

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

216359Orig1s000

OTHER REVIEW(S)



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

Date	8/5/2022		
To:	Erica Keafer		
Requesting Center/Office:	CDER/OPQ	Clinical Review Division:	Other
From	Porsche Bennett OPEQ/OHT3/DHT3C		
Through (Team)	Courtney Evans, Team Lead, Injection Team OPEQ/OHT3/DHT3C		
Through (Division) *Optional	CPT Alan Stevens, Division Director, Injection Team OPEQ/OHT3/DHT3C		
Subject	NDA216359, Midazolam ICC2200302_ICC2200303 ICCR00837383		
Recommendation	Filing Recommendation Date: 5/23/2022 ☐ CDRH did not provide a Filing Recommendation ☐ Device Constituent Parts of the Combination Product are acceptable for Filing. ☐ Device Constituents Parts of the Combination Product are Acceptable for Filing with Information requests for the 74-Day Letter, See Appendix A ☐ Device Constituents Parts of the Combination Product are Not Acceptable for Filing - See Section 5.4 for Deficiencies Inspection Recommendation: ☐ No inspection required ☐ Pre-approval inspection recommended ☐ Post-approval inspection recommended Mid-Cycle Recommendation Date: 6/14/2022 ☐ CDRH did not provide a Mid-Cycle Recommendation ☐ CDRH has no approvability issues at this time. ☒ CDRH has additional Information Requests, See Appendix A ☐ CDRH has Major Deficiencies that may present an approvability issue, See Appendix A. Final Recommendation Date: 8/5/2022 ☐ Device Constituent Parts of the Combination Product are Approvable. ☒ Device Constituent Parts of the Combination Product are Approvable with Post-Market Requirements/Commitments, See Section 2.3 ☐ Device Constituent Parts of the Combination Product are Not Approvable - See Section 2.2 for Complete Response Deficiencies		

Digital Signature Concurrence Table		
Reviewer	Team Lead (TL)	Division (*Optional)
Porsche P. Bennett -S Digitally signed by Porsche P. Bennett -S Date: 2022.08.05 13:16:05 -04'00'		 Alan M. Stevens -S3

1. SUBMISSION OVERVIEW

Submission Information	
Submission Number	NDA216359
Sponsor	RAFA LABORATORIES LTD
Drug/Biologic	Midazolam
Indications for Use	Treatment of status epilepticus in adults
Device Constituent	Auto-Injector
Related Files	DMF (b) (4), DMF (b) (4), IND 147559, NDA212319, PMR3446-1: ICC1901051

Review Team		
Lead Device Reviewer	<i>Porsche Bennett</i>	
Discipline Specific Consults	Reviewer Name (Center/Office/Division/Branch)	CON #
N/A	N/A	N/A

Important Dates	
Discipline-Specific Review Memos Due	N/A
Final Lead Device Review Memo Due	07/08/2022
Interim Due Dates	
	Meeting/Due Date
Receipt Date	03/28/2022
Filing	04/19/2022
74-Day Letter	06/10/2022
Mid-Cycle	06/14/2022
Primary Review	08/01/2022
PDUFA	08/05/2022
Sponsor Meeting(s)	Unknown

2. EXECUTIVE SUMMARY AND RECOMMENDATION

CDRH recommends the combination product is:

- Approvable – the device constituent of the combination product is approvable for the proposed indication.
- Approvable with PMC or PMR, [See Section 2.3](#)
 - Not Acceptable – the device constituent of the combination product is not approvable for the proposed indication. We have Major Deficiencies to convey, [see Section 2.2](#).

Section	Adequate			Reviewer <u>Notes</u>
	Yes	No	NA	
Device Description	X			
Labeling	X			Potential inadequacies have been found with the instructions for use and noted below in comment 1 to CDER. Adequacy of instructions for use is deferred to CDER.
Design Controls	X			
Risk Analysis	X			
Design Verification	X			
Consultant Discipline Reviews			X	
Clinical Validation	X			
Human Factors Validation			X	
Facilities & Quality Systems	X			Facilities review was not fully conducted as a post approval inspection was recommended; however, a quality systems review was conducted and determined to appear adequate.
Reliability		X		Refer to recommended PMR in Appendix A.

2.1. **Comments to the Review Team**

- CDRH does not have any further comments to convey to the review team.
- CDRH has the following comments to convey to the review team:

Comment #1: On page 2 of the *draft -labeling-text-instructions-for-use* there appears to be a spacing issue in some of the text. Additionally, the instructions for use does not include the indications for use. However, the indications for use does state the drug product name and includes steps to determine if the 10 mg Midazolam autoinjector is appropriate based on age/dose and recognize if the patient is in status epilepticus. Determination of instructions for use adequacy is deferred to CDER. **Resolved.**

Comment #2: On page 14, risks 4.1 and 4.4 of *QD-RM-012 Midazolam Auto-Injector Risk Analysis Rev. 1.1* there are risks (b)(4) that do not appear to be reduced as far as possible in accordance to ISO14971: 2012. The risks were not determined to be acceptable and the firm stated, “further analysis required.” The failure modes appear to be process failure (b)(4) as opposed to design failure modes; however, the firm should provide further detail for this failure mode will be further analyzed and process controls that are in place to reduce the risk as far as possible.

2.2. Complete Response Deficiencies

- There are no outstanding unresolved information requests, therefore CDRH does not have any outstanding deficiencies.
- The following outstanding unresolved information requests should be communicated to the Sponsor as part of the CR Letter:

2.3. Recommended Post-Market Commitments/Requirements

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

Post-Market Commitment or Requirement: Provide an updated Fault Tree Analysis and the associated reliability requirements and specifications to demonstrate that Midazolam Injection, 10 mg/0.7 mL, autoinjector will provide successful injection with at least 99.999% reliability at the 95% confidence interval. The Fault Tree Analysis must include information from your combination product's design and manufacturing methods by identifying all basic failure modes anticipated.

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3. PURPOSE/BACKGROUND

3.1. Scope

RAFA LABORATORIES LTD is requesting approval of Midazolam. The device constituent of the combination product is an auto-Injector.

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

Technical engineering request for a new Original Priority Review request for NDA 216359 that was received on 3/28/2022. The PDUFA is scheduled for 9/28/2022, but the clinical division will be targeting an earlier action date (07/28/2022) due to the high level attention because this product is intended to replace the no longer manufactured DoD CANA (diazepam autoinjector) for the treatment of nerve agent induced SE.

The goal of this memo is to provide a recommendation of the approvability of the device constituent of the combination product. This review will cover the following [review areas](#):

- Device Performance
- Device Biocompatibility
- Device Reliability (95/99.999%)
- Facilities Inspection Recommendation

This review will not cover the following review areas:

- Human Factors Review
- Pre-approval Inspection Review (Post-approval inspection recommended)
- Drug Substance and Drug Product Review

The original review division will be responsible for the decision regarding the overall safety and effectiveness for approvability of the combination product.

3.2. Prior Interactions

FDA had the following previous interactions with the firm prior to this NDA submission (Notable excerpts from CDRH):

- **Pre-IND 147559 Meeting – 16 March 2020 (Meeting Minutes in Module 1.6.3)**
 - Discussion related to CDRH: Obtain concurrence that the **reliability study performed for the atropine autoinjector in accordance with NDA 212319 PMR 3446-1** supports the approval of the currently proposed product.
 - FDA Response:

Question 1 (a, b): Briefly, as described in Section 5, Midazolam Injection, 10 mg is manufactured at Rafa Laboratories, Ltd. using a conventional pharmaceutical manufacturing process including (b) (4)

1(a). Does the Agency agree that the specifications for the API, filled cartridges and the fully assembled drug product are acceptable?

FDA Response to Question 1(a):

In general, the proposed test parameters for the API, filled cartridges, and assembled product appear appropriate; however, you should address the concerns below. The adequacy of the analytical procedures and acceptance criteria will be a matter for review.

You list the device constituent specifications that will be measured at lot release in Table 13; these include activation force, solution volume, needle effective length, injection speed, safety pin extraction force, amongst others. Please see the following comments regarding your device release specifications:

- Ensure that the "Solution Volume" test incorporates the volume measurement after it is dispensed from the injector after activation, in alignment with FDA recognized standards ISO 11608-5 - Needle-based injection systems for medical use — Requirements and test methods— Part 5: Automated functions and USP Chapter (697) CONTAINER CONTENT FOR INJECTIONS, Injections in Cartridges or Prefilled Syringes, and that this test is not simply cartridge fill volume.
- Clarify if the injection speed test is determining the dispense time of the solution from the injector after activation.
- In a future submission, when listing your device release specifications, please include the AQL levels with acceptance/rejection limits for each release test/specification. Your acceptance limits should be established around the risk associated with failure to meet the corresponding specification.

1(b). Does the Agency agree with the proposed stability plan for the primary stability batches?

FDA Response to Question 1(b):

In general, the proposed stability plan appears acceptable. However, we recommend that safety pin extraction force be verified after aging to the proposed shelf life, given the intended use of your product, and that the force to remove the safe pin is necessary for the user to complete a successful injection.

Question 2: Except for the minor changes described in Section 3.5.3, the container closure configuration and autoinjector device components used for Midazolam Injection, 10 mg are identical to those approved in Rafa Laboratories, Ltd.'s Atropine Injection, 2 mg NDA (NDA 212319, approved July 9, 20198). In accordance with NDA 212319 PMR 3446-1, Rafa conducted a reliability demonstration study as described in Section 4.4.

Does the Agency agree that the reliability, as demonstrated via NDA 212319 PMR 3446-1, is acceptable to support the proposed indication?

FDA Response to Question 2:

Specific to reliability of Successful Injection, with a specification of 99.999% reliability, as determined by a fault tree analysis (FTA), using design and manufacturing elements, it is possible that you may be able to leverage reliability information from the FTA conducted in NDA 212319 to support the reliability, measured by FTA, for the proposed midazolam injection device, given the similarities between the midazolam injection device and the approved atropine device design and assembly process that you describe. However, for you to be able to appropriately leverage the reliability information from the atropine injection device, the overall device design (including critical component design, the device/component manufacturing, and overall design control strategy) must be identical or very similar as well. Otherwise, additional information will be necessary.

See the following comments that will require further information to determine if reliability information, derived from your FTA for the Atropine injection device (approved under NDA 212319), can be leveraged:

- Aside from the colors of the needle cap and safety ^{(b) (4)} confirm if the proposed midazolam injector device design is identical and if the components and component design are identical to the approved atropine injector device. If not, in a future submission, you should provide a comparison of these aspects and identify in the FTA how the differences could result in different failure modes.
- Confirm that the proposed midazolam injection device manufacturing/assembly process is identical to the approved atropine injector device. If these are not identical, in a future submission you should provide a comparison of these aspects and link to the appropriate data in the FTA.
- In a future submission, you should provide a full comparison of the design control strategy for the proposed midazolam injection device to that of the approved

atropine injection device; this should include a comparison of the respective acceptance/receiving controls, in-process controls, and release controls that are in place.

Specific to the verification of your reliability specifications for Successful Injection, it is unclear if verification testing from the atropine injection device can be leveraged and used to support verification of your reliability specifications for the midazolam injection device. Midazolam (10 mg) and atropine (2 mg) are different solutions, likely with different fluid viscosities and other fluid characteristics. Since the fluid characteristics may influence the device functional results, we expect verification of the device essential performance requirements (EPRs) will be conducted using the final finished combination product. Your reliability testing should include verifying the EPRs of your device constituent to support the reliability specifications of your combination product, over the expiry period, considering worst case use conditions and preconditioning: i.e., shipping, aging, storage orientation/conditions, vibration, shock, environmental factors, etc.

Given that your top-level reliability specification should be based around "successful injection", we recommend that performance attributes that are considered as essential for completing a successful injection be verified. For your product design, we expect this to include:

- Dose Accuracy
- Extended Needle Length
- Dispense Time
- Activation Force
- Safe Pin Removal Force

Please note that the NDA 212319, PMR 3446-1 Final Report is currently under FDA review and that a determination has not yet been made that the PMR conditions have been met.

- **Type C Meeting (PIND147559)- 19 May 2021 (Written responses in Module 1.6.3)**
 - Discussion related to CDRH: The purpose of this Type C meeting is to further discuss the product quality and reliability and to clarify the Division's non-hold comments and responses to the sponsor's questions that were included in the February 9, 2021, May Proceed letter.
 - FDA Response:

Question 1: Does the Agency agree that Depth of Penetration and Needle Integrity Post-Injection results for Atropine Injection, 2 mg (NDA 212319 PMR 3446-1) can be referenced to support approval of the NDA for Midazolam Injection, 10 mg?

FDA Response to Question 1:

We reviewed your supporting information to eliminate the Depth of Penetration and Needle Integrity Post-Injection testing from the Midazolam functional testing plans and to rely instead on historical data generated from the Atropine functional testing studies, which used methylene blue dye solution without active pharmaceutical ingredient. You stated that the autoinjector device assembly proposed for use with Midazolam, including the device design, components, and design of components (with the exceptions of injector cap color and safety pin), along with the instructions for use related to handling and injection of the drug product (with the exception of use only as buddy aid), are the same as those described in Rafa's Atropine Injection (NDA 212319, approved July 9, 2018). The proposed Midazolam injection device

(b) (4)

(b) (4)

(b) (4)

(b) (4)

You included the results of your Atropine Depth of Penetration and Needle Integrity Post-Injection tests in NDA 212319 in Report R1703303-02-01, "Rafa (b) (4) Atropine Auto-injector Performance Testing: Depth of Penetration and Needle Integrity Post Injection Testing." You stated that the statistical analysis found that changing the drug did not affect the essential parameters of Delivered Volume and Injection Time, which are related to the flow characteristics of solutions, and that the density of fluids is almost identical. Therefore, it can be concluded that the Depth of Penetration will also behave essentially identically and that the Atropine data are representative of the Midazolam data. However, your evaluation of flow characteristics did not consider drug solution viscosity, which may be different due to the difference in drug concentrations (2 mg Atropine vs. 10 mg Midazolam in solution) and which may impact the flow

characteristics. Based on this, please discuss drug solution viscosity in your flow characteristics evaluation and address how a difference would impact the Depth of Penetration and Needle Integrity Post-Injection test results. In addition, please include standard deviations in your Delivered Volume and Injection Time results and provide a rationale for why the (b) (4) difference in Injection Time should not be considered significant in flow characteristics.

Question 5: Does the Agency agree that data available from the reliability study will suffice, so there is no need to test injection time after wear I or II on a routine basis?

FDA Response to Question 5:

You state that Injection Time will be tested after rigorous preconditioning wear cycles as part of the Midazolam Reliability Study for the Midazolam Autoinjector investigational product. To support a high degree of reliability, we recommend that your worst-case discussion address how your proposed pre-conditioning compares to the Erosion I and Erosion II cycles, and why it should be considered the worst-case wear condition. We also note that the acceptability of your reliability study will still be determined at the time of NDA submission.

Question 6: Does the Agency agree there is no need for biocompatibility study?

FDA Response to Question 6:

We acknowledge that the injector cap and safety pin of the autoinjector device are not in contact with the drug product included in the cartridge. However, it is necessary to assess the biocompatibility of the injector cap and safety pin because they will likely be in transient contact with the patient's skin during use. Hence, please perform biological evaluation of these components using a risk-based approach per FDA's Biocompatibility Guidance "Use of International Standard ISO 10993-1, 'Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process,'" (<https://www.fda.gov/media/85865/download>). Depending on the risk associated with the materials of construction, the biological evaluation may include testing and/or the scientific rationale for why testing of these components is not needed.

ADDITIONAL CDRH COMMENTS

1. **Additional feedback on your statistical analysis:**

Your lot-to-lot variability analysis included two lots with a sample size of at least 64 units from each lot. We recommend that you should test at least three lots to determine the lot-to-lot variability/consistency with statistical confidence, and, in addition, discuss why a sample size of 64 units represents statistical significance.

• **Pre-NDA Meeting- 19 August 2021 (Meeting Minutes in Module 1.6.3)**

- Discussion related to CDRH: The purpose of the pre-NDA meeting is to identify of any issues that would prevent filing of the application. The sponsor plans to submit an NDA through the 505(b)(2) regulatory pathway and to rely on the safety and effectiveness of the listed drug Seizalam (NDA 209566).
- FDA Response

Question 1: Does the Agency have any comments on orphan-drug exclusivity?

FDA Response to Question 1:

We acknowledge receipt of the letter from Meridian Medical Technologies (Meridian) dated April 16, 2021, which indicates that Meridian has agreed to selectively waive unexpired orphan-drug exclusivity for Seizalam for the treatment of status epilepticus, solely with respect to the autoinjector formulation of midazolam that Rafa Laboratories (Rafa) is developing for the treatment of status epilepticus. Due to this selective waiver, Rafa is not required to demonstrate clinical superiority of its autoinjector formulation of midazolam over Meridian's autoinjector formulation of midazolam for the treatment of status epilepticus in order to receive marketing approval. However, please be aware that, if another midazolam product receives marketing approval for the treatment of status epilepticus prior to Rafa receiving marketing approval for this indication, Rafa may then be required to demonstrate clinical superiority of its autoinjector formulation of midazolam over the other approved midazolam product(s).

Question 5: Will the Agency consider scheduling the facility inspection to support both the routine CGMP inspection and the pre-approval inspection for Midazolam Injection, 10 mg?

FDA Response to Question 5:

The necessity and timing for a pre-approval inspection are dependent upon multiple factors. The Agency will make the determination regarding the need for pre-approval inspection during the review of the NDA. For further information, please refer to FDA's drug compliance and pre-approval inspection programs:
<https://www.fda.gov/media/71498/download>

Question 11a: Does the Agency agree that the long-term and accelerated stability specifications are acceptable for the NDA submission to support commercial production?

FDA Response to Question 11a:

Acceptability of your proposed stability specification, including acceptance criteria and tests methods, will be determined at the time of NDA submission, when all of the data can be evaluated in their entirety. At this time, we have the following comments:

- Identification solely by a single chromatographic retention time is not regarded as being specific. We recommend that you include a second identification test in your proposed drug product specification. The use of two chromatographic procedures, where the separation is based on different principles, or a combination of tests into a single procedure, such as HPLC/UV diode array, HPLC/MS, or GC/MS, is generally acceptable.
- Include viscosity, deliverable volume, and (b) (4) tests in the proposed specifications or provide justification for not including these tests.
- List acceptance limits for each known impurity separately in the proposed drug product specification.

Rafa Response:

Rafa thanks the Agency for comments on the specification.

Rafa comment for first bullet: a second identification method will be added as per FDA's request.

Rafa comment for second bullet: Viscosity: Rafa would like the FDA to consider the following justification for not including viscosity in the product's specifications:

- Viscosity is not a Key Quality Attribute for the drug product because the viscosity of Midazolam Injection is very close to the viscosity of water.

(b) (4)

Does the Agency agree with the justification for not including viscosity in the proposed drug product specification?

Meeting Discussion:

The Agency agreed that, if the formulation is (b) (4) (b) (4) then the applicant does not need to include viscosity testing in the product specification.

Deliverable Volume:

Rafa would like to clarify that deliverable volume (solution volume/dispensed volume as described in Table 17 of the meeting briefing package) is already included in the specification for the autoinjector. In addition to container volume testing at Rafa, (b) (4) tests dispensed volume. Deliverable volume is tested by (b) (4) and the relevant details reported in section 3.2.P.7 of the IND will be moved to section

3.2.P.5.1 of the NDA.

Does the Agency agree that the appropriate location of the deliverable volume details is Section 3.2.P.5.1 of the NDA?

Meeting Discussion:

The Agency recommended that the deliverable volume details be submitted in section 3.2.P.7 along with other device performance data. The Agency asked the applicant to provide a justification to support their proposed specification in the NDA submission.

Question 11f: Does the Agency agree that the NDA can be filed with 6 months of stability data if 12-month data will be available for submission within 60 days of the original submission to expedite availability of this critical drug product?

FDA Response to Question 11f:

The Agency typically expects 12 months of stability data at the time of NDA filing. However, given the military importance of the proposed product, the Agency will review 9- and 12-month stability data submitted within 60 days of the original submission.

Question 13b: Does the Agency agree that the specifications for the API, filled cartridges, and assembled autoinjectors are acceptable?

FDA Response to Question 13b:

See the response to Question 11a for comments on the proposed drug product specification. Note that the final product specifications should apply to the fully assembled autoinjector.

The API specifications appear reasonable for the NDA filing. The final decision on the adequacy of the specification will be done when reviewing the full NDA submission and any cross-referenced drug master files (DMFs). Please provide a Letter of Authorization to cross-reference a DMF. If information is provided in a DMF, we request that the following information be provided in the NDA for ease of review: general information, physico-chemical properties, and specifications. Please also submit a Certificate of Analysis of the drug substance.

Rafa Response:



Meeting Discussion:

The Agency clarified that the regulatory specification applies to the fully assembled product and that an appropriate test should be included in the specification. The applicant may adopt an alternative test for lot release. However, if a quality concern is identified later, the product must meet the regulatory test.

Question 14: Does the Agency agree that upon NDA approval, the first three commercial batches will be considered validation batches?

FDA Response to Question 14:

The Agency does not approve process validation approaches, protocols, or the number of specific batches used in process validation studies. The actual protocols, acceptance criteria, and study outcomes (as applicable) will be evaluated during a pre-approval inspection of your manufacturing facilities. The product design and the suitability of manufacturing processes and control strategy will be evaluated during

the NDA review cycle. It is your responsibility to conduct all studies necessary to assure your commercial manufacturing process is capable of consistently delivering quality product.

The Agency requires that drug manufacturers validate their manufacturing processes [21 CFR 211.100(a) and 211.110(a)] prior to commercialization but does not prescribe how that is to be accomplished because it will depend on multiple factors, some of which are specific to the complexity of the product and process. The process validation protocol should be built on an understanding of the process gathered from experience executing development batches (Process Validation Stage 1). Subsequent design of the facility and qualification of equipment/utilities and operational performance qualification (Process Validation Stage 2) should be incorporated into the proposed commercial scale manufacturing process and control strategy. Likewise, knowledge obtained during transfer and scale up activities can be useful in further developing the control strategy. Successful process validation should also include a plan for continued process verification (Stage 3).

For additional information, please see references cited after our response to Question 18.

Question 15: Does the Agency agree that Depth of Penetration and Needle Integrity Post-Injection results for Atropine Injection, 2 mg (NDA 212319) can be referenced to support approval of the NDA for Midazolam Injection, 10 mg, given the viscosity results for these drug products?

FDA Response to Question 15:

We acknowledge you have measured the viscosities of the midazolam vs. atropine solutions to compare their flow characteristics. The percent relative difference in viscosity for midazolam vs. atropine was found to be 0.3% (Table 20; $p \geq 0.05$), which led to your conclusion that flow characteristics are similar between the drug products, and that, therefore, the atropine Depth of Penetration and Needle Integrity Post-Injection results of atropine are representative of those for midazolam. Based on this finding, it may be reasonable to leverage the Depth of Penetration and Needle Integrity Post-Injection testing of atropine injection.

Question 16: Does the Agency agree that no further evaluation of the biocompatibility of the components is needed?

FDA Response to Question 16:

We reviewed the supporting information provided to eliminate biocompatibility testing of the injector cap and safety pin. Based on this information, it appears that there is no increased risk for toxic effects on skin and, hence, a risk assessment may be adequate to address the biological evaluation of the injector cap and safety pin.

Question 18: Does the Agency agree with the control strategy approach for Midazolam Injection, 10 mg?

FDA Response to Question 18:

Regarding the control strategy for the commercial manufacturing process, your approach appears reasonable

(b) (4)

(b) (4)

Reference:

(1) 21 CFR Part 211 Current Good Manufacturing Practice for Finished Pharmaceuticals

(2) FDA's Guidance for Industry, Process Validation: General Principles and Practices

(3) FDA's Guidance for Industry, Q8(R2) Pharmaceutical Development

(4) FDA's Guidance for Industry, Q9 Quality Risk Management

(5) FDA's drug Compliance and pre-approval inspection programs:
<https://www.fda.gov/media/71498/download>

(6) Guidance for Industry for the Submission Documentation for Sterilization Process Validation in Applications for Human and Veterinary Drug Products, 1994:
<https://www.fda.gov/regulatory-information/search-fda-guidance-documents/submission-documentation-sterilization-process-validation-applications-human-and-veterinary-drug>

(b) (4)

Reviewer Comment

The firm had a few discussions with FDA, with the follow key takeaways:

- **No additional biocompatibility testing needed:** The injector cap and safety pin are of a different color than the firm’s previously approved combination product. However, the firm submitted adequate assessment to demonstrate there are no increased risks for toxic effects on the skin and therefore, historic data from the previously approved AI can be leveraged. Therefore, it does not appear that the firm needs biocompatibility data for the autoinjector.
- **No additional depth of penetration and needle integrity post injection data needed:** The firm requested to leverage depth of penetration and needle integrity post injection data from their previously approved AI (NDA212319). The firm conducted a viscosity assessment comparing flow characteristics. It was determined that the firm’s previously approved autoinjector data for depth of penetration and needle integrity post injection could be leveraged.
- **9 and 12 month stability data can be submitted by the firm within 60 days of submission:** FDA agreed the firm could submit 6 months stability data for filing submission and then FDA would review 9 and 12 month stability data within 60 days of submission.
- **NDA212319 PMR 3446-1 reliability may be reasonable to leverage if certain conditions are met:** overall device design, manufacturing, and control strategy must be the same or very similar. Note: The PMR was still under review during the time of the meeting request and FDA informed the firm adequacy of the PMR was not yet determined at that time. Thus, leveragability is contingent on overall device design, manufacturing, and control strategy must be the same or very similar, as well as acceptability of reliability for the leverageable combination product.
- **Control strategy appeared reasonable-** Should include in-coming inspection, in-process controls, and release testing.

3.2.1. *Related Files*

- PIND147559: Pre-IND to this submission
- NDA212319: The firm received approval for atropine injection NDA212319, July 2018. The firm requests to leverage PMR 3446-1 for conducted reliability study. The autoinjector used for Midazolam Injection, 10 mg is the same as the one used for Atropine Injection, 2 mg (NDA 212319), with the exception of the colors of the cap and safety pin.
- NDA209566: The firm wants to rely on the safety and effectiveness of NDA209566

3.3. Indications for Use

Combination Product	Indications for Use
Midazolam	Treatment of status epilepticus in adults
Auto-Injector	Delivery of the Drug Product

3.4. Materials Reviewed

Materials Reviewed	
Sequence	Module(s)
0001	3.2.P.7 Container Closure System
0001	1.6.3 Correspondence Regarding Meetings (FDA previous interactions with the firm for this submission)
0001	1.14 Labeling (container, carton, pouch, IFU)
0001	5.3.1.2 Comparative BA and Bioequivalence Study Report (Phase 1 open label comparison study)
0001	3.2.P.8 Stability

0005	3.2.P.7 Container Closure System
0007	3.2.P.7 Container Closure System
0010	3.2.P.8 Stability
0001, 0005, 0007, 0008 and 0011	1.11.1 Quality Information Amendment

4. DEVICE DESCRIPTION

4.1. Device Description

The firm is developing an autoinjector delivery system to support the U.S. government efforts for improved nerve agent countermeasures.

The proposed combination product, Midazolam is a single-dose autoinjector prefilled with 10 mg Midazolam (0.7 mL) for single-patient use. The injection site is the mid-outer thigh in the vastus lateralis muscle, into which the 22-gauge needle is inserted approximately (b) (4) mm – (b) (4) mm. The autoinjector can be used by trained healthcare or military personnel in both clinical settings and austere operational environments (i.e., chemical, biological, radiological, and nuclear [CBRN] battlefield) as buddy aid.

The mechanical device is a nose-pressure-activated automatic injector suitable for rapid intramuscular (IM) administration of the contained medication. The container closure system consists of two parts: 1) the cartridge (primary packaging), including (b) (4) cylinder containing the medicinal solution, stainless-steel needle, (b) (4); and 2) the firing mechanism (functional secondary packaging), which delivers the medicinal content of the cartridge to the patient. The dose cannot be adjusted. At rest, the container closure system does not permit visibility into the contents, including the needle. Following activation by removing the safety cap and firmly injecting into the outer thigh, the needle is ejected by the plunger in the firing action, providing visual feedback that the injection was completed.

*The firing mechanism is (b) (4).
Once the injector is pressed (b) (4) (b) (4)*

Figure 3: Midazolam Injection, 10 mg/0.7 mL Device Assembly Components

(b) (4)



4.2. Steps for Using the Device

4.3. Device Description Conclusion

DEVICE DESCRIPTION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
<u>Reviewer Comments</u> The safety cap has to be removed to allow for device activation. There is visual feedback that the injection was completed (i.e., extended needle). These two design capabilities should be essential performance requirements and have associated testing and C/R, especially given the device is for emergency use. It is confirmed that the firm has determined both safety pin extraction force and needle effective length to be EPRs. Adequacy of testing of EPRs will be discussed and determined in section 9, Design verification review. There were no IRs issued for the device description. The device description was determined to be adequate.		
CDRH sent Device Description Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

5. FILING REVIEW

CDRH performed Filing Review	☒
CDRH was not consulted prior to the Filing Date; therefore, CDRH did not perform a Filing Review	☐

5.1. Filing Review Checklist

Filing Review Checklist				
Description	Present			
	Yes	No	N/A	
Description of Device Constituent (3.2.P.7 Container closure system)	X			
Device Constituent Labeling (1.14.1.1 Labeling- Instructions for use, and 1.14.1.2.carton and container label)	X			
Letters of Authorization			X	
Essential Performance Requirements defined by the application Sponsor (3.2.P.7- Container-closure- system, page 8/62).	X			
Design Requirements Specifications included in the NDA / BLA by the application Sponsor (3.2.P.7- Specifications for Atropine Autoinjectors)	X			
Design Verification Data included in the NDA / BLA or adequately cross-referenced to a master file. (3.2.P.7- QD-VSR-011 Verification and Validation Summary Report)	X			
Risk Analysis supplied in the NDA / BLA by the application Sponsor		X		
Traceability between Design Requirements, Risk Control Measures and V&V Activities		X		
Verification/ Validation Check	Full Test Reports for Verification and Validation Testing		X	
	Engineering Performance (must include Safety Assurance Case for Infusion Pumps)	X		
	Reliability	X		
	Biocompatibility (3.2.P.2- Pharmaceutical Development- Rationale that biocompatibility assessment isn't needed) , (3.2.P.7, Appendix B, justification for using risk assessment to evaluate injector cap and safety pin pg. 23/26).			X
	Sterility (autoinjector isn't sterile, primary container (prefilled syringe) is assessed by CDER)			X
	Software			X
	Cybersecurity			X
	Electrical Safety			X
	EMC/RF Wireless			X
	MR Compatibility			X
	Human Factors (3.2.P.7, Appendix C, page 25 and 26/26- Justification for leveraging Atropine's Human Factor validation study for midazolam injection)			X
	Shelf Life, Aging and Transportation (3.2.P.7- PQR- VAL-006 Shipping Validation Summary Report).	X		
	Clinical Validation (5.3.1.2- Clinical study report (bioequivalence study), 5.3.1.3- Study MVLN-MDZ-010): Comparability report to waive in vivo studies)	X		
	Human Factors Validation (3.2.P.7, Appendix C, page 25 and 26/26- Justification for leveraging Atropine's Human Factor validation study for midazolam injection)			X
Description of Device Manufacturing Process (3.2.P.7- Container closure system, page 56, section 7.9)	X			

Quality Systems/ Manufacturing Controls Check	Description of Quality Systems (Drug cGMP-based, Device QSR-based, Both)- (3.2.P.7- Container closure system, page 60, section 7.10)	X		
	CAPA Procedure ((3.2.P.7- Container closure system, page 62, section 7.10.3)	X		
	Control Strategy provided for EPRs		X	

Reviewer Comment

Risk Analysis- The firm did not provide an adequate risk analysis. The firm provided a report, QD-RM-013 Risk Management Report Rev. 1.0; however, the report does not include an analysis of the risk of the device but more so expound on the risk management plan. The firm has set low confidence and reliability levels for low, medium, and high risks, so it is important to ensure the risk determination for performance attributes are adequate. **Refer to Information Request 5**, and Section 8 (Risk Management Review) for additional assessment and determination of adequacy.

Traceability matrix- It does not appear the firm has included a trace matrix in their NDA submission. **Refer to Information Request 5**, and Section 8 (Risk Management Review) for additional assessment and determination of adequacy.

Full test report- The firm has provided test reports for some, but not all performance attributes, particularly essential performance requirements. It is important to obtain an adequate summary of performance for each attribute that included data analysis. **Refer to Information Request 1**, and Section 9 (Design Verification Review) for additional assessment and determination of adequacy.

Transportation validation report- The firm provided a summary report which states the attributes that were tested (EPRs), the sample size, test method, and that performance was tested before and after simulation; however, the firm did not provide actual data in the report for data analysis, but solely stated whether testing passed or failed. **Refer to Information Request 1**, and Section 9 (Design Verification Review) for additional assessment and determination of adequacy.

Aging testing- The firm tested the device at accelerated, long term, and intermediate time points. The firm conducted the intermediate study (30 ± 2°C /75 ± 5%RH testing condition) in the event a significant change occurs during accelerated testing at 40 ± 2°C/75 ± 5%RH. The firm noted in 3.2.P.8.3- stability- summary, page 3, footnote 1, to date, there have been no out-of-specification results. The firm did not provide detailed data information such as min, max, and standard deviation for the stability data, the firm solely provided what appears to be the mean of the data. Additionally, the firm did not conduct any data analysis (e.g., k factor) to demonstrate reliability. Lastly, the firm did not specify if the testing was done sequentially (i.e., post transportation simulation). **Refer to Information Request 1**, and Section 9 (Design Verification Review) for additional assessment and determination of adequacy.

Quality systems and CAPA procedure: the firm did not provide enough detail with regards to their quality systems and CAPA procedure. **Refer to Information Requests 2 and 3**, and Section 12.2.2 and 12.2.3 for additional assessment and determination of adequacy.

Control strategy: The firm provided a high level process/manufacturing description and explains certain controls at specific manufacturing steps; however, the overall control of each EPR is unclear. **Refer to Information Request 4** and Section 12.2.4 for additional assessment and determination of adequacy.

Design Validation- It is unclear if the firm used the to-be-marketed configuration in the bioequivalence study. **Refer to Information Request 6**.

5.3. Quality System Documentation Triage Checklist

Was the last inspection of the finished combination product manufacturing site, or other site, OAI for drug or device observations?	☐ Yes ☒ No ☐ UNK
Is the device constituent a PMA or class III device?	☐ Yes ☒ No ☐ UNK
Is the final combination product meant for emergency use?	☒ Yes ☐ No ☐ UNK
Is the combination product meant for a vulnerable population (infants, children, elderly patients, critically ill patients, or immunocompromised patients)?	☐ Yes ☐ No ☐ UNK
Does the manufacturing site have a significant and known history of multiple class I device recalls, repeat class II device recalls, a significant number of MDRs/AEs, or OAI inspection outcomes?	☐ Yes ☐ No ☐ UNK
Is the combination product meant for users with a condition in which an adverse event will occur if the product is not delivered correctly (example insulin products for specific diabetic patients)?	☐ Yes ☒ No ☐ UNK
Does the manufacturing process for the combination product device constituent part use unique, complicated, or not well understood methods of manufacturing?	☐ Yes ☒ No ☐ UNK
cGMP Risk:	
☐ Low or Moderate Risk of cGMP issues: If yes is not checked above, please fill out the checklist and deficiencies only. A review summary is optional.	
☒ High Risk of cGMP issues: If yes is checked anywhere above, consider filling out the checklist, the deficiencies, and the review summary. If a full review is not warranted due to other factors such as device constituent classification (class I and class II devices), a low or moderate overall risk of device constituent failure, or positive compliance history, please document your rationale below for not conducting a full ICCR review.	

5.4. Filing Review Conclusion

FILING REVIEW CONCLUSION	
Acceptable for Filing: ☒ Yes ☐ No (Convert to a RTF Memo) ☐ N/A	
Facilities Inspection Recommendation: ☐ (PAI) Pre-Approval Inspection ☒ Post-Approval Inspection ☐ Routine Surveillance ☐ No Inspection ☐ N/A	
Site(s) needing inspection: Shalon Chemical Industries Ltd. 14 Heshvan St. Kiryat, Gat. Israel, 8202373 FEI: 3012775596	
<u>Reviewer Comments</u> N/A	
Refuse to File Deficiencies: ☐ Yes ☒ No ☐ N/A	
74-Day Letter Deficiencies: ☒ Yes ☐ No ☐ N/A 6 Information Requests were sent to the firm on 06/14/2022 with a requested due date of 06/21/2022. The 74 day Information Request were not high level deficiencies where overall documentation was missing, but more so granular deficiencies. Therefore, refer to the Risk management, design verification, design validation, and facilities sections below for discussion and adequacy determination of the 6 Information Request responses from the firm.	

6. LABELING

6.1. General Labeling Review

The labeling, including the device constituent labeling, user guides, patient information, prescriber information and all other labeling materials provided for review were reviewed to meet the following general labeling guidelines as appropriate:

General Labeling Review Checklist	Adequate?		
	Yes	No	N/A
Indications for Use or Intended Use; including use environment(s); route(s) of administration for infusion, and treatment population.	X		
Drug name is visible on device constituent and packaging	X		
Device/Combination Product Name and labeling is consistent with the type of device constituent	X		
Prescriptive Statement/Symbol on device constituent	X		
Warnings (<i>do not freeze, excursion permissions, injection only sites, Rx Only</i>)	X		
Contraindications	X		
Instructions for Use (<i>device label and instructions for use</i>)	X		
Final Instructions for Use Validated through Human Factors		X (<i>draft labeling only</i>)	
Electrical Safety Labeling/Symbols			X
EMC Labeling/Symbols			X
Software Version Labeling			X

MRI Labeling/Symbols			X
RF/Wireless Labeling/Symbols			X

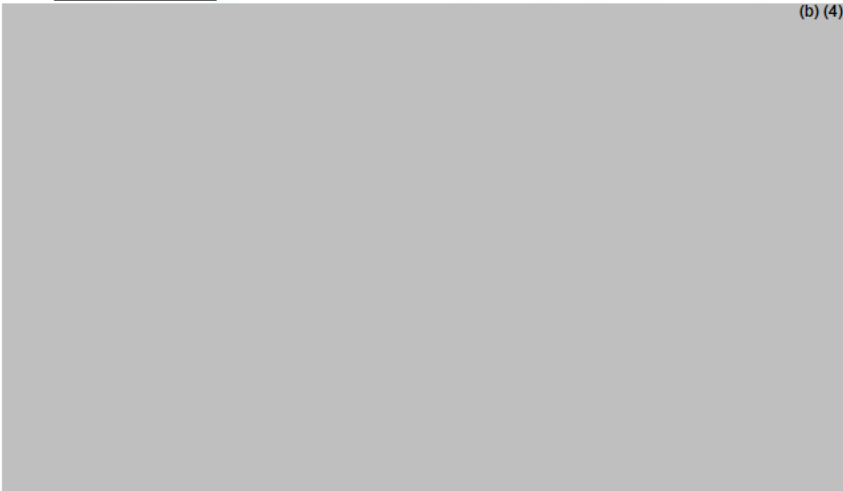
40 Carton



480 Carton Label



Device Label



Outer Plastic Sleeve (Device Pouch)

(b) (4)



Reviewer Comments

Instructions for Use

- There is a spacing issue on page 2 of the *draft -labeling-text-instructions-for-use*.
- The *draft -labeling-text-instructions-for-use* does not include the indications for use.
- The IFU instructs users to use another autoinjector if the first one does not work. (b) (4)

(b) (4) This statement should be reworded.

Refer to **Comment 1 to CDER**. These comments have also been included in the IFU review in SharePoint and alignment has been made with CDER.

Auto-injector label- label includes the IFU (patient population, injection site, and intended use), product name, (b) (4) (b) (4), Rx only, and manufacturer.

- Note: the firm provided the draft labeling and intends to leverage prior HF validation data for the device constituent part. HF validation is reviewed by DMEPA and out of scope of this review.

Carton label- includes indications for use, name of product, storage, lot number, and expiry.

Pouch label- appears to be adequate.

6.2. Labeling Review Conclusion

LABELING REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments Refer to Comment 1 to CDER with regards to potential labeling deficiencies of the Instructions for Use. Otherwise, all other labeling appears to be adequate.		
CDRH sent Labeling Deficiencies or Interactive Review Questions to the Sponsor: ☐ Yes ☒ No		

7. DESIGN CONTROL SUMMARY

7.1. Summary of Design Control Activities

Risk Analysis Attributes	Yes	No	N/A
Risk analysis conducted on the combination product	X		
Hazards adequately identified (e.g., FMEA, FTA, post-market data, etc.)	X		
Mitigations are adequate to reduce risk to health	X		
Version history demonstrates risk management throughout design / development activities	X		
Design Inputs/Outputs	Yes	No	N/A
Design requirements / specifications document present (essential performance requirements included)	X		
Design Verification / Validation Attributes	Yes	No	N/A
Validation of essential requirements covered by clinical and human factors testing	X		
To-be-marketed device was used in the pivotal clinical trial	X		
Bioequivalence Study utilized to-be-marketed device	X		
Verification methods relevant to specific use conditions as described in design documents and labeling	X		
Device reliability is acceptable to support the indications for use (i.e., emergency use combination product may require separate reliability study)		X	
Traceability demonstrated for specifications to performance data	X		

Reviewer Comments All design control information requests have been adequately addressed; however, there is a PMR needed for device reliability. Refer to PMR 4319-1

7.2. Design Inputs and Outputs

Essential Performance Requirements

Design Inputs (Essential Performance Requirement)	Design Outputs (Specification)
Solution Volume	(b) (4)
Needle Effective Length	
Injection Time	
Activation Force	
Safety Pin Extraction Force	

7.3. Applicable Standards and Guidance Documents

Generally Applicable Standards and Guidance Documents:

Standard or Guidance	Conformance (Y/N/NA)
AAMI / ANSI / ISO 14971:2007/(R)2010 (Corrected 4 October 2007), medical devices - applications of risk management to medical devices	Y
Standard Practice for Performance Testing of Shipping Containers and Systems; ASTM D4169-09	Y
IEC 60601-1-2:2014	NA
Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products (2017)	Y
Mobile Medical Applications Guidance for Industry and Food and Drug Administration Staff (2015)	NA
Guidance for Industry and FDA Staff – Medical Devices with Sharps Injury Prevention Features (2005)	NA
Use of International Standard ISO 10993-1, Biological evaluation of medical devices - Part 1: Evaluation and testing within a risk management process"	NA
Applying Human Factors and Usability Engineering to Medical Devices	NA

Device Specific Standards and Guidance Documents

Standard or Guidance	Recognized (Y/N/NA)	Conformance (Y/N/NA)
ISO11608-1: 2014 : Needle-based injection systems for medical use – Requirements and test methods – Part 1: Needle-based injection systems	Y	Y
ISO 11608-5: 2012: Needle-based injection systems for medical use — Requirements and test methods—Part 5: Automated functions	Y	Y

Technical Considerations for Demonstrating Reliability of Emergency-Use Injectors Submitted under a BLA, NDA or ANDA: Guidance for Industry and Food and Drug Administration Staff	Y	Y

7.4. Design Control Review Conclusion

DESIGN CONTROL REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☐ Yes ☒ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> The firm appears to have adequately conducted design controls; however, further information and assessment is needed with regards to the device reliability.		
CDRH sent Design Control Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

8. RISK ANALYSIS

8.1. Risk Management Plan



(b) (4)

8.2. Hazard Analysis and Risk Summary Report

(b) (4)



8.3. Risk Analysis Review Conclusion

RISK ANALYSIS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☐ No ☐ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☐ No ☐ N/A
Reviewer Comments In the firm's initial submission, the firm included <i>QD-RM-013 Risk Management Report Rev. 1.0</i> ; however, the report is high level and includes information that would be adequate for a risk management plan and not a report as the report provided does not include an analysis of the risks of the device, how high risks were mitigated and control, and does not include a risk/benefit analysis. The assessment of device failure is particularly important as the device is indicated for emergency use. Refer to Information Request 5.		
CDRH sent Risk Analysis Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 6/15/2022	Date/Sequence Received: 6/22/2022
Information Request #5		

	(b) (4)
Sponsor Response	
Reviewer Comments	Review of the risk analysis (QD-RM-012) concludes the following: • Hazard analysis appears adequate • (b) (4) • (b) (4) Refer to Information Request 8. • Design risks assessment of EPRs appear to be adequately assessed and risks reduced as far as possible. • (b) (4) • (b) (4) Refer to Comment 2 to CDER.
Response Adequate:	☐ Yes ☒ No, See IRs #7 and 8 Sent on 7/5/2022

Follow-On Deficiency	Date Sent: 7/8/2022	Date/Sequence Received: 7/13/2022
Information Request #7		

		(b) (4)
Sponsor Response		
Reviewer Comments	The firm's kfactor analysis appears acceptable to justify the sample size adequacy.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

Follow-On Deficiency	Date Sent:	Date/Sequence Received:	
	7/8/2022	7/13/2022	(b) (4)
Information Request #8			
Sponsor Response			

	(b) (4)
Reviewer Comments	The firm added risk 2.3 potential hazard Injector is not functioning with a potential cause of <i>“penetration of significant amount of air particulates (dust/sand) into the auto-injector results in failure to activate the auto injector when needed, or in delivery of only partial amount of the drug.”</i> The auto-injector is stored in secondary packaging which is a (b) (4) (b) (4) until point of use (b) (4) (b) (4) The risk of sand and dust getting into the auto-injector preventing adequate functionality of the auto-injector has been reduced with the packaging and appears to be adequately assessed in the risk assessment. Therefore, the information request response is deemed adequate.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

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



9.3. Discipline Specific Sub-Consulted Review Summary

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

10.RELIABILITY REVIEW

MDR Signal Information: Per MAUDE MDR search there are no reports found for the manufacturer. This is particularly important as the firm has experience and is leveraging information and data from a previously improved combination product that has the same device constituent part (Atropine).

Reliability Approach Review: The firm utilized historical data from Atropine to assess and determine the overall reliability of Midazolam. The differences between Atropine and Midazolam are the drug product and the safety pin and injector cap colors.

Midazolam reliability specifications are as follows:



Overall Reliability of Device Assessment:

The overall approach and method for assessment and calculating reliability aligns with Atropine which was determined to be acceptable. The firm asked in Pre-IND147559. FDA stated that the firm may be able to leverage Atropine, but it was contingent upon similarities between the two device, manufacturing process, design, etc. Also, FDA informed the firm that the Atropine PMR 3446-1 was still under review for adequacy so leveragability would also be based on the adequacy of Atropine reliability. The reliability assessment was finalized a few months later for Atropine and determined to be acceptable. Therefore, the reliability review for Midazolam primarily focuses on differences between the two that could impact performance and the overall reliability of the combo product. It appears reasonable that the firm utilizes the same approach and methods to determine the reliability of Midazolam as they took with Atropine. (b) (4)

(b) (4)

(b) (4)

Refer to information request 14 below and PMR4319-1 below for additional information.

Given the review is on a priority/expedited timeline, there wasn't enough time for the firm to adequately address IR14 and therefore a PMR is recommended. Given the firm's performance, shelf life, transportation and precondition testing were acceptable, there isn't reason to believe the device is unsafe for use. **However, overall Midazolam reliability cannot be determined until the firm has adequately addressed IR14/PMR4319-1.** When the firm responds to the IR14/PMR4319-1 reliability should be reviewed from the beginning as the IR14/PMR deficiencies impact the overall reliability calculations and assessment of Midazolam. **The following is a recommendation for the PMR assessment when the firm responds:**

- 1. Ensure the approach to the overall reliability assessment is the same as what the firm submitted in their original submission and/or Atropine. If the approach is difference, ensure improvements have been made and are adequate. If the same, for consistency in communication of Atropine reliability, the approach/method is acceptable.**
- 2. Ensure the firm has not use Atropine reliability data for any aspects of device performance that are impacted by the DP (e.g., deliverable volume, injection time, etc.) or differences between Atropine and Midazolam (e.g., cap and safety pin color since those changes can impact device performance due to the differences in manufacturing, molding, etc.).**
- 3. Ensure any new/additional data is acceptable (e.g., method, preconditioning, sample size, etc.)**
- 4. Ensure the overall reliability of the device is adequately calculated and traces from the bottom, up (basic event to top level event).**
- 5. Ensure the firm has adequately addressed all aspects of IR14/PMR4319-1.**

	Date Sent: 8/2/2022	Date/Sequence Received: 8/3/2022
Information Request #14	(b) (4)	
Sponsor Response		

(b) (4)

Reviewer Comments	The firm's response is reasonable as they have agreed to update the FTA and also explained the safety pin and cap reliability. The firm has agreed to address the Information Request (14) via a post market requirement. Refer PMR below and Appendix A, section 14.4 for additional information.
Response Adequate:	☐ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

	Date Sent: 8/2/2022	Date/Sequence Received: 8/3/2022
PMR 4319-1	Please confirm your understanding of the postmarketing requirement (PMR) listed below, and please acknowledge your agreement with the proposed milestone dates. This may not be a complete list of the PMRs and PMCs that we would require in the event of approval. Please respond by August 3, 2022. 1. Provide an updated Fault Tree Analysis and the associated reliability requirements and specifications to demonstrate that Midazolam Injection autoinjector will provide successful injection with at least 99.999% reliability at the 95% confidence interval. The fault tree analysis must include information from your combination product's design and manufacturing methods by identifying all basic failure modes anticipated. Final Protocol Submission: 11/2022 Study/Trial Completion: 02/2023 Final Report Submission: 03/2023	
Sponsor Response	<i>Rafa confirms understanding of the PMR received August 2, 2022 regarding providing an updated FTA and the associated reliability requirements and specifications listed above.</i> <i>Rafa respectfully requests the following proposed milestone dates to accommodate contracting activities:</i> <i>Final Protocol Submission: 01/2023</i> <i>Study/Trial Completion: 04/2023</i> <i>Final Report Submission: 05/2023</i>	

Reviewer Comments	CDRH thinks the firm's request for an additional 2 months for each milestone is reasonable and the request can be granted. However, the final decision for additional time and wording of the PMR will be deferred to CDER.
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.

11. CLINICAL VALIDATION REVIEW

11.1. Review of Clinical Studies Clinical Studies

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

This information was obtained from the following [documents](#): Module 5.3.1.2, *RLM-559-01*

Study Name	
Study Type	Phase 1, Open-Label, Comparison Study to Evaluate the Safety and Pharmacokinetics of a Single Intramuscular Administration of 10 mg Midazolam Using an Auto-Injector vs Marketed Midazolam Vials in Healthy Adults.
Objectives/Endpoints	Primary objectives: - To assess the safety profile of a single intramuscular (IM) administration of 10 mg Midazolam using Rafa Laboratories' auto-injector in healthy, adult subjects. - To assess the pharmacokinetic (PK) characteristics of a single IM administration of 10 mg Midazolam using Rafa Laboratories' auto-injector. - To assess the injection time of a single IM administration of 10 mg Midazolam using Rafa's auto-injector versus 10 mg of a marketed (Seizalam™) Midazolam vial for IM injection using a syringe. Secondary objectives: - To assess relative bioavailability of a single IM administration of 10 mg Midazolam using Rafa Laboratories' auto-injector versus 10 mg of a marketed (Seizalam) Midazolam vial for IM injection (50 mg/10 mL). - To assess the time to injection of a single IM administration of 10 mg Midazolam using Rafa Laboratories' auto-injector versus 10 mg of a marketed (Seizalam) Midazolam vial for IM injection (50 mg/10 mL) using a syringe.
Drug/Device Studied	The final to-be-marketed autoinjector was used in the relative BA study (RLM-559-01)
Number and Type of Subjects	40 subjects were enrolled. *Refer to Clinical study protocol or report for details on subject inclusion and exclusion criteria.

Brief description of protocol	<u>Primary:</u> • Safety: The safety population included randomized subjects who received at least one dose of study treatment and had at least one post baseline safety assessment (which could include a response from a subject indicating that no adverse events (AEs) occurred). The following analyses were performed: ▪ Frequency of injection site reactions and systemic reactions in the study population that were characterized as severe or resulted in a serious adverse event (SAE) during the 29-day study period. ▪ Participant incidence of treatment-related SAEs. ▪ Participant incidence of serious new onset chronic illness (NOCIs). ▪ Clinically significant changes in physical exam, ECG, and vital signs. ▪ Clinically significant changes in blood results or urinalysis (defined as higher than 1.5 times the upper limit of normal [ULN] or lower than 0.5 times the lower limit of normal [LLN]) between pre-dose measurement and Day 29. ▪ Frequency of device-related AEs in the study population that were characterized as severe or resulted in an SAE during the 29-day study period. • PK: The PK population included all participants who received the investigational Midazolam Injection, 10 mg and/or the marketed Seizalam Midazolam injection, completed enough sampling in order to get an accurate PK profile, had no major protocol violations expected to affect PK, and did not have > 5% of C_{max} Midazolam or the primary metabolite, 1'-hydroxymidazolam, on Day 15 prior to drug administration. The PK population was used for all PK analyses. The following PK parameters were performed for Midazolam and 1'-hydroxymidazolam: ▪ T_{max} ▪ T_{1/2} ▪ C_{max} ▪ AUC_{0-last} ▪ AUC_{0-∞} • Time: Investigator or delegate measured injection time of a single dose of Midazolam Injection, 10 mg using Rafa Laboratories' auto-injector and the syringe injection. <u>Secondary:</u> • PK: The secondary endpoints that were measured with the PK population included Midazolam PK parameters to compare the systemic response of investigational Midazolam Injection, 10 mg to the marketed Seizalam Midazolam injection. Although statistical comparisons were not performed, plasma PK of the primary metabolite, 1'-hydroxymidazolam, between the test and reference products were evaluated. Summary statistics were computed for each of the following: ▪ T_{max} ▪ t_{1/2} ▪ C_{max} ▪ AUC_{0-last} ▪ AUC_{0-∞} ▪ Additional PK parameters may be calculated. • Time: Investigator or delegate measured time to injection of a single dose of Midazolam Injection, 10 mg using Rafa Laboratories' auto-injector and the marketed Seizalam vial and syringe injection. Endpoint measures included two parts: ▪ Obtaining the product from the cabinet/fridge to counter or basket to having it ready for injection. ▪ Picking up the auto-injector or syringe from the bedside table, uncapping it, and putting the needle in the injection site.
Results	Study Population Results: APPEARS THIS WAY ON ORIGINAL Overall, 39 of 40 enrolled subjects received Midazolam using the auto-injector and 38 of 40 enrolled subjects received Midazolam using the marketed vials. Twenty subjects (100.0% of the auto-injector marketed vials sequence) received the first dose of Midazolam with the 10 mg auto-injector during Period 1 and 18 subjects (90.0% of this sequence) received the marketed Midazolam vials during Period 2. Twenty subjects (100% of the marketed vials, auto-injector sequence) received the marketed Midazolam vials during Period 1 and 19 subjects (95.0%) received Midazolam with the auto-injector during Period 2.

PK Results:

PK results of this study indicated that Midazolam exposure after IM dosing via the auto-injector and marketed vials by syringe were equivalent, with 90% CI of geometric least squares (LS) mean of C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ falling within the bioequivalence limits 80-125%. With the exception of T_{max} analysis of log-transformed parameters demonstrated equivalence between the 2 treatments, as well as analysis of non-transformed C_{max} and T_{max} . Analysis of Midazolam concentrations at 9 of the 16 nominal time points showed equivalence between the 2 treatments.

- Maximum Midazolam concentrations were observed at (median) 0.5 hours post dose for both treatments.
- Elimination $t_{1/2}$ for Midazolam was comparable between the 2 treatments (approximately 4.5 hours).
- Inter-subject variability (geometric CV% range) for Midazolam C_{max} , AUC_{0-last} , and $AUC_{0-\infty}$ was similar for the auto-injector (range 28.4 to 40.0%) and marketed vials by syringe (range 25.8 to 39.1%).
- Maximum 1'-hydroxymidazolam concentrations were observed at (median) 1 hour post Midazolam dosing for both treatments.
- Elimination $t_{1/2}$ for 1'-hydroxymidazolam was comparable between the 2 treatments (approximately 6 hours).
- Inter-subject variability (geometric CV% range) for 1'-hydroxymidazolam C_{max} , C_{0-last} , and $AUC_{0-\infty}$ was similar for the auto-injector (range 36.2 to 37.8%) and marketed vials by syringe (range 37.7 to 47.3 %).
- This study demonstrated bioequivalence between the auto-injector and the marketed vials by syringe.

APPEARS THIS WAY ON ORIGINAL

Safety Results:

Of the 39 subjects who received Midazolam via the auto-injector, 13 subjects experienced a total of 15 AEs, the most common of which was injection site pain (3 subjects) followed by anemia, hypertension, and systolic hypertension (2 subjects each). One AE (syncope) was considered serious and led to discontinuation following Period 1. There was one AE considered drug-related (blood in urine) and 5 AEs in 5 subjects considered device-related (3 cases of injection site pain, 1 contusion, and 1 muscular weakness). None of these events required medical intervention.

Of the 38 subjects who received Midazolam via the marketed vial, 9 subjects experienced a total of 15 AEs, the most common of which were dizziness and tachycardia (2 subjects each). All other reported AEs occurred in a single subject. Five subjects experienced a total of 10 drug-related AEs (2 subjects experienced tachycardia, 2 experienced dizziness, and 1 subject each experienced AST increase, hepatic enzyme increase, nausea, vomiting, flushing, and hypotension). Two subjects experienced a single device-related AE each (injection site pain and hepatic enzyme increase). None of these events were considered serious, and none required medical intervention.

Injection Time Results:

Of the 39 subjects administered Midazolam via the auto injector, the LS mean time from cabinet or fridge to ready for injection was 196.71 seconds with a range of 60 to 840 seconds. This was significantly faster ($p = 0.0266$) than the average time to prepare the marketed vials for injection (LS mean 294.56 seconds; range of 120 to 900 seconds). There was no significant difference in the time to pick up and inject the needle or injection time between the auto-injector and marketed vials.

Conclusions:

The PK profile of Midazolam and 1-hydroxymidazolam following IM injection with Rafa Laboratories auto injector was comparable to the PK profiles following IM injection with the marketed vials. The time to prepare an injection of Midazolam using Rafa Laboratories' auto injector was significantly shorter when compared to marketed vials, providing a distinct advantage for rapidity of drug delivery to subjects suffering from a status epilepticus (SE) event. The safety profiles of subjects following injection

	with the auto injector were relatively similar to those seen with the marketed vials and did not raise any safety concerns. The clinical data supports safety and bioavailability of Midazolam Injection, 10 mg using Rafa Laboratories' auto-injector for SE indication.
Device Related Comments	The firm noted 5 AEs that were considered device related which included 3 cases of injection site pain, 1 contusion, and 1 muscular weakness. None of the events required medical intervention. There were no significant differences notes in the time to pick up and inject the needle or injection time between the auto-injector and marketed vials. However, it was noted that there was a significantly shorter time to prepare the injection with the auto-injector when compared to the vials.
Reviewer Comments	The firm determined the study demonstrated bioequivalence.
Reviewer Conclusion	The firm stated that the safety profiles of the subjects following injection from the auto injector were relatively similar to those seen when been injected from the vials and thus did not raise any safety concerns. The 5 AEs noted that were considered to be device related do not appear to indicate inadequacy in device performance. However, CDRH recommendation for safety will be based on adequacy of device performance as demonstrated in design verification testing. Adequacy in usability of the device will be deferred to DMEPA (human factors adequacy) and determination of adequacy of the overall device performance in the clinical study is deferred to CDER.

○ **Clinical Validation Review Conclusion**

CLINICAL VALIDATION REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
Reviewer Comments The clinical study does not appear to raise any concerns of device safety and effectiveness. However, adequacy in effectiveness will be determined based on design verification. Refer to section 9 above.		
CDRH sent Clinical Validation Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

	Date Sent: 6/15/2022	Date/Sequence Received: 6/22/2022
Information Request #6	(b) (4)	
Sponsor Response		
Reviewer Comments	The firm's response is adequate as the final to be marketed configuration was utilized during the BA study.	
Response Adequate:	☒ Yes ☐ No, See IR # Sent on Click or tap to enter a date.	

12. HUMAN FACTORS VALIDATION REVIEW

CDRH Human Factors Review conducted	■
Human Factors deferred to DMEPA	■

13.FACILITIES & QUALITY SYSTEMS

13.1. Facility Inspection Report Review

CDRH Facilities Inspection Review conducted	☐
CDRH Facilities Inspection Review was not conducted	☒

CDRH recommends a post approval inspection. Refer to section 5.2, *Facilities Information* above for additional rationale for recommendation.

13.2. Quality Systems Documentation Review

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

13.2.1. Description of the Device Manufacturing Process

(b) (4)

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13.4. Facilities & Quality Systems Review Conclusion

FACILITIES & QUALITY SYSTEMS REVIEW CONCLUSION		
Filing Deficiencies: ☐ Yes ☒ No ☐ N/A	Mid-Cycle Deficiencies: ☒ Yes ☐ No ☐ N/A	Final Deficiencies: ☐ Yes ☒ No ☐ N/A
<u>Reviewer Comments</u> A post-approval inspection is recommended and therefore facilities adequacy and CFR compliance was not assessed. The quality systems summary the firm provided appears adequate.		
CDRH sent Facilities & QS Deficiencies or Interactive Review Questions to the Sponsor: ☒ Yes ☐ No		

<<END OF REVIEW>>

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/s/

ERICA F KEAFER
08/05/2022 03:55:10 PM

MEMORANDUM

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

DATE: 7/22/2022

TO: Division of Neurology II (DN II)
Office of Neuroscience (ON)

FROM: Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

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

RE: NDA 216359

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

Rationale

OSIS conducted a Remote Record Review (RRR) for the site in (b) (4), which falls within the surveillance interval. The RRR was conducted under the following submission: (b) (4)

The following item was discussed with the site during the RRR close out meeting:

- The site excluded valid, reportable data from precision and accuracy statistical analyses.

After review of the discussion items and the site's response, OSIS determined that data from the reviewed studies were reliable ([Final OSIS Review](#) (b) (4))

Site

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

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/s/

JAMES J LUMALCURI
07/22/2022 10:23:35 AM

MEMORANDUM
REVIEW OF REVISED LABEL AND LABELING
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

Date of This Memorandum: July 21, 2022
Requesting Office or Division: Division of Neurology 2 (DN 2)
Application Type and Number: NDA 216359
Product Name and Strength: Midazolam Injection, 10 mg/0.7 mL
Applicant/Sponsor Name: Rafa Laboratories, Ltd.
OSE RCM #: 2022-609-1
DMEPA 2 Safety Evaluator: Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader: Stephanie DeGraw, PharmD

1 PURPOSE OF MEMORANDUM

The Applicant submitted revised container label and carton labeling received on July 20, 2022 for Midazolam. The Division of Neurology 2 (DN 2) requested that we review the revised container label and carton labeling for Midazolam (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.^a

2 CONCLUSION

The Applicant implemented all of our recommendations and we have no additional recommendations at this time.

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^a Kalonia, J. Label and Labeling Review for Midazolam (NDA 216359). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUN 24. RCM No.: 2022-609.

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/s/

JUSTINE H KALONIA
07/21/2022 03:05:10 PM

STEPHANIE L DEGRAW
07/21/2022 03:34:29 PM

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

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

Memorandum

Date: July 19, 2022

To: Steven Dinsmore, M.D.
Division of Neurology II (DN-II)

Harold Sano, Regulatory Project Manager, DN-II

Tracy Peters, Associate Director for Labeling, DN-II

From: David Foss, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Aline Moukhtara, RN, MPH, Team Leader, OPDP

Subject: OPDP Labeling Comments for MIDAZOLAM injection, for intramuscular use, CIV

NDA: 216359

In response to DN-II's consult request dated March 30, 2022, OPDP has reviewed the proposed product labeling (PI), Instructions for Use (IFU), and carton and container labeling for the original NDA submission for Midazolam Injection.

Labeling and IFU: OPDP's comments on the proposed PI and IFU are based on the draft labeling received by electronic mail from DN-II (Harold Sano) on July 6, 2022, and are provided below.

Carton and Container Labeling: OPDP has reviewed the attached proposed carton and container labeling submitted by the Sponsor to the electronic document room on March 28, 2022, and our comments are provided below.

Thank you for your consult. If you have any questions, please contact David Foss at (240) 402-7112 or david.foss@fda.hhs.gov.

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/s/

DAVID F FOSS
07/19/2022 04:57:31 PM

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

PATIEN LABELING REVIEW

Date: July 15, 2022

To: Harold Sano
Regulatory Project Manager
Division of Neurology II (DN2)

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

Sharon W. Williams, MSN, BSN, RN
Senior Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

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

Subject: Review of Patient Labeling: Close-out Memo

Drug Name (established name): Midazolam Injection

Dosage Form and Route: for intramuscular use, CIV

Application Type/Number: NDA 216359

Applicant: Rafa Laboratories, Ltd. (Rafa)

1 INTRODUCTION

On March 28, 2022, Rafa Laboratories, Ltd. (Rafa) submitted for the Agency's review an original New Drug Application (NDA) 216359 for Midazolam Injection, for intramuscular use, CIV.

The proposed indication for Midazolam Injection, for intramuscular use, CIV is for the treatment of status epilepticus in adults. Midazolam Injection uses a single-dose, emergency-use autoinjector delivery system for midazolam and is being developed considering the U.S. Government's efforts for improved nerve agent treatment systems.

On March 31, 2022, the Division of Neurology II (DN2) requested that the Division of Medical Policy Programs (DMPP) perform a review of the Instructions for Use (IFU) for Midazolam Injection, for intramuscular use, CIV.

This memorandum documents DMPP's close-out of the above-referenced consult request for Midazolam Injection, for intramuscular use, CIV.

2 CONCLUSIONS

The Prescribing Information (PI) for Midazolam Injection, for intramuscular use, CIV states that this product is to be administered in (b) (4).

The Comparative Analysis: Rafa Laboratories Midazolam Auto-injector 10 mg/0.7 mL document submitted by the Applicant (dated July 2, 2021), states that service members using the midazolam auto-injector will be trained on use of the auto-injector prior to having the auto-injector provided to them in their chemical exposure kit and service members will also be required to complete an annual Chemical, Biological, Radiological and Nuclear (CBRN) subject area training requirement in addition to reviewing the Instructions for Use.

The intended users of Midazolam Injection are healthcare professionals and trained service members. Further, the IFU will not be the sole source of instruction for service members on use of this device. Therefore, no DMPP review of the IFU for Midazolam Injection is warranted at this time.

Please notify us if you have any questions.

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/s/

NYEDRA W BOOKER
07/15/2022 07:14:14 AM

SHARON W WILLIAMS
07/15/2022 08:15:10 AM



MEMORANDUM
Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research

Date: July 1, 2022

To: Nick Kozauer, M.D., Director
Division of Neurology II
Office of Neuroscience

Through: Dominic Chiapperino, Ph.D., Director
Josh Lloyd, M.D., Medical Officer Team Leader
Controlled Substance Staff

From: Emily Deng, M.D., MPH, Medical Officer
Controlled Substance Staff

Subject: **Drug:** Midazolam Injection, emergency-use autoinjector delivery system
NDA Number: 216359
Indication: treatment of status epilepticus in adults
Dosage: 10 mg, single-dose autoinjector
Applicant: Rafa Laboratories, Ltd. (Rafa)
PDUFA Goal Date (priority review): September 28, 2022; targeted action date: July 29, 2022

Materials Reviewed:

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I. EXECUTIVE SUMMARY

1. Background

This memorandum responds to a consult request from the Division of Neurology II (DN2) for the Controlled Substance Staff (CSS) to evaluate a New Drug Application (NDA) and proposed labeling for a drug-device combination product containing midazolam 10 mg in a prefilled autoinjector for intramuscular use. The proposed indication is for the treatment of status epilepticus in adults, and the product is intended to support Department of Defense military personnel in the event of a nerve agent terrorist attack. The proposed product is for single dose emergency use and is intended to be administered by buddy aid in potentially austere operational conditions.

The Applicant submitted this NDA through the 505(b)(2) regulatory pathway referencing the Agency's prior safety and efficacy findings for the listed drug (LD) Seizalam (Meridian Medical Technologies, Inc.; NDA 209566, approved 14 September 2018) for approval. The proposed product has the same active ingredient, dosage form, route of administration, recommended dose, and indication as the LD and only differs with respect to the concentration of the active ingredient, the excipients contained in the formulation, and the device (i.e., autoinjector).

The Applicant performed a Phase 1 pharmacokinetic (PK)/relative bioavailability study to establish the scientific bridge between Midazolam Injection and Seizalam. Additionally, the Applicant proposes to leverage the data supporting approval of their Atropine autoinjector (Atropine Injection, 2 mg), which was approved under NDA 212319 on July 9, 2018, for the Midazolam autoinjector, as the two devices are the same with the exception of the colors of the cap and safety pin.

During the drug development stage (IND 147559), multiple meetings were held between FDA and the Applicant, including pre-IND, Type C (written responses), and pre-NDA meetings. The Pre-NDA meeting was held on August 19, 2021, where CSS provided comments regarding monitoring for and reporting the occurrence of abuse-related adverse events (AEs) in any clinical studies conducted with the proposed product (e.g., bioavailability/bioequivalence studies), as well as that the NDA submission should include all information related to abuse of the drug, a proposal for scheduling, and any information on any studies related to overdose.

2. Conclusions

- Midazolam is controlled under schedule IV of the Controlled Substances Act (CSA) and has a demonstrated potential for misuse, abuse, and subsequent development of addiction.

As with other drugs in the benzodiazepine (BZD) class, continued use of midazolam at therapeutic doses for a prolonged period may lead to clinically significant physical dependence, as manifested by a well-characterized withdrawal syndrome.

- The Applicant's Midazolam injection 10 mg autoinjector is bioequivalent to the reference product Seizalam (NDA 212319).
- No abuse potential studies were conducted in support of this application. Although review of the adverse event data from the single clinical study submitted in this application revealed no reported abuse-related adverse events, the abuse-related adverse event profile for midazolam is expected to be consistent with what is known for the benzodiazepine class of drugs.

3. Recommendations

Based on our findings, as captured in the Conclusions section, we recommend the following:

The labeling is being negotiated with the Applicant at the time of this review. The sections of labeling relevant to abuse and dependence (Boxed Warning, Warnings and Precautions, and Section 9 Abuse and Dependence) will align with the approved labeling of the reference product Seizalam (NDA 212319).

II. DISCUSSION

1. Chemistry

1.1 Substance Information

Name: Midazolam

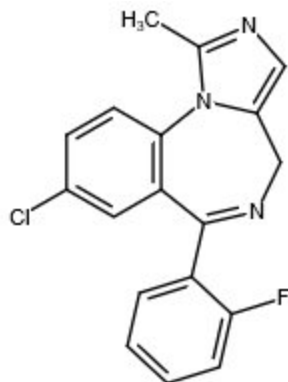
Chemical Properties

Chemical name: 8-chloro-6-(2-fluorophenyl)-1-methyl-4*H*-imidazo[1,5-*a*][1,4]benzodiazepine

Chemical formula: C₁₈H₁₃ClFN₃

Molecular weight: 325.77

Molecular Structure:



1.2 Drug product

The proposed product, Midazolam Injection, is a drug-device combination product consisting of an autoinjector prefilled with 10 mg midazolam and is intended to be administered by a person who has had adequate training in the recognition and treatment of status epilepticus and/or nerve agent poisoning and first aid/basic airway management. The proposed shelf-life for Midazolam Injection is 24 months. The components and quantitative composition of the drug product are listed in the table below:

Table 1: Midazolam Injection USP Drug Product Composition

Component	Function	Unit Formula (mg per mL)	Delivered Dose (mg per 0.7 mL)
Midazolam USP	Active	(b) (4)	10.0 mg
Sodium Chloride USP	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
Hydrochloric Acid 5N USP ¹	pH Adjustment	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)
(b) (4)	(b) (4)	(b) (4)	(b) (4)

QS = Quantum sufficient; USP = United States Pharmacopeia

Source: NDA 216359 submission, Module 3.2.P.1

The Applicant proposes quality control specifications for the drug product as shown below:

Table 1: Quality Control Specification for the Analytical and Microbial Testing at Rafa for Midazolam 10mg/0.7 mL Cartridges

Test		Acceptance Criteria	Test Method ¹
Appearance		(b) (4)	Visual
(b) (4)		(b) (4)	HPLC ²
(b) (4)		(b) (4)	HPLC
Assay (HPLC)		(b) (4)	HPLC ²
Impurities	Impurity 1	(b) (4)	HPLC ²
	Impurity 2	(b) (4)	
	Any unknown impurity	(b) (4)	
	Total Impurities	(b) (4)	
		(b) (4)	(b) (4)

Table 1: Quality Control Specification for the Analytical and Microbial Testing at Rafa for Midazolam 10mg/0.7 mL Cartridges (Continued)

Test	Acceptance Criteria	Test Method ¹
pH	(b) (4)	OI-QC-048
Container Volume	(b) (4)	USP <697>
(b) (4)		
Sterility	(b) (4)	Ph. Eur method 2.6.1 USP <71> TM-MID-001
Bacterial Endotoxins (LAL) EU/mg	(b) (4)	Ph. Eur. Method 2.6.14 USP <85> OI-MB-052
Particulate matter (≥ (b) (4) μm)	(b) (4)	Ph. Eur. Method 2.9.19 USP <788> OI-MB-051
Particulate matter (≥ (b) (4) μm)	(b) (4)	Ph. Eur. Method 2.9.19 USP <788> OI-MB-051

¹ All test methods are performed by Rafa Laboratories, Ltd. except for (b) (4) or other approved vendor) and tests for mechanical properties and visual controls (Shalon).

² Method performed per USP Monograph for Midazolam Injection (b) (4)

GC = Gas chromatography; HPLC = High performance liquid chromatography; (b) (4)
(b) (4) LAL= Limulus ameocyte lysate; NLT = Not less than; NMT = Not more than;
ppm = Parts per million

Source: NDA 216359 submission, Module 3.2.P.5.1

Please refer to the CMC review for a complete discussion of their findings.

2. Nonclinical Pharmacology

No abuse-related nonclinical pharmacology data were submitted.

Established Mechanism of Action

The exact mechanism of action for midazolam in the treatment of status epilepticus is not fully understood. However, midazolam may involve potentiation of GABAergic

neurotransmission resulting from binding at the benzodiazepine site of the GABA_A receptor.

3. Clinical Pharmacology

The Applicant performed a Phase 1, open-label, study to evaluate the safety and pharmacokinetics of a single intramuscular administration of 10 mg midazolam using an autoinjector compared to Seizalam in 40 healthy adults. The proposed product is bioequivalent to the reference product, Seizalam. The following is excerpted from the draft labeling proposed by the Applicant:



Please refer to the clinical pharmacology review for a complete discussion of their findings.

4. Clinical Studies

No abuse potential studies were conducted in support of or were required for this application. As noted in Section 3 above, the Applicant conducted a single relative bioavailability study in support of this NDA. Participants were monitored for adverse events (AEs) and serious AEs after single dose injections, throughout the 30-hour monitoring onsite period, post-injection, and at each visit (14 days after each injection, i.e., Day 15 and Day 29). The AEs reported in this study are summarized in the table below:

Table 2.7.4.3: Summary of Adverse Events by System Organ Class and Preferred Term (Safety Population)

System Organ Class Preferred Term	Auto-Injector (N=39) [n(%)]	Marketed Vials (N=38) [n(%)]
Number of adverse events during period	15	15
Number of subjects with any adverse event during period	13 (33.3)	9 (23.7)
General disorders and administration site conditions	3 (7.7)	1 (2.6)
Injection site pain	3 (7.7)	1 (2.6)
Vascular disorders	3 (7.7)	1 (2.6)
Hypertension	2 (5.1)	0
Systolic hypertension	2 (5.1)	0
Flushing	0	1 (2.6)
Hypotension	0	1 (2.6)
Blood and lymphatic system disorders	2 (5.1)	1 (2.6)
Anaemia	2 (5.1)	1 (2.6)
Investigations	2 (5.1)	3 (7.9)
Blood urine present	1 (2.6)	0
Gamma-glutamyltransferase increased	1 (2.6)	0
Aspartate aminotransferase increased	0	1 (2.6)
Blood calcium decreased	0	1 (2.6)
Blood potassium decreased	0	1 (2.6)
Hepatic enzyme increased	0	1 (2.6)
Gastrointestinal disorders	1 (2.6)	1 (2.6)
Diarrhoea	1 (2.6)	0
Nausea	0	1 (2.6)
Vomiting	0	1 (2.6)
Injury, poisoning and procedural complications	1 (2.6)	0
Contusion	1 (2.6)	0
Musculoskeletal and connective tissue disorders	1 (2.6)	0
Muscular weakness	1 (2.6)	0
Nervous system disorders	1 (2.6)	2 (5.3)
Syncope	1 (2.6)	0
Dizziness	0	2 (5.3)
Cardiac disorders	0	2 (5.3)
Tachycardia	0	2 (5.3)
Infections and infestations	0	1 (2.6)
Otitis externa	0	1 (2.6)

Note: An AE is assigned to a specific treatment if the AE occurred during or after the treatment administration and prior to either the start of the subsequent treatment, if in study period 1, or the end of study visit, if in study period 2.

Note: AEs are coded using MedDRA v24.1. Frequencies in system organ class (SOC) and preferred term (PT) rows are numbers of subjects who experienced at least one AE in that SOC or PT. Subjects experiencing more than one AE in a given SOC or PT are counted only once for that particular SOC or PT.

Source: NDA 216359 submission, Module 2.7.6

As summarized in the table above, no abuse-related AEs were reported in the completed Phase 1 study. Assessment for withdrawal and rebound events is not applicable, as it was a single dose study.

Drug accountability responsibilities were prospectively defined in Protocol RLM-559- 01, v2. In the completed study, investigator was responsible for storage and dispensing of product supplies. Subjects were dosed at the site by trained clinical investigator and subjects were not allowed to take investigational product with them from the site. There were no drug accountability issues reported in the completed phase 1 study.

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USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	June 15, 2022
Requesting Office or Division:	Division of Neurology 2 (DN2)
Application Type and Number:	IND 147559 (NDA 216359) ¹
Product Type:	Combination Product (Drug-Device)
Drug Constituent Name and Strength:	Midazolam Injection, 10 mg
Device Constituent:	Autoinjector
Rx or OTC:	Rx
Applicant/Sponsor Name:	Rafa Laboratories, Ltd. (Rafa)
Submission Dates:	July 15, 2021, August 2, 2021, August 24, 2021, September 8, 2021, and October 12, 2021
OSE RCM #:	2021-1613
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Team Leader (Acting):	Colleen Little, PharmD
DMEPA 2 Associate Director for Human Factors:	Lolita White, PharmD
DMEPA 2 Director:	Danielle Harris, PharmD

¹ During the course of this review, the Sponsor submitted NDA 216359 for midazolam injection on March 28, 2022 and NDA 216359 is currently under review.

1. REASON FOR REVIEW

This review evaluates the use-related risk analysis (URRA) and comparative analyses (CA) submitted under IND 147559 for Midazolam autoinjector (AI) to determine whether Rafa needs to submit the results of a human factors (HF) validation study and, if so, whether it is acceptable for them to submit the results of a HF validation study as part of a post-market requirement (PMR).

1.1. PROPOSED PRODUCT DESCRIPTION

Midazolam injection is a proposed combination product with an autoinjector device constituent part that is indicated for the treatment of status epilepticus in adult warfighters exposed to nerve agents in Chemical, Biologic, Radiological, and Nuclear (CBRN) environments. See Figure 1 below and Appendix A for additional product characteristics.

Figure 1. Midazolam Injection



1.2. COMPARATOR PRODUCT DESCRIPTION

The comparator product, Atropine injection (NDA 212319), is an approved combination product with an autoinjector device constituent part indicated for the treatment of poisoning by susceptible organophosphorus nerve agents having anticholinesterase activity as well as organophosphorus or carbamate insecticides in adults and pediatric patients weighing more than 41 kg (90 pounds). For additional product information, please see Figure 2 below and Appendix A.

Figure 2. Atropine Injection



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

In the Type B Pre-IND written response issued on March 16, 2020, we requested that Rafa submit a comprehensive URRAs and CAs along with justification that the results of a HF validation study do not need to be submitted for the marketing application.² On July 15, 2021, Rafa submitted the requested URRAs and CAs under IND 147559 as part of a Type B Pre-NDA meeting request. We sent an Information Request (IR) on July 23, 2021³ to request Rafa submit the URRAs and CAs separately under the IND for our review. Thus, on August 2, 2021, Rafa submitted the justification and referenced the URRAs and CAs submitted on July 15, 2021. The August 2, 2021 “Justification for Not Conducting a HF Validation Study” submission also included the following questions:

- a. Does the Agency agree that the HF validation study of Atropine Injection, 2 mg can be leveraged to support approval of Midazolam Injection, 10 mg?
- b. Does the Agency agree that, should FDA determine a HF validation study is required for Midazolam Injection, 10 mg, it may be submitted post-approval?

For these questions, we provide our responses to Rafa below in Section 4.1.

2. MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide information used to inform our findings and evaluation of each material reviewed.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Background Information Previous HF Reviews (DMEPA)	B
Use-related risk analysis and comparative analyses	C
Information Requests Issued During the Review	D
CDRH Human Factors Consult Review	E – N/A

² Sano, H. Meeting Request - Written Responses for IND 147559. Silver Spring (MD): FDA, CDER, ON, DN2 (US); 2020 MAR 16.

³ Ogbonna, C. Information Request for IND 147559 for midazolam autoinjector. Silver Spring (MD): FDA, CDER, OSE (US); 2021 JUL 23.

Table 1. Materials Considered for this Review	
Material Reviewed	Appendix Section (for Methods and Results)
Product Sample, Label and Labeling, Packaging	F

N/A=not applicable for this review

3. OVERALL ASSESSMENT OF MATERIALS REVIEWED

The sections below provide our evaluation of the use-related risk analysis (URRA) and comparative analyses.

3.1 USE-RELATED RISK ANALYSIS

Rafa submitted a URRA to support their determination that the results of a HF validation study do not need to be submitted for their proposed product, Midazolam AI. The Sponsor identified and evaluated the tasks involved in the use of the proposed product, the errors that users might commit, the tasks they might fail to perform, and the potential negative consequences of use errors. The Sponsor determined that the existing risk mitigation strategies are adequate to ensure that the user interface is safe and effective for use by the intended users and that HF validation testing is not needed to support the marketing application.

We reviewed the URRA to ensure that all potential use errors and risks involved in the use of the proposed product have been considered. Based on our review of the URRA, we agree that the tasks evaluated are comprehensive and appropriate for the proposed product. We did not identify any new or unique risks for the proposed product.

(b) (4)

⁴ Draft Guidance for Industry and FDA Staff: Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications. Food and Drug Administration. 2018. Available from: <https://www.fda.gov/media/122971/download>.

3.2 COMPARATIVE ANALYSES

Rafa provided a physical comparison, comparative task analysis, and labeling comparison between the proposed product and Atropine AI. Like the proposed product, Atropine shares the same device (pre-filled, single-use, ready-to-use autoinjector), intended users (active military service members) and intended use environment (CBRN battlefield). As such, we find the Atropine AI is an acceptable comparator.

3.2.1 PHYSICAL COMPARISON

Rafa identified the following physical differences between the proposed product and the Atropine AI.⁵ Rafa provided the following justification for the acceptability of these physical differences in their initial submission: “the slight differences found between the midazolam and atropine AI are not considerable enough to impact how the user will interact with the midazolam AI. The differences identified were expected as the two AIs treat different conditions and therefore need to be visibly differentiated by the user.”

- Outer Appearance of the device: See Figure 3 below. Rafa categorized the differences in Figure 3 as “other differences”.

Figure 3. Outer Appearance Differences

Midazolam Auto-injector	Atropine Auto-injector (Comparator 1)
1. Needle end: Needle has orange tip 2. (b) (4) product details are placed on orange label 3. Safety cap: Located on the opposite end of the auto-injector from the needle and is grey in color	1. Needle end: Needle has green tip 2. (b) (4) product details are placed on yellow and green label 3. Safety cap: Located on the opposite end of the auto-injector from the needle and is yellow in color
(b) (4)	(b) (4)

Our evaluation of the Sponsor-identified physical color differences finds the color differences between the needle end and safety cap impact the critical task of cap removal and may lead to patient harm should the task be performed incorrectly.

⁵ The Sponsor’s physical comparison miscategorized some labeling differences as physical differences. Our review of the labeling differences is provided in Section 3.2.3.

We acknowledge the differences in shape and size between the needle end of the proposed AI and the safety cap of the Atropine AI. However, we were concerned the similarities in color between the orange needle end of the proposed Midazolam AI and the yellow safety cap of the Atropine AI may not mitigate the risk of needle stick injury or dose omission with experienced Atropine AI users if the needle end of the proposed AI is mistaken for the safety cap (see figure 4 below).

Thus, on November 15, 2021,⁶ we sent an information request (IR) to Rafa to verify whether the needle end of the Midazolam AI and the Atropine AI safety cap are similar in color. Rafa submitted the requested information on November 19, 2021,⁷ acknowledging our concern that users familiar with Atropine autoinjector may mistake the needle end for the safety cap when using the proposed Midazolam autoinjector due to the similarity in color as shown in the figure they provided below:

Figure 4. Midazolam and Atropine Autoinjectors



However, they provided the following justifications:

- The orange color for the Midazolam AI needle end was chosen in consultation with the Department of Defense.
- Mitigations for this concern:

⁶ Killen, M. Information Request for Midazolam IND 147559. Silver Spring (MD): FDA, CDER, OSE (US); 2021 NOV 15.

⁷ Response to Information Request dated 15 November 2021 for Midazolam IND 147559. Jerusalem, Israel: Rafa Laboratories, Ltd.; 2021 NOV 19: <\\CDSESUB1\evsprod\ind147559\0015\m5\53-clin-stud-rep\535-rep-effic-safety-stud\status-epilepticus\5354-other-stud-rep\threshold-analysis\response-to-information-request-dated-15-november-2021.pdf>.

- The Atropine AI is carried only by medics and healthcare providers and not carried by the individual Warfighter. The only circumstance that the Atropine and Midazolam AIs could be carried together in a military setting is by medics and healthcare providers who go through additional schooling and are trained to differentiate between the two devices.
- Rafa's proposed Midazolam AI is intended to replace the current Diazepam autoinjector. The Midazolam AI was designed to have the same safety cap and needle end color as the current Diazepam AI (NDA 20124), which standardizes operations.
- The packaging and labeling for the Atropine and Midazolam AIs are different. The major difference in the label colors should allow easy differentiation between the two autoinjectors when there is enough light to see.



We reviewed the information submitted and based on the use-related risks of this product, in this use environment, in these particular intended users, in conjunction with the Sponsor's description of their discussions with Department of Defense, in this particular case, we find Rafa's justifications and mitigations reasonable. Thus, we find the identified physical differences between the proposed Midazolam AI and the Atropine AI do not warrant the submission of HF validation study data in the marketing application.

3.2.2 COMPARATIVE TASK ANALYSIS

According to the information provided by Rafa⁸, users will complete the same tasks in the same sequence for both products. As such, we do not find that any new tasks have been introduced or eliminated for the proposed Midazolam AI when compared to Atropine AI. Thus, we did not identify any differences in tasks that warrant the submission of HF validation study data in the marketing application.

3.2.3 LABELING COMPARISON

⁸ The Sponsor's comparative task analyses miscategorized some physical differences and labeling differences as task differences. Our review of the physical and labeling differences is provided in Section 3.2.1 and 3.2.3, respectively.

Rafa identified the following labeling differences⁹ between the proposed product and Atropine AI, and categorized these differences as “other differences”. Rafa provided the following justification for the acceptability of these physical differences in their initial submission: “differences identified were expected as the two AIs treat different conditions, therefore the medication, concentration, dosage, and patient population in the instructions must be different.”

- The Midazolam container label is orange and black. The Atropine container label is yellow and green.
- Midazolam injection is intended for use in status epilepticus whereas Atropine injection is intended for the treatment of nerve agent and insecticide poisoning.
- Midazolam is a schedule IV controlled drug and Atropine injection is not a controlled drug.
- Dosage and patients are specific to the medication.
- The qualifications for treatment determination are different between the two medications.
- The comparator provides instructions for administering additional doses if necessary, while the proposed product does not.

The proposed product provides instructions for monitoring after administering a dose, but the comparator does not. We find the identified differences above may impact critical administration tasks. However, we also find that the color differences between the container labels do not add new use tasks or remove existing use tasks and the remaining differences are acceptable product specific differences. As such, we do not expect these differences to impact a user’s ability to use the product safely and effectively.

Rafa identified the following labeling difference between the proposed product and Atropine AI, and categorized this difference as “minor”.

- The proposed product is administered as a “buddy-aid” treatment only (i.e., administered to a patient), while the comparator can be self-administered or as “buddy-aid” treatment.

Per Rafa, the proposed product is indicated for patients who are unlikely to self-administer (e.g., continuous seizure activity lasting five minutes or more, multiple seizures without recovery between seizures, unconscious or severe signs or

⁹ The Sponsor’s labeling comparison miscategorized some physical and task differences as labeling differences. Our review of the physical and task differences is provided in Section 3.2.1 and Section 3.2.2, respectively.

symptoms of nerve agent poisoning). Therefore, it is unlikely that a patient requiring treatment with Midazolam AI will be able to self-administer; whereas patients requiring treatment with the Atropine AI may have mild symptoms and the ability to self-administer. Thus, we find this difference acceptable.

Based on our review of the IFU comparison, we determined that the identified differences are product specific, do not add new use tasks, or remove existing use tasks. Thus, we find it unlikely that these differences will introduce any new risk in the intended user group for the proposed Midazolam AI when compared to Atropine AI. As such, these differences do not warrant the submission of HF validation study data in the marketing application.

4. CONCLUSION AND RECOMMENDATIONS

Based on our review of the use-related risk analysis, comparative analyses and justifications submitted by Rafa for Midazolam Injection IND 147559, we determined that Rafa does not need to submit the results of a HF validation study as part of the marketing application. We provide a letter-ready responses to Rafa in Section 4.1

4.1 RECOMMENDATIONS FOR RAFA LABORATORIES, LTD.

General Comments

We have reviewed your use-related risk analysis (URRA), comparative analyses, and justification, and responses to our information requests. At this time, we have determined that you do not need to submit the results of a human factors (HF) validation study to support your marketing application for your proposed product Midazolam injection. Please note that if you modify the product user interface, the advice regarding submission of the results of HF validation study may change.



While submission of revised URRA is not

¹⁰ Draft Guidance for Industry and FDA Staff: Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications. Food and Drug Administration. 2018. Available from <https://www.fda.gov/media/122971/download>.

needed at this time, we recommend for any future HF activities you revise your URRRA to categorize tasks as critical that, if performed incorrectly or not performed at all, would or could cause harm to the patient or user, where harm is defined to include compromised medical care.

4.1.2 FDA Responses to Rafa's Questions:

Rafa's Question #1: Does the Agency agree that the HF validation study of Atropine Injection, 2 mg can be leveraged to support approval of Midazolam Injection, 10 mg?

FDA's Response: Yes. You do not need to submit the results of a HF validation study for your proposed Midazolam autoinjector to support your marketing application at this time. Please note that if you modify the product user interface, the advice regarding submission of the results of HF validation study may change.

Rafa's Question #2: Does the Agency agree that, should FDA determine a HF validation study is required for Midazolam Injection, 10 mg, it may be submitted post-approval?

FDA's Response: See our response to Question #1.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. DRUG PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 3 presents relevant product information for Midazolam received on August 2, 2021 from Rafa, the reference listed drug (RLD) Seizalam Prescribing Information approved on September 14, 2018,¹¹ and the comparator product Atropine Prescribing Information approved on July 9, 2018.¹²

Table 3. Relevant Product Information for Midazolam, the Reference Listed Drug (RLD), and the Comparator			
Product Name	Midazolam (proposed)	Seizalam (midazolam) (RLD)	Atropine (Comparator)
Application Number	IND 147559	NDA 209566	NDA 212319
Product Manufacturer	Rafa Laboratories, Ltd.	Meridian Medical Technologies	Rafa Laboratories, Ltd.
Initial Approval Date	N/A	09/14/2018	07/09/2018
Therapeutic Drug Class or New Drug Class	benzodiazepine		cholinergic muscarinic antagonist
Active Ingredient	midazolam		atropine
Indication	Treatment of status epilepticus in adults.	Treatment of poisoning by susceptible organophosphorus nerve agents having anticholinesterase activity as well as organophosphorus or carbamate insecticides in adults and pediatric patients weighing more than 41 kg (90 pounds).	

¹¹ Seizalam NDA 209566 [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 SEP 16. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/209566Orig1s000lbl.pdf.

¹² Atropine NDA 212319 [Prescribing Information]. Drugs@FDA. U.S. Food and Drug Administration. 2021 SEP 16. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/212319s002lbl.pdf.

Route of Administration	Intramuscular into the mid-outer thigh (vastus lateralis muscle)	Intramuscular into the mid-lateral outer thigh	
Dosage Form	Injection		
Strength	10 mg/0.7 mL (14.3 mg/mL)	50 mg/10 mL (5 mg/mL)	1.67 mg/0.7 mL atropine base (equivalent to 2 mg atropine sulfate)
Dose and Frequency	10 mg [frequency not provided]	10 mg [frequency not provided]	<i>For Mild Symptoms:</i> If the patient experiences two or more mild symptoms, administer one injection intramuscularly into the mid-lateral thigh. If, at any time after the first dose, the patient develops any of the severe symptoms, administer two additional injections intramuscularly in rapid succession. <i>For Severe Symptoms:</i> If a patient has any of the severe symptoms, immediately administer three injections intramuscularly into the patient's mid-lateral thigh in rapid succession.
How Supplied	Each carton contains 480 single-dose prefilled autoinjectors each containing 10 mg/0.7 mL (14.3 mg/mL).	Each carton contains 10 multiple-dose vials each containing 50 mg/10 mL (5 mg/mL).	Each carton contains 480 single-dose prefilled autoinjectors each containing 1.67 mg/0.7 mL atropine base (equivalent to atropine sulfate 2 mg/0.7 mL).
Storage	Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C and 30 °C (59 °F and 86 °F). Do not freeze. [See USP	Store at 20 °C to 25 °C (68 °F to 77 °F); excursions permitted between 15 °C and 30 °C (59 °F and 86 °F) [See USP	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [see USP Controlled Room Temperature]. Do Not Freeze.

	Controlled Room Temperature].	Controlled Room Temperature].	
Container Closure/Device Constituent	Autoinjector (b) (4)	Vial (b) (4)	Autoinjector (b) (4)
Intended Users and Training	Active military service members ¹³ who receive initial training and annual follow up	Medical Professionals who have clinical training	Active military service members who receive initial training and annual follow up
Intended Use Environment	CBRN Battlefield	CBRN Battlefield or adjacent medical area or civilian hospital	CBRN Battlefield

APPENDIX B. BACKGROUND INFORMATION

B.1 PREVIOUS HF REVIEWS

B.1.1 Methods

On July 12, 2021, we searched the L: drive and AIMS using the terms, IND 147559 to identify reviews previously performed by DMEPA or CDRH.

¹³ Under the NDA submission, we sent an IR to confirm the user groups. The response is available here: [Response to Request for Information for Midazolam Injection NDA 216359. Frederick \(MD\): Rafa Laboratories, Ltd.; 2022 JUN 06. Available from: \\CDSESUB1\evsprod\nda216359\0003\m1\us\111-information-amendment\response-to-request-for-information.pdf.](#)

B.1.2 Results

Our search did not identify any previous reviews.

APPENDIX C. USE-RELATED RISK ANALYSIS AND COMPARATIVE ANALYSES

The use-related risk analysis submitted on July 15, 2021 can be accessed in EDR via:

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The comparative analyses submitted on July 15, 2021 can be accessed in EDR via:

<\\CDSESUB1\evsprod\ind147559\0009\m5\53-clin-stud-rep\535-rep-effic-safety-stud\status-epilepticus\5354-other-stud-rep\threshold-analysis\threshold-analysis-report-body.pdf>

The *Justification for not conducting a HF validation study* submitted on August 2, 2021 can be

accessed in EDR via: <\\CDSESUB1\evsprod\ind147559\0010\m1\us\112-other-correspondence\justification-for-not-conducting-a-hf-validation-study.pdf>

APPENDIX D. INFORMATION REQUESTS ISSUED DURING THE REVIEW

In response to the July 15, 2021 Type B Pre-NDA meeting request, under which Rafa submitted the URRAs and CAs we sent an Information Request (IR) on July 23, 2021¹⁴ to request Rafa submit this information separately under the IND for our review. Thus, they submitted the justification separately under IND 147559 on August 2, 2021 and referenced the URRAs and CAs submitted on July 15, 2021.

We issued an Information Request (IR) on August 17, 2021,¹⁵ to request Rafa identify a single comparator (i.e., Atropine or Seizalam) for our evaluation of their Comparative Analyses. On August 24, 2021,¹⁶ Rafa responded to our IR and asked the following clarifying questions:

¹⁴ Ogbonna, C. Information Request for IND 147559 for Midazolam Autoinjector. Silver Spring (MD): FDA, CDER, OSE (US); 2021 JUL 23.

¹⁵ Ogbonna, C. Information Request for Midazolam IND 147559. Silver Spring (MD): FDA, CDER, OSE (US); 2021 AUG 17.

¹⁶ Response to Information Request dated 17 August 2021 for Midazolam IND 147559. Jerusalem, Israel: Rafa Laboratories, Ltd.; 2021 AUG 24. Available from: <\\CDSESUB1\evsprod\ind147559\0011\m1\us\111-information-amendment\response-to-information-request-dated-17-august-2021.pdf>.

- Should the information related to one of the two comparators be removed from the Threshold Analyses and the revised document submitted to the IND (Section 5.3.5.4)?
- If the Threshold Analysis must be revised, Rafa needs to respectfully request an extension of the deadline of August 24, 2021. Would it be acceptable for Rafa to instead submit the revised Threshold Analysis, should it be required, as soon as possible?
- Which specific comparator did the Agency intend to recommend for comparison in Question 4 in the Pre-IND feedback dated March 16, 2020?

On September 2, 2021,¹⁷ we provided our response via an IR, and we requested Rafa to clarify which comparator is more suitable for evaluation of the comparative analyses, and they confirmed that Atropine AI is the more suitable comparator. Rafa submitted the requested information on September 8, 2021.¹⁸

We issued another IR on October 7, 2021,¹⁹ to request Rafa categorize all tasks in their URRAs as either critical or non-critical. Rafa submitted the requested information on October 12, 2021.²⁰ The revised use-related risk analysis submitted on October 12, 2021 can be accessed in EDR via: <\\CDSESUB1\evsprod\ind147559\0014\m5\53-clin-stud-rep\535-rep-effic-safety-stud\status-epilepticus\5354-other-stud-rep\urra\urra-report-body.pdf>

On November 15, 2021 we issued an IR²¹ to request Rafa verify whether the needle end of the Midazolam autoinjector and the Atropine autoinjector safety cap are similar in color. Rafa submitted the requested information on November 19, 2021.²²

¹⁷ Dunson, A. RE: Information Request for Midazolam IND 147559. Silver Spring (MD): FDA, CDER, OSE (US); 2021 SEP 02.

¹⁸ Response to Information Request dated 2 September 2021 for Midazolam IND 147559. Jerusalem, Israel: Rafa Laboratories, Ltd.; 2021 SEP 08: <\\CDSESUB1\evsprod\ind147559\0013\m5\53-clin-stud-rep\535-rep-effic-safety-stud\status-epilepticus\5354-other-stud-rep\threshold-analysis\response-to-information-request-dated-2-september-2021.pdf>.

¹⁹ Killen, M. Information Request for Midazolam IND 147559. Silver Spring (MD): FDA, CDER, OSE (US); 2021 OCT 07.

²⁰ Response to Information Request dated 7 October 2021 for Midazolam IND 147559. Jerusalem, Israel: Rafa Laboratories, Ltd.; 2021 OCT 12: <\\CDSESUB1\evsprod\ind147559\0014\m5\53-clin-stud-rep\535-rep-effic-safety-stud\status-epilepticus\5354-other-stud-rep\urra\urra-report-body.pdf>.

²¹ Killen, M. Information Request for Midazolam IND 147559. Silver Spring (MD): FDA, CDER, OSE (US); 2021 NOV 15.

²² Response to Information Request dated 15 November 2021 for Midazolam IND 147559. Jerusalem, Israel: Rafa Laboratories, Ltd.; 2021 NOV 19: <\\CDSESUB1\evsprod\ind147559\0015\m5\53-clin-stud-rep\535-rep-effic-safety-stud\status-epilepticus\5354-other-stud-rep\threshold-analysis\response-to-information-request-dated-15-november-2021.pdf>.

APPENDIX E: CDRH HUMAN FACTORS CONSULT REVIEW-N/A

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LABEL AND LABELING REVIEW
Division of Medication Error Prevention and Analysis 2 (DMEPA 2)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

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

Date of This Review:	June 24, 2022
Requesting Office or Division:	Division of Neurology 2 (DN 2)
Application Type and Number:	NDA 216359
Product Name and Strength:	Midazolam Injection, 10 mg/0.7 mL
Product Type:	Combination Product (Drug-Device)
Rx or OTC:	Prescription (Rx)
Applicant/Sponsor Name:	Rafa Laboratories, Ltd.
FDA Received Date:	March 28, 2022
OSE RCM #:	2022-609
DMEPA 2 Safety Evaluator:	Justine Kalonia, PharmD
DMEPA 2 Acting Team Leader:	Stephanie DeGraw, PharmD

1 REASON FOR REVIEW

As part of the approval process for Midazolam Injection, the Division of Neurology 2 (DN 2) requested that we review the proposed Midazolam Injection prescribing information (PI), instructions for use (IFU), container label, and carton labeling for areas of vulnerability that may lead to medication errors.

1.1 REGULATORY HISTORY

NDA 216359 is a 505(b)(2) NDA and the listed drug product is Seizalam, NDA 209566.

Under IND 147559, the Sponsor submitted a Comparative Analysis (CA) and Use-Related Risk Analysis (URRA), and Justification for Not Conducting a Human Factors (HF) Validation Study for our review on July 15, 2021 and August 2, 2021, respectively. The comparator product, Atropine injection (NDA 212319), is marketed by Rafa, and utilizes the same autoinjector device in a similar patient population and use environment (i.e., adult warfighters in a Chemical, Biologic, Radiological, and Nuclear (CBRN) battlefield). In our review of the CA and URRA, we determined that the Sponsor does not need to submit the results of a HF Study as part of the marketing application.^a

NDA 216359 was submitted on March 28, 2022. Based on the submission, the intended user group was unclear, thus, we sent an information request (IR) on May 3, 2022 to confirm this information. In response to the IR, Rafa submitted the following response on June 6, 2022:^b

“Rafa would like to reiterate that all Midazolam 10 mg product will be distributed directly to the U.S. Government, specifically, the Department of Defense (DoD), (b) (4)

the ultimate intended users will be “military personnel,” as stated in IND 147559 and NDA 216359.”

2 MATERIALS REVIEWED

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B – N/A

^a Kalonia, J. URRA and CA Review for Midazolam (IND 147559). Silver Spring (MD): FDA, CDER, OSE, DMEPA 2 (US); 2022 JUN 15. RCM No.: 2021-1613.

^b Response to Request for Information for Midazolam Injection NDA 216359. Frederick (MD): Rafa Laboratories, Ltd.; 2022 JUN 06. Available from: <\\CDSESUB1\evsprod\nda216359\0003\m1\us\111-information-amendment\response-to-request-for-information.pdf>.

Table 1. Materials Considered for this Label and Labeling Review	
Material Reviewed	Appendix Section (for Methods and Results)
ISMP Newsletters*	C – N/A
FDA Adverse Event Reporting System (FAERS)*	D – N/A
Other	E – N/A
Labels and Labeling	F

N/A=not applicable for this review

*We do not typically search FAERS or ISMP Newsletters for our label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 CONCLUSION AND RECOMMENDATIONS

The proposed prescribing information (PI), instructions for use (IFU), container labels, and carton labeling may be improved to promote the safe use of this product from a medication error perspective. We provide the identified medication error issues, our rationale for concern, and our proposed recommendations to minimize the risk for medication error in Section 4 for the Division and in Section 5 for Rafa Laboratories, Ltd.

4 RECOMMENDATIONS FOR DIVISION OF NEUROLOGY 2 (DN 2)

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Prescribing Information (PI) and Instructions for Use (IFU) – General Issues			
1.	A recommended frequency of administration is not stated in the PI or IFU. We note this is the same as the RLD, Seizalam.	Without this information in the PI and IFU, it is unclear whether the dose of 10 mg is intended to be a one-time dose, or if it can be repeated. We are concerned that the proposed product’s intended users (active military service members), which are different from those of Seizalam (medical professionals), may not understand if subsequent doses may be administered to a single patient.	We defer to the review team to determine whether language is needed to convey a recommended frequency of administration (e.g., one-time or otherwise) in the PI or IFU.

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
2.	The strength presentation is inconsistent between the PI, IFU, and container label and carton labeling. In the PI, it is expressed as “10 mg/0.7 mL (14.3 mg/mL)”, while in the IFU it only states “10 mg”. On the container label and carton labeling it is stated as “10 mg/0.7 mL”.	We find that the strength presentation in the PI and IFU is not consistent with USP Chapter <7> which states “For containers that hold a volume of less than 1 mL, the quantity per fraction of a milliliter should be the only expression of strength.” Additionally, we note in our <i>Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors</i> that products containing a volume less than 1 mL “should not be labeled with a concentration of mg/mL, since this may lead end users to mistakenly think the container has more drug in it than it actually does, which can lead to underdosing.” Inconsistency in the strength presentation between the PI, IFU, and container label and carton labeling may lead to confusion.	Therefore, we recommend the strength statement in the PI and IFU be revised to “10 mg/0.7 mL” to align with USP Chapter <7> requirements and for consistency with the container label and carton labeling.
Full Prescribing Information – Section 16 How Supplied/Storage and Handling			
1.	The (b) (4) is not described in Section 16 of the PI. We note the Sponsor’s description of the container closure system states that (b) (4)	It is unclear if the submitted (b) (4) (received on March 28, 2022) will be available separately from the (b) (4) carton (i.e., the 480-count carton).	See recommendation for Rafa Laboratories below in the “Packaging” section of Table 3. Consider including information for the (b) (4) presentation in Section 16.1 to align with

Table 2. Identified Issues and Recommendations for Division of Neurology 2 (DN 2)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	will be packaged in a 480-count (b) (4) carton.		Rafa's response to our request.

5 RECOMMENDATIONS FOR RAFA LABORATORIES, LTD.

Table 3. Identified Issues and Recommendations for Rafa Laboratories, Ltd. (entire table to be conveyed to Applicant)			
	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
Container Label and Carton Labeling			
1.	As currently presented, a placeholder for the National Drug Codes (NDCs) are missing from the container label and carton labeling. We note that you have provided an NDC for the 480-count carton configuration within Section 16 of the PI.	We strongly encourage including NDCs on all drug labels and labeling to assist with identification and verification of the product.	Consider including the unique NDCs for this product on the container label and carton labeling.
2.	The package type term listed in the PI (i.e., single-dose) is not present on the container label and carton labeling.	This is inconsistent with <i>Guidance for Industry: Selection of the Appropriate Package Type Terms and Recommendations for Labeling Injectable Medical Products Packaged in Multiple-Dose, Single-Dose, and Single-Patient-Use.</i>	Add the package type term, "single-dose" to the container label and carton labeling. For example, consider revising the net quantity statement on the carton labeling from "(b) (4)" and "(b) (4)" to read "(b) (4)" and "480 single-dose autoinjectors", respectively.
3.	As currently presented, the linear barcode is missing from the container label and carton labeling.	The drug barcode is often used as an additional verification before drug administration; therefore, it is an important safety	Therefore, we request you add the product's linear barcode to each individual container label and carton labeling as

Table 3. Identified Issues and Recommendations for Rafa Laboratories, Ltd. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
		feature that should be part of the label whenever possible.	required per 21 CFR 201.25(c)(2). Additionally, ensure the barcode is: - surrounded by sufficient blank space so that the bar code can be scanned correctly and remain intact under normal conditions of use in accordance with 21 CFR 201.25(c)(1)(i) and 21 CFR 201.25(c)(1)(ii), respectively; and - oriented such that it is scannable despite the curvature of the autoinjector.^c
Carton Labeling			
1.	The strength statement on the carton labeling lacks adequate spacing between the numerical strength and unit of measure.	Lack of adequate spacing may impact readability and result in wrong strength medication errors.	To improve readability, we recommend placing adequate space between the numerical strength and unit of measure (e.g., 10 mg/0.7 mL instead of 10mg/0.7 mL)
Packaging			
1.	(b) (4)		

^c Neuschwander M. et al. Practical guide to bar coding for patient medication safety. Am J Health Syst Pharm. 2003 Apr 15;60(8):768-79.

Table 3. Identified Issues and Recommendations for Rafa Laboratories, Ltd. (entire table to be conveyed to Applicant)

	IDENTIFIED ISSUE	RATIONALE FOR CONCERN	RECOMMENDATION
	(b) (4)		

APPENDICES: METHODS & RESULTS FOR EACH MATERIAL REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 4 presents relevant product information for Midazolam Injection that Rafa Laboratories, Ltd. submitted on March 28, 2022.

Table 4. Relevant Product Information for Midazolam Injection	
Initial Approval Date	N/A
Active Ingredient	midazolam
Indication	for the treatment of status epilepticus in adults
Route of Administration	intramuscular injection
Dosage Form	Injection
Strength	10 mg/0.7 mL
Dose and Frequency	10 mg administered by intramuscular injection using the pre-filled autoinjector.
How Supplied	Each single-dose pre-filled autoinjector containing 10 mg/0.7 mL of midazolam is supplied in a clear pouch. The proposed carton configurations may include either (b) (4) autoinjectors or 480 autoinjectors.
Storage	Store at 20°C to 25°C (68°F to 77°F); excursions permitted between 15°C and 30°C (59°F and 86°F) [See USP Controlled Room Temperature]. DO NOT FREEZE.
Container Closure	Each single-dose pre-filled autoinjector is supplied in a clear pouch (outer plastic sleeve). Each carton contains (b) (4) or 480 autoinjectors.

APPENDIX F. LABELS AND LABELING

F.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,^d along with postmarket medication error data, we reviewed the following Midazolam Injection PI, IFU, container label and carton labeling submitted by Rafa Laboratories, Ltd. received on March 28, 2022.

- Container label
- Carton labeling
- Instructions for Use, available from <\\CDSESUB1\evsprod\nda216359\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-instructions-for-use-word.docx>
- Prescribing Information (Image not shown), available from <\\CDSESUB1\evsprod\nda216359\0001\m1\us\114-labeling\draft\labeling\draft-labeling-text-word.docx>

F.2 Label and Labeling Images

Container label



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

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

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/s/

JUSTINE H KALONIA
06/24/2022 03:24:07 PM

STEPHANIE L DEGRAW
06/24/2022 04:03:54 PM

MEMORANDUM

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

DATE: June 22, 2022

TO: Nicholas Kozauer, MD
Director
Division of Neurology II (DNII)
Office of Neuroscience (ON)
Office of New Drugs (OND)

FROM: Sarmistha Sanyal, Ph.D.
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Seongeun (Julia) Cho, Ph.D.
Director
Division of Generic Drug Study Integrity (DGDSI)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Routine inspection of M3 Wake Research, 3100 Duraleigh Road, Suite 304, Raleigh, NC 27612, USA.

1. Inspection Summary

The Office of Study Integrity and Surveillance (OSIS) arranged a clinical inspection of study RLM-559-01, conducted at M3 Wake Research, 3100 Duraleigh Road, Suite 304, Raleigh, NC 27612, USA.

At the inspection close-out, Form FDA 483 was not issued. The final inspection classification is No Action Indicated (NAI).

After reviewing the study report and the findings in the establishment inspection report, I conclude that the audited study data is reliable.

1.1 Surveillance Recommendation

Studies of similar design conducted at the inspected site between the previous inspection [REDACTED] (b) (4) and before the end of the current surveillance interval should be considered reliable without an inspection.

2. Inspected Study:

NDA 216359

Study Number: RLM-559-01

Study Title: Phase 1, Open-Label, Comparison Study to Evaluate the Safety and Pharmacokinetics of a Single Intramuscular Administration of 10 mg Midazolam Using an Auto-Injector vs Marketed Midazolam Vials in Healthy Adults.

Dates of conduct: 05/25/2021 (Study initiation) -
09/17/2021 (Study completion)

Clinical site: M3 Wake Research
3100 Duraleigh Road, Suite 304
Raleigh NC 27612, USA.

3. Inspectional Findings

ORA investigator Scott Laufenberg inspected M3 Wake Research, 3100 Duraleigh Road, Suite 304, Raleigh, NC 24612 from May 17-20, 2022.

(b) (4)

(b) (4)

The current inspection included auditing the following items:

- Case report forms (CRFs)
- Informed consent process
- Protocol deviations
- Institutional review board approvals
- Test article accountability, dosing and storage
- Randomization
- Adverse events and concomitant medication

At the conclusion of the inspection, investigator Laufenberg did not observe any objectionable conditions and did not issue Form FDA 483 to the clinical site.

Final Classification:

NAI M3 Wake Research
3100 Duraleigh Road, Suite 304, Raleigh, NC
USA, 27612
FEI#: 3003001661
Principal Investigator: Dr. Singaravelu Jagadeesan
FEI#: 3014126616

cc:
OTS/OSIS/Kassim/Mitchell/Fenty-Stewart/ Haidar/Mirza
OTS/OSIS/DNDSI/Bonapace/Dasgupta/Ayala/Biswas/
OTS/OSIS/DGDSI/Cho/Benson/Skelly/Au/Lewin/Sanyal

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Draft: SS 6/15/2022, 6/17/22, 6/21/22
Edit: SA 06/15/2022, 6/17/22, 6/21/22; SC 6/21/22, 6/22/22

ECMS: Cabinets/CDER_OTS/Office of Study Integrity and
Surveillance/INSPECTIONS/BE Program/CLINICAL/M3 Wake Research,
Raleigh, NC, USA

OSIS File#: BE 9425

Assignment ID# 198005 and **OP ID#** 223406

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

/s/

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