4)	YES	N/A – same as RLD	YES	YES	YES
Delivered Volume		YES	N/A – same as RLD	YES	YES	YES
Visual/Audible Feedback		YES	N/A – same as RLD	YES	YES	YES
Activation Force		YES	N/A – same as RLD	YES	YES	YES

Extended Needle Length	19-22 mm	YES	N/A – same as RLD	YES	YES	YES
Needle Gauge	22 G	YES	N/A – same as RLD	YES	N/A – not required	YES
Needle Connection Type	Prestaked	N/A	N/A	N/A	N/A	N/A

The following is taken from the ANDA documentation to demonstrate the verification of the product specifications after aging/wear, after shipping, and at lot release:

Table 3.2.P.7–7. Initial Qualification Testing

Activation Force			
Test	Remove the Yellow Safety Release from the injector. Place the injector in a suitable device capable of applying and measuring the required loads. Apply a load axially to the injector with the least possible impact and increase the load until the injector is activated. Examine the injector to determine if the front end has become dislodged during activation.		
	Requirement	Acceptance Criteria	AQL
Atropine Sulfate Injection USP, 2 mg/0.7 mL	The force needed to activate the injector (subsequent to the removal of the safety pin [yellow safety cap]) shall not be less than (b) (4)	(b) (4)	

Dispensed Volume			
Test	Using a suitable apparatus, activate the injector and determine the dispensed volume dispensed by weight, corrected for specific gravity.		
	Requirement	Acceptance Criteria	AQL
Atropine Sulfate Injection USP, 2 mg/0.7 mL	The firing action shall consist of rapidly extending the needle from the end of the injector and simultaneously ejecting the solution through the needle. The volume of the solution ejected shall be (b) (4) Appropriate volumetric or gravimetric validated methods may be used.	(b) (4)	

Dispensing Time			
Test	While measuring volume, measure to the nearest second, the time between start of flow and the stop of the flow of medication from the needle.		
	Requirement	Acceptance Criteria	AQL
Atropine Sulfate Injection USP, 2 mg/0.7 mL	Speed of firing in air (the average time interval between the activation of the auto-injector and the ejection of the solution) shall not be more than (b) (4)	(b) (4)	

Needle Extended Length after Dispensing			
	Requirement	Acceptance Criteria	AQL
Atropine Sulfate Injection USP, 2 mg/0.7 mL	The needle should be suitable for IM injection. Its length shall be 0.75 to 0.875 inch (19 to 22 mm).	19 to 22 mm	(b) (4)

Rub Test			
Test	Rub the labeling on the auto-injector ten times with fingers using moderate pressure. Examine for legibility and permanency of marking or labeling.		
	Requirement	Acceptance	AQL

		Criteria	
Atropine Sulfate Injection USP, 2 mg/0.7 mL	Without any visible damage; proper label information; the inscription on the label shall be clear and legible; and, the label shall be firmly attached to the injector with no non-adhering corners or margins.	The marking on the labels shall remain clear and legible. The label shall be entirely affixed to the injector.	(b) (4)

Compression Load Test			
Test	On appropriate test equipment apply an axial load of (b) (4) is applied to the auto-injector. The injector should not activate.		
	Requirement	Acceptance Criteria	AQL
Atropine Sulfate Injection USP, 2 mg/0.7 mL	The injector shall contain a safety mechanism to prevent accidental activation of the injector or dispensing of medication due to transport/handling or application of axial power to the auto-injector. Any of the above shall not trigger or cause activation of the auto-injector.	There shall be no signs of breakage or any other reason rendering the test auto-injector unsuitable for use without touching the safety catch, apply a force of (b) (4) on each injector.	(b) (4)

Leak Test			
Test	Visually examine the injector for evidence of medication leakage.		
	Requirement	Acceptance Criteria	AQL
Atropine Sulfate Injection USP, 2 mg/0.7 mL	Leakage tightness of the auto-injector	Suitable validated method	(b) (4)

Table 3.2.P.7–10. Activation (Firing) Force Averages, Standard Deviations, and Ranges

	Activation force								
	Before Wear			After Wear I			After Wear II		
			(b) (4)			(b) (4)			(b) (4)
LOT	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
21883	1.820	0.535		1.750	0.452		1.515	0.370	
21884	1.785	0.479		1.865	0.511		1.515	0.305	
21971	2.305	0.525		2.455	0.566		1.930	0.306	
100962	2.025	0.439		2.310	0.446		1.615	0.379	
101680	2.350	0.425		2.340	0.319		1.625	0.342	
108936	1.780	0.456		1.960	0.486		1.960	0.518	
109160	2.352	0.645		1.750	0.484		1.795	0.592	
109189	2.156	0.547		2.085	0.695		1.735	0.396	
701039	1.628	0.462		1.915	0.571		1.790	0.425	
701042	1.854	0.533		2.260	0.508		1.840	0.441	
701076	1.740	0.507		1.950	0.498		1.740	0.378	

Table 3.2.P.7–11. Auto-injector Release Testing Results for Solution Volumes

	Solution Volume								
	Before Wear			After Wear I			After Wear II		
			(b) (4)			(b) (4)			(b) (4)
LOT	Mean	SD	Range	Mean	SD	Range	Mean	SD	Range
21883	0.733	0.015		0.727	0.012		0.721	0.016	
21884	0.736	0.014		0.731	0.012		0.728	0.010	
21971	0.734	0.012		0.738	0.008		0.733	0.012	
100962	0.739	0.011		0.730	0.011		0.726	0.018	
101680	0.738	0.011		0.736	0.012		0.729	0.013	
108936	0.741	0.010		0.736	0.009		0.724	0.011	
109160	0.751	0.015		0.738	0.014		0.727	0.011	
109189	0.735	0.011		0.729	0.018		0.724	0.019	
701039	0.727	0.009		0.721	0.006		0.715	0.008	
701042	0.731	0.011		0.727	0.007		0.709	0.011	
701076	0.734	0.011		0.736	0.008		0.729	0.009	

Table 3.2.P.7–13. Pass/fail Results for Needle Measurements During Release Testing of Auto-injectors

Effective Needle Length & Diameter						
	Needle Length			Needle Diameter		
	19 - 22 mm (0.75 - 0.875 inches)			0.73 - 0.785 mm		
LOT	Result	Fail #	n =	Result	Fail #	n =
21883	Pass	N/A	N/A	Pass	N/A	N/A
21884	Pass	N/A	N/A	Pass	N/A	N/A
21971	Pass	N/A	N/A	Pass	N/A	N/A
100962	Pass	N/A	N/A	Pass	N/A	N/A
101680	Pass	N/A	N/A	Pass	N/A	N/A
108936	Pass	0.000	50	Pass	0.000	50
109160	Pass	0.000	50	Pass	0.000	50
109189	Pass	0.000	50	Pass	0.000	50
701039	Pass	0.000	50	Pass	0.000	50
701042	Pass	0.000	50	Pass	0.000	50
701076	Pass	0.000	50	Pass	0.000	50

Table 3.2.P.7–15. Auto-injector Dose Delivery Duration During Release Testing

Delivery Duration			
	Before Wear (b) (4)		
LOT	Mean	SD	Range
21883	0.260	0.010	N/A
21884	0.270	0.010	N/A
21971	0.250	0.010	N/A
100962	0.260	0.010	N/A
101680	0.290	0.010	N/A
108936	0.232	0.011	(b) (4)
109160	0.249	0.016	
109189	0.262	0.015	
701039	0.235	0.014	
701042	0.239	0.010	
701076	0.237	0.014	

The specifications of the subject device are identical in their functional performance characteristic to the RLD Atropen.

The Sponsor provided the following verification testing to support the device maintaining the proper extended needle length and needle integrity when injected through clothing:

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(b) (4)

7. RISK ANALYSIS

Risk Analysis Attributes

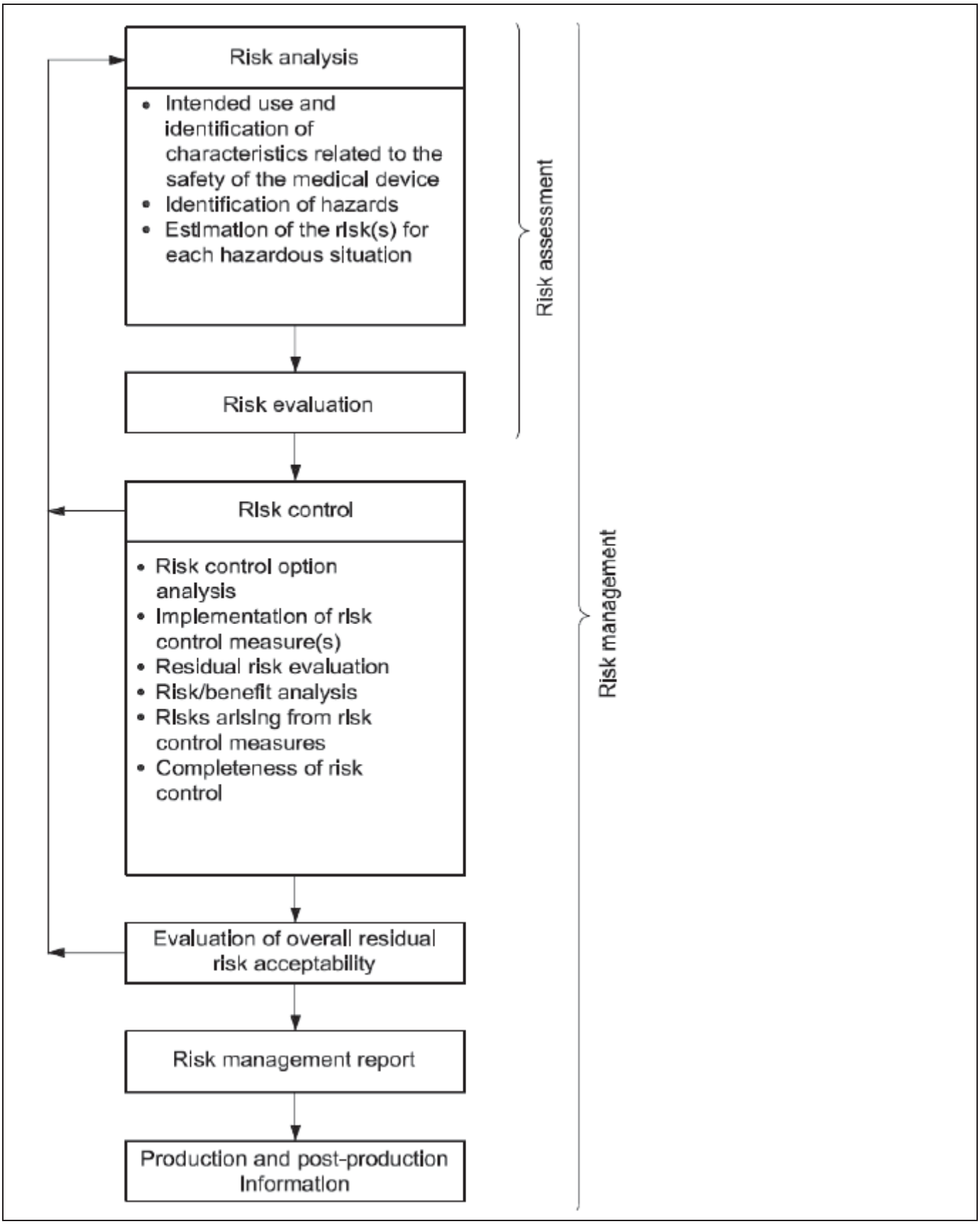
Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g. FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities			X

The Sponsor provided the following risk analysis information in Attachment (b) (4) Risk Management Procedure, which is in conformance with ISO 14971:2012 (2007 version recognized by FDA currently). It is noted that the design of the subject device is identical in its specifications to the approved RLD.

Summary of Risk Analysis:

The management of (b) (4) has established, maintains and documents an ongoing process covering the lifecycle of each medical device in which the associated hazards are identified; risks are estimated and evaluated; identified risks are controlled and the effectiveness of the controls are monitored.

The elements of the Risk Management process include risk analysis, risk evaluation, risk control, evaluation of overall residual risk, risk/benefit analysis, risk management report and production & post-production information.


Risk analysis
• Intended use and identification of characteristics related to the safety of the medical device
• Identification of hazards
• Estimation of the risk(s) for each hazardous situation
Risk evaluation
Risk control
• Risk control option analysis
• Implementation of risk control measure(s)
• Residual risk evaluation
• Risk/benefit analysis
• Risks arising from risk control measures
• Completeness of risk control
Evaluation of overall residual risk acceptability
Risk management report
Production and post-production information
Risk assessment
Risk management

Delivery Error Hazards	*Per Rafa Laboratories*
Device fluid path occlusion	*Has been adequately addressed*
Failure to inject/incomplete injection	*Has been adequately addressed*
Unexpected separation of components	*Has been adequately addressed*
Excessive drug delivery	*Has been adequately addressed (injected volume measurement)*
Component failure	*Has been adequately addressed*
Inadequate container dimensions	*Has been adequately addressed*
Inadequate/Insufficient device activation	*Has been adequately addressed*
Device aging, shipping, storage and/or use conditions result in device malfunction prior to expiry	*Has been adequately addressed*
Injection initiates prior to needle reaching the correct tissue depth of penetration	*Not yet tested; however, testing is proposed to support product approve under Abbreviated New Drug Application (ANDA)*
Premature retraction of needle before injection ends	*Has been adequately addressed by device design (i.e., dispensing time less* (b) (4) (b) (4)
Needle fracture (e.g., injection through clothing, skin	*Has been adequately addressed*
Needle unable to penetrate to correct depth of penetration (clothing, skin, etc.)	*Has been adequately addressed*

Reviewer Comments:
The Sponsor provided adequate risk analysis procedures and documentation within the DHF per ISO 14971:2012. The Sponsor adequately addressed the delivery error hazards identified by the Agency. The risk analysis documentation will be considered complete once the Fault Tree Analysis requested for the reliability of the product is provided in full.

8. LABELING

The following is the labeling in the Fact Sheets that was provided by the Sponsor – to date the FDA has provided several labeling recommendations to which the Sponsor has complied. The following is the most recent version of the Fact Sheets labeling for the HCP and Patients that incorporates recommendations from the Agency based on the testing provided by the Sponsor:

FIGURE 2: Instructions on how to administer 2 mg Rafa Atropine Auto-injector to yourself or others

8 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

11.RECOMMENDATION

Device Constituent Parts of the Combination Product are APPROVABLE with 1 Post-Market Requirement.

The Sponsor failed to supply the necessary reliability information requested on 03/29/2018 and discussed via teleconference with the Sponsor on 05/01/2018 and through a Request for Comments on 06/06/2018. Without adequate reliability information regarding the auto-injector, the consultant reviewer would normally find the application not approvable.

However, the lead review division stated during an internal meeting in June 2018 that given the context of the application and public need (i.e. lack of alternative therapies on the market for emergency-use product) it is acceptable to obtain the necessary reliability data as a post-market requirement. The following is a paraphrased statement from the lead review division:

Recognizing the importance of the product quality deficiencies and agreeing with Dr. Wilson-Lee (and CDRH consultant John McMichael) that such deficiencies would ordinarily preclude approval, I find that resolution of remaining product quality issues via the proposed PMRs and PMC is an appropriate strategy to support the approval of the atropine autoinjector given the serious and life-threatening nature of nerve agent exposure and the urgent public health need that it will address.

Recommended PMR Language:

(b) (4)

(b) (4)

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/s/

SUSAN B DAUGHERTY
07/06/2018

HUMAN FACTORS AND LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)

Office of Medication Error Prevention and Risk Management (OMEPRM)

Office of Surveillance and Epidemiology (OSE)

Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	July 3, 2018
Requesting Office or Division:	Division of Neurology Products (DNP)
Application Type and Number:	NDA 212319
Product Name and Strength:	Atropine injection, 2 mg/0.7 mL
Product Type:	Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Rafa Laboratories
Submission Date:	December 2, 2016; May 26, 2017; June 27, 2018
OSE RCM #:	2017-2330
DMEPA Safety Evaluator:	Ebony Whaley, PharmD, BCPPS
DMEPA Team Leader:	Lolita White, PharmD
DMEPA Associate Director for Human Factors:	QuynhNhu Nguyen, MS

1 REASON FOR REVIEW

This review is written in response to a request from the Division of Neurology Products (DNP) to review the proposed atropine injection (NDA 212319) autoinjector. This is a single-ingredient combination product intended for the treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides by military personnel. The reference listed drug (RLD) Atropen (NDA 17106) was approved May 15, 1973.

1.1. PRODUCT DESCRIPTION

Atropine injection (NDA 212319) is supplied as an autoinjector and is intended for administration by military personnel only in emergency settings. We note the RLD Atropen has different packaging configurations, labeling, and intended users as compared to the proposed product. For example, The RLD Atropen is also labeled for civilian use. (b) (4) We also note that the proposed product will be available in the 2 mg/0.7 mL strength and the RLD Atropen is available in 2 mg/0.7 mL, 1 mg/0.7 mL, 0.5 mg/0.7 mL and 0.25 mg/0.3 mL strengths.

Additionally, the proposed product is identical to an emergency use authorization (EUA) product, atropine injection EUA 27, from the same sponsor.[a]

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

The sponsor originally submitted an abbreviated new drug application (ANDA 209833) on December 2, 2016. The ANDA received a Refuse to File action and was subsequently resubmitted to the Agency on May 26, 2017. ANDA 209833 was administratively converted to a 505(b)(2) application on June 26, 2018 (NDA 212319).

[a] Whaley E. Emergency Use Authorization and Labels and Labeling Review for Atropine Autoinjector (EUA 27). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 DEC 22. 12 p. OSE RCM No.: 2016-2180.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Table 1. Materials Considered for this Comparative Analyses and Label and Labeling Review

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

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

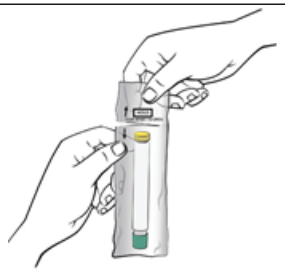
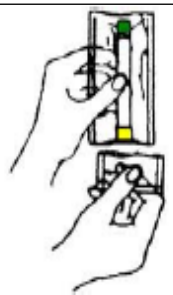
3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

The sponsor submitted comparative analyses as part of their justification for not conducting a human factors (HF) validation study.

3.1 COMPARATIVE ANALYSES: PHYSICAL COMPARISON OF DEVICE AND PRODUCT CHARACTERISTICS, TASK ANALYSIS, AND IFU LABELING DIFFERENCES

The sponsor submitted the following comparative analyses of their proposed atropine autoinjector as compared to the RLD Atropen autoinjector: (1) physical comparison of the device constituent parts and product characteristic differences, (2) comparative task analysis, and (3) labeling comparison (i.e., Instructions for Use [IFU]). We reviewed the sponsor's comparative analyses and we provide our assessment in Table 2 below.

Table 2. Comparative Analyses for proposed atropine autoinjector and Atropen				
Element	**Differences Identified**		**Sponsor's Assessment of the Differences**	**DMEPA's Assessment of the Differences**
	Proposed Product	**RLD Atropen**		
Physical Comparison o Device Constituent Parts and Product Characteristic	(b) (4) [redacted] *FDA identified difference	 (b) (4) [redacted]	The sponsor determined that there are no physical differences in the design or operation of the proposed product "that would result in user injury or treatment delays or failures compared to the RLD". We note that the sponsor identified dimensional differences in the yellow safety cap but did not identify the difference in finger flange of the yellow safety cap (see DMEPA assessment in next column).	Our review of the differences in the device constituent parts and product characteristics notes dimensional differences in the yellow safety cap of the proposed product compared to the RLD (e.g. the yellow safety cap of the proposed product is longer in length and smaller in diameter than the RLD). Our review also finds that proposed product does not have a finger flange, which is present in the RLD. The presence of a finger flange on the yellow safety cap of the RLD Atropen might assist users in removal of the cap. Although the proposed autoinjector does not contain a finger flange on the yellow safety cap, the cap does contain grooved indentations to facilitate gripping and removal. The design differences in the yellow cap may impact how user perform the critical task of cap removal. We note the sponsor did not provide additional information or data such as data from a HF validation study.

				As such, in the absence of additional information or data, we are unable to determine the impact of these differences.
Labeling Comparison: IFU (excerpt)	 (A) Hold the plastic sleeve on both sides of the perforation and tear apart at edge to open. Remove the auto-injector from the plastic sleeve. *Caution: Do not place fingers on green tip.*	 (A) Snap the grooved end of the plastic sleeve down and over the yellow safety cap. Remove the AtroPen® from the plastic sleeve. *Caution: Do not place fingers on green tip.*	The sponsor provided a side-by-side comparison of the proposed IFU and the RLD Atropen IFU. In their comparison, the sponsor noted difference in product name used and noted the exclusion of references to the 1 mg/0.7 mL, 0.5 mg/0.7 mL and 0.25 mg/0.3 mL products (not proposed by this NDA). The sponsor did not specifically comment on the differences in text used to described how to open the plastic sleeve of the proposed product as compared to the RLD. We note that since submission of the comparative human factors information, the sponsor has updated the language used to describe this task and included a revised image.	We evaluated the sponsor's IFU labeling comparison and find the instructions to open the plastic sleeve on the proposed autoinjector include steps to "Hold the plastic sleeve on both sides of the perforation and tear apart at edge to open". However, the steps to open the plastic sleeve on the RLD Atropen include steps to "snap the grooved end of the plastic sleeve down". We find the difference in the terminology for removing the plastic sleeve of the proposed product and the RLD acceptable. We have no further recommendation.
Comparative Task Analysis (excerpt)	- The proposed atropine autoinjector IFU includes the task: (b) (4) (b) (4)	- The RLD includes the task: "*Snap the grooved end* of the plastic sleeve	The sponsor's comparative task analysis notes a difference in the instructions for opening the	Our review of the comparative task analysis identified the difference in terminology for the task of opening the plastic sleeve. We find the

	(b) (4) - *Note: since submission of the comparative human factors information, the sponsor has updated the language used to describe this task to "Hold the plastic sleeve on both sides of the perforation and tear apart at edge to open".	down and over the yellow safety cap".	plastic sleeve that encloses each autoinjector of the proposed product as compared to the RLD. The sponsor finds that the comparative task analysis "demonstrates that the design and operation of the drug product is sufficiently similar to the RLD such that patients in an emergency situation could use the auto-injector safely and effectively in accordance with instructions provided for the RLD without additional physician intervention or retraining prior to use".	differences acceptable. We have no further recommendation.

3.2 LABELS AND LABELING

Our review of the proposed Prescribing Information (PI) labeling, Instructions for Use (IFU) labeling, container label and carton labeling identified areas of the PI, container label, and carton labeling which may be improved to decrease risk of medication error.

Prescribing Information

1. In the Dosage and Administration section, the route of administration is not specified.

Carton labeling

1. The carton labeling does not reflect the proposed packaging configurations.
2. The carton labeling does not include a usual dose statement as required per 21 CFR 201.55.
3. The format for the expiration date is not defined.

Container label

1. The format for the expiration date is not defined.

We provide recommendations regarding these areas below in Section 4.1 and 4.2 to help minimize the potential for medication errors to occur.

4 CONCLUSION & RECOMMENDATIONS

We find the differences in the design of the yellow cap of the proposed product compared to the RLD (e.g. the yellow safety cap of the proposed product is longer in length and smaller in diameter than the RLD) raise some question about whether the intended users (e.g. military personnel in combat gear) will be able to remove the cap and administer the injection in a reasonable time given the expected clinical manifestation of organophosphate poisoning and limited time for response in this emergency use scenario. As such, we expect that the sponsor provides data to demonstrate that military personnel, under simulated conditions expected for use of this product, will be able to use the product safely and effectively. However, we note that there is currently a drug shortage for this product. We believe from a public health perspective that the benefit of having product available for use on the market outweighs the usability concerns identified at this time. As such, we recommend making this product available as soon as possible, barring any other identified concerns, and we would ask that the data is collected by the sponsor in a HF validation study as part of a post-market requirement to demonstrate the product user interface can support safe and effective use by intended users for intended uses and in the intended environments.

Furthermore, our evaluation of the proposed container labels and carton labeling identified areas of vulnerability that may lead to medication errors. We provide recommendations in Section 4.1 for the Division and Section 4.2 for the Applicant.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information
   1. The Dosage and Administration section does not specify the route of administration. We recommend this information (e.g. intramuscular route of administration) is referenced under the subheadings "Treatment of Mild Symptoms" and "Treatment of Severe Symptoms" to mitigate the risk of incorrect route of administration errors.

B. Human Factors – Post-Marketing Requirement
   1. We identified differences in the yellow cap of the combination product as compared to the RLD Atropen (NDA 17106) (e.g. the yellow safety cap of the proposed product is longer in length and smaller in diameter than Atropen). The sponsor has not provided evidence to demonstrate that the intended users can complete the critical task of cap removal.

      Therefore, we have determined that the sponsor is required to conduct the following as a post-marketing requirement:

      "Conduct a human factors (HF) validation study that assesses the critical task of removal of the yellow cap. This study should be conducted with 15 representative users. The users should be outfitted with dress and gear that it is representative of what they would wear in a real-life scenario. Submit the human factors validation study protocol for FDA review and agreement prior to commencing the study."

      The sponsor will conduct this study according to the following schedule:

Draft HF Validation Protocol Submission:	11/2018
Final HF Validation Protocol Submission:	01/2019
HF Validation Study Completion:	04/2019
Final HF Validation Study Report Submission:	07/2019

4.2 RECOMMENDATIONS FOR RAFA

We recommend the following be implemented prior to approval of this NDA:

A. Carton labeling
    1. The carton labeling does not appear to reflect the proposed packaging configurations (40 count and 480 count). Submit separate carton labeling for each packaging configuration.
    2. The carton labeling does not include a usual dose statement as required per 21 CFR 201.55. Revise the carton labeling to include a usual dose statement such as "See prescribing information".
    3. As currently presented, the format for the expiration date is not defined. To minimize confusion and reduce the risk for deteriorated drug medication errors, identify the format you intend to use. We recommend using a format like either:

        DDMMMYYYY (e.g., 31JAN2013)

        MMMYYYY (e.g., JAN2013)

        YYYY-MMM-DD (e.g., 2013-JAN-31)

        YYYY-MM-DD (e.g., 2013-01-31)

B. Container label
    1. Refer to recommendations A.3. and revise accordingly.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Atropine that Rafa submitted on December 2, 2016, and the listed drug (LD).

Table 4. Relevant Product Information for Atropine and the Listed Drug

Product Name	**Atropine**	**Atropen**
Initial Approval Date	N/A	May 15, 1973
Active Ingredient	atropine sulfate	atropine sulfate
Indication	Treatment of poisoning by susceptible organophosphorous nerve agents having cholinesterase activity as well as organophosphorous or carbamate insecticides	
Route of Administration	Intramuscular	Intramuscular
Dosage Form	Injection solution	Injection solution
Strength	2 mg/0.7 mL	0.25 mg/0.3 mL, 0.5 mg/0.7 mL, 1 mg/0.7 mL, 2 mg/0.7 mL
Dose and Frequency	- *Adults and children weighing over 90 lbs. (41 kg) (generally over 10 years of age):* 2 mg *Mild symptoms* One (1) Atropine sulfate injection is recommended if two or more MILD symptoms of nerve agent (nerve gas) or insecticide exposure appear in situations where exposure is known or suspected. Two (2) additional Atropine sulfate injections given in rapid succession are recommended 10 minutes after receiving the first ATROPEN injection if the victim has any of the SEVERE symptoms.	- *Adults and children weighing over 90 lbs. (41 kg) (generally over 10 years of age):* 2 mg - *Children weighing 40 lbs. to 90 lbs. (18 to 41 kg) (generally 4 to 10 years of age):* 1 mg - *Children weighing 15 lbs. to 40 lbs. (7 to 18 kg) (generally 6 months to 4 years of age):* 0.5 mg - *Infants weighing less than 15 lbs. (7 kg) (generally less than 6 months of age):* 0.25 mg *Mild symptoms* One (1) ATROPEN is recommended if two or more MILD symptoms of nerve agent (nerve gas) or insecticide exposure appear in situations where exposure is known or suspected. Two (2) additional ATROPEN injections given in rapid succession are recommended 10 minutes after

	Severe symptoms If a victim is encountered who is either unconscious or has any of the SEVERE symptoms, immediately administer three (3) Atropine sulfate injections into the victim's mid-lateral thigh in rapid succession	receiving the first ATROPEN injection if the victim has any of the SEVERE symptoms. *Severe symptoms* If a victim is encountered who is either unconscious or has any of the SEVERE symptoms, immediately administer three (3) ATROPEN injections into the victim's mid-lateral thigh in rapid succession
How Supplied	Autoinjector (military use) - 40 count bulk package - 480 count bulk package	Autoinjector; military bulk pack contains 24 units per box
Storage	Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Keep from freezing. (b) (4)	Store at 25°C (77°F); excursions permitted to 15–30°C (59–86°F) [see USP Controlled Room Temperature]. Keep from freezing. Protect from light.
Container Closure/ Device Constituent(s)	(b) (4)	

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On June 25, 2018, we searched the L:drive and AIMS using the term, "atropine" to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified did not identify previous reviews for NDA 212319. However, we note that DMEPA reviewed this proposed autoinjector device under EUA 27.[bcde] We confirmed that our recommendations for EUA 27 were implemented or considered.

[b] Whaley, E. Emergency Use Authorization and Label and Labeling Review EUA 27. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2016 DEC 22. RCM No.: 2016-2180.

[c] Whaley, E. Label and Labeling Memorandum EUA 27. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 JAN 10. RCM No.: 2016-2180-1.

[d] Whaley, E. Label and Labeling Memorandum EUA 27. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 14. RCM No.: 2016-2180-2.

[e] Whaley, E. Emergency Use Authorization and Label and Labeling Review EUA 27. Silver Spring (MD): FDA, CDER, OSE, DMEPA (US); 2017 MAR 21. RCM No.: 2016-2180-3.

APPENDIX C. HUMAN FACTORS SUBMISSION

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APPENDIX G. LABELS AND LABELING

E.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,[f] along with postmarket medication error data, we reviewed the following atropine injection labels and labeling submitted by Rafa.

- Carton labeling on April 11, 2017 under EUA 27
- Container label on April 11, 2017 under EUA 27
- Prescribing Information (Image not shown) on December 2, 2016
    - PI includes Instructions for Use

E.2 Labeling images

Carton labeling

Container label

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


(b) (4)

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/s/

EBONY A WHALEY
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