CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

216359Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

IND 147559

MEETING MINUTES

Rafa Laboratories, Ltd.
c/o Ology Bioservices, Inc.
Attention: Angela Bellos, PhD, RAC
Regulatory Affairs Manager
8490 Progress Drive, Suite 150
Frederick, MD 21701

Dear Dr. Bellos:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for midazolam injection.

We also refer to the telecon between representatives of your firm and the FDA on August 19, 2021. The purpose of the pre-NDA meeting was to discuss any potential issues that would prevent filing the NDA.

A copy of the official minutes of the meeting/telecon is enclosed for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, contact Harold Sano, Regulatory Project Manager, by email at harold.sano@fda.hhs.gov or by telephone at (301) 796-2429.

Sincerely,

{See appended electronic signature page}

Nick Kozauer, MD
Director
Division of Neurology 2
Office of Neuroscience
Center for Drug Evaluation and Research

Enclosure:

- Meeting Minutes

U.S. Food and Drug Administration
Silver Spring, MD 20993
www.fda.gov

MEMORANDUM OF MEETING MINUTES

Meeting Type: B
Meeting Category: Pre-NDA

Meeting Date and Time: August 19, 2021, 9 am to 10 am ET
Meeting Location: Teleconference

Application Number: 147559
Product Name: Midazolam injection

Proposed Indication: Treatment of status epilepticus in adults
Sponsor Name: Rafa Laboratories, Ltd.
Regulatory Pathway: 505(b)(2) of the Federal Food, Drug, and Cosmetic Act

Meeting Chair: Nick Kozauer, MD
Meeting Recorder: Michael Matthews, MS

FDA ATTENDEES

Office of Neuroscience
Billy Dunn, MD, Director

Division of Neurology 2
Nick Kozauer, MD, Director
Paul R. Lee, MD, PhD, Deputy Director
Philip Sheridan, MD, Clinical Team Leader
Steve Dinsmore, DO, Clinical Reviewer
Tracy Peters, PharmD, Associate Director for Labeling

Office of Clinical Pharmacology
Gopichand Gottipati, PhD, Team Leader
Adarsh Gandhi, PhD, Reviewer

Office of Product Quality
Martha Heimann, PhD, CMC Lead
Renishkumar Delvadia, PhD, CMC Reviewer
Khalid Khan, PhD, Process/Facility Evaluation Reviewer

Center for Devices and Radiological Health/Office of Product Evaluation and Quality
Papatya Kaner, PhD, Reviewer

Office of Orphan Products Development
Roberta Szydlo, RPh, MBA, Regulatory Reviewer

Office of Management, Division of User Fee Management
Jeen Min, RPh, RAC, Branch Chief
Peter Chen, Program Management

Controlled Substance Staff
Joshua Lloyd, MD, Team Lead
Emily Deng, MD, PhD, Medical Officer

Office of Surveillance and Epidemiology
Casmir Ogbonna, PharmD, Safety Regulatory Health Project Manager

Division of Medication Error Prevention and Analysis
Justine Kalonia, PharmD, Reviewer
Stephanie DeGraw, PharmD, Reviewer

Division of Risk Management
Yasmeen Abou-Sayed, PharmD, Senior Risk Management Analyst

Office of Drug Security, Integrity, and Response
Sara Keller, JD, Regulatory Counsel

Office of Combination Products
Patricia Love, MD, MBA, Deputy Director

Counter-Terrorism and Emergency Coordination Staff
Rosemary Roberts, MD, Director
Susan McDermott, MD, Medical Countermeasure Development
Gerald Poley, MD, Medical Officer
Matthew Hornung, PharmD, Regulatory Project Manager

Division of Regulatory Operations for Neuroscience
Michael Matthews, MS, Regulatory Project Manager

SPONSOR ATTENDEES

Rafa Laboratories, Ltd.
Yael Tomer, Regulatory and Medical Director
Tzufit Waraftig, R&D Manager
Daniel Bornstein, Analytical R&D Manager
Miriam Ben-Yashar, Clinical Specialist

(b) (4)

(b) (4)

(b) (4)

Department of Defense (JPEO-CBRND/DTRA JSTO; CBRN Medical)

(b) (4)

1.0 BACKGROUND

The sponsor, Rafa Laboratories, Ltd., is developing a midazolam 10 mg autoinjector for the treatment of status epilepticus in adults and to support the U.S. Government's effort for improved nerve agent medical countermeasures. The sponsor recently received FDA approval for atropine injection (NDA 212319; July 2018) that uses a similar autoinjector system to that planned for the midazolam injection.

On March 16, 2020, Type B pre-IND written responses were provided to the sponsor that discussed product quality, reliability, human factors engineering, and limitations on the reliance of the listed drug because of orphan drug exclusivity.

On May 19, 2021, Type C written responses were provided to the sponsor that continued the discussion on product quality and reliability and clarified the Division's non-hold comments and responses to the sponsor's questions that were included in the February 9, 2021, May Proceed letter.

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).

The Division sent Preliminary Comments to the sponsor on August 16, 2021. The sponsor requested discussion of Questions 4, 6, 10, 11a, 13b, Controlled Substance Staff Additional Comments 1 and 2, Additional Information on the Prospective Assessments of Suicidal Ideation, and Additional Information on Prescribing Information (Pregnancy and Lactation Labeling Rule).

2.0 DISCUSSION

2.1. Administrative/Regulatory

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).

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 2: Does the Agency agree that Midazolam Injection, 10 mg is exempt from the requirement for pediatric studies under PREA?

FDA Response to Question 2:

We agree that PREA is not triggered, and, therefore, pediatric studies are not required.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 3: Does the Agency agree with the approach for the labeling for Midazolam Injection, 10 mg?

FDA Response to Question 3:

Your overall approach of using the listed drug's labeling as the basis for the proposed labeling for your drug appears appropriate. Final labeling language for your product will be a review issue after the NDA is submitted.

We note that you mention including (b) (4) (b) (4)

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 4: Does the Agency agree that an Environmental Assessment will not be required in the NDA for Midazolam Injection, 10 mg?

FDA Response to Question 4:

We agree that a claim for categorical exclusion pursuant to 21 CFR §25.31(a) would be appropriate if there is no increase in use of the actual moiety. However, use of the autoinjector in the field may result in some increased use. Therefore, the categorical exclusion pursuant to 21 CFR §25.31(b) would be the appropriate claim. However, rather than the general scenario from the FDA environmental assessment (EA) guidance of a continual use of the product throughout the year across the

United States (which is used to estimate an expected introduction concentration [EIC] for comparison to the 1 ppb exclusion concentration), the scenario and EIC would need to be based on an estimated use of the product during a reasonable worst-case short-term situation within a limited geographic area, whereby adjustments would need to be made accordingly to the liters per day entering (limited) publicly owned treatment works (POTWs) and to the number of days.

Rafa Response:

It is estimated that Rafa will be using approximately (b) (4) kg of the active ingredient annually for direct use in any of the next five years. According to information obtained from (b) (4), (b) (4) kg of Midazolam were sold in (b) (4) worldwide; and (b) (4) kg of Midazolam were sold in (b) (4) (b) (4) (b) (4) Therefore, Rafa's use of the active moiety is not significant: Furthermore, recent evaluation of the Swedish Fass database of pharmaceuticals suggests that Midazolam poses an insignificant environmental risk to the Swedish water systems, which is reassuring.[1,2] Rafa is evaluating the Swedish studies to determine if they can be leveraged in estimating use of the product during a worst-case situation within a limited geographic area.

If Rafa takes this approach, could the EA be reviewed during review of the NDA?

Meeting Discussion:

The Agency agreed that the approach described appears reasonable. The justification for this approach should be included in the NDA and its adequacy would be a matter for review.

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

[1] Vestel J et al. Use of acute and chronic ecotoxicity data in environmental risk assessment of pharmaceuticals. Environ Toxicol Chem. 2016 May;35(5):1201-12.

[2] https://noharm-global.org/documents/environmentally-classified-pharmaceuticals-2014-2015

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 6: Does the Agency agree that Midazolam Injection, 10 mg is eligible for such an exemption under Section 582(b)?

FDA Response to Question 6:

At this time, the Agency has insufficient information regarding whether this product is eligible for an exemption from section 582(b) requirements. The Agency will make a determination on this product's eligibility for such an exemption during the NDA review. Please be advised that the Agency may request additional information related to the firm's plans regarding its expected trading partners, product storage, product identifiers, product tracing, record keeping, and other plans related to the Drug Supply Chain Security Act (DSCSA) during the NDA review process.

Rafa Response:

Rafa's understanding of the Guidance on Section 582 is that serialization will be at the carton level. **Does the Agency agree?**

Meeting Discussion:

Section 582(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requires a manufacturer to affix or imprint a product identifier to each package and homogenous case of a product intended to be introduced in a transaction into commerce. *Package* is defined under section 581(11) of the FD&C Act as the "smallest individual saleable unit of product for distribution by a manufacturer or repackager that is intended by the manufacturer for ultimate sale to the dispenser of such product." Therefore, if the sponsor intends the carton to be the smallest container of product for individual sale to a dispenser, then FDA agrees that serialization will occur at the carton level. If needed, FDA has published guidance, *Product Identifiers Under the Drug Supply Chain Security Act, Questions and Answers*, that contains helpful information regarding the product identifier requirement under the Drug Supply Chain Security Act (DSCSA).

Question 7: Since a REMS was not required for Seizalam (NDA 209566) or for Atropine Injection, 2 mg (NDA 212319), does the Agency agree that a REMS is not necessary for Midazolam Injection, 10 mg?

FDA Response to Question 7:

At this time, the Office of New Drugs and the Office of Surveillance and Epidemiology has insufficient information to determine whether a risk evaluation and mitigation strategy (REMS) will be necessary to ensure that the benefits of the drug outweigh the risks, and, if it is necessary, what the required elements would be. We will determine the need for a REMS during the review of your application.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 8: Does FDA agree that the Table of Contents appears appropriately organized and complete for filing the 505(b)(2) application for Midazolam Injection, 10 mg?

FDA Response to Question 8:

Section 1.17 – Postmarketing studies - The Proposed eCTD Table of Contents (TOC) contains the Correspondence regarding postmarketing commitments and the Correspondence regarding postmarketing requirements in Sections 1.17.14 and 1.17.15.

The Correspondence regarding postmarketing commitments should be in section 1.17.1

The Correspondence regarding postmarketing requirements should be in section 1.17.2

Please refer to the Comprehensive Table of Contents Headings and Hierarchy Section 1.17 for more details.

From a technical perspective (and not content related), all other sections proposed in the eCTD-IND Table of Contents appear acceptable.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 9: Does the Agency have any comments on strategy to file with 6-month stability and E&L data, Interim Reliability Report, and Analytical Comparability Report (biowaiver), and to submit additional stability and E&L data and the Final Reliability Report and Clinical Study Report as soon as they are available?

FDA Response to Question 9:

At least 12 months of long-term stability data and 6-months of accelerated stability data are usually required at the time of filing in order to grant a commercially viable expiry. However, given the clinical need for this product, your proposal to submit 6 months of stability and extractables/leachables stability data at the time of filing is acceptable. See the responses to Questions 11(a-f) and 17 for additional comments on the proposed stability and E&L data submission strategy.

In general, your proposed approach to submit the Interim Reliability Report at the time of filing and Final Reliability Report as soon as it is available during the NDA review appears reasonable. However, we note that the acceptability of your Final Reliability Report, including acceptance criteria and tests methods, will be a matter of review when it is submitted as part of your NDA submission

The final Clinical Study Report, along with all the relevant datasets, for the ongoing relative bioavailability study (RLM-559-01) must be submitted at the time of NDA submission. See also the responses to Question 12 and Question 19.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 10: Does the Agency agree that Rafa qualifies for a public health waiver of the application fee for Midazolam Injection?

FDA Response to Question 10:

An official request for a public health waiver of an application fee should be submitted to the Division of User Fee Management via email to CDERCollections@fda.hhs.gov. We refer you to the October 2019 FDA guidance for industry *Prescription Drug User Fee Act Waivers, Reductions, and Refunds for Drug and Biological Products* (Waivers Guidance) (here). Specifically, Section VI of the Waivers Guidance provides instructions on the address for submitting requests, on the timing of requests, and on the content and format of requests.

Applicants should submit requests for waivers of application fees approximately 3-4 months before submission of the application. Under normal circumstances and depending on available resources, the Agency will try to make its determination on the waiver request before the application is submitted and the fee is due. However, if a waiver decision has not been made at the time the application is ready for submission, an applicant may choose to pay the application fee. Subsequently, if the waiver is granted, the Agency will refund the application fee.

Under section 736(d)(1)(A) of the Federal Food, Drug, and Cosmetic Act, an applicant may qualify for a public health waiver or reduction of an application fee where the Agency finds:

- The product protects the public health; and
- The applicant shows that a waiver or reduction is necessary to continue an activity that protects the public health.

To determine whether a waiver of or reduction in user fees is necessary to continue an activity that protects the public health, the Agency considers not only the benefit to the public health, but also the financial resources of the applicant. A waiver or reduction may be necessary where the applicant, including its affiliates, have limited resources of less than $20 million in working capital (Waivers Guidance at 9).

Should you wish to pursue an official request for a public health waiver, you should submit the justifications in section 16.1.10 of the pre-NDA briefing package and any additional supporting information, including Rafa's financial statements for a recent 12-month period.

If you have additional questions concerning this matter, please contact the Prescription Drug User Fee staff at CDERCollections@fda.hhs.gov.

Rafa Response:

Rafa cannot claim having limited resources of less than $20 million in working capital. However, Rafa is selling only emergency autoinjectors to the U.S. market, in

relatively small quantities and to U.S. Government only, and the PDUFA fee is a significant expense for Rafa. Rafa acknowledges that any pursuit of an official request for a public health waiver should be submitted to the Division of User Fee Management via email to CDERCollections@fda.hhs.gov.

Does the Agency have any comments about feasibility of a PDUFA waiver being granted in light of the additional financial information provided?

Meeting Discussion:

The Agency indicated that FDA's Waiver Guidance clarifies that an applicant, including its affiliates, should show that it has limited resources of less than $20 million in working capital (current assets - current liabilities). At a minimum, an applicant's waiver request should provide financial statements that include its current assets and current liabilities over a recent 12-month period. Even if the applicant cannot demonstrate limited resources of less than $20 million, the financial information should still be submitted since it can be helpful in determining whether a departure from guidance is warranted.

The Agency explained that FDA may depart from guidance with appropriate justification and supervisory concurrence. The applicant should justify why, despite not being able to meet the financial criterion, it should be granted a public health waiver. In doing so, it should provide specific relevant details. FDA will review what the applicant submits and will follow up with the applicant in case additional information or clarification is needed.

Upon receipt and review of the applicant's waiver request, the Division of User Fee Management will consult with relevant offices to ensure that an appropriate decision is made with respect to the applicant's waiver request.

2.2. Chemistry, Manufacturing and Controls

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 a (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 11b: Does the Agency agree that the approach to long-term and accelerated stability data and thermal cycling are acceptable to support the NDA filing?

FDA Response to Question 11b:

In general, your proposed approach for the long-term, accelerated, and thermal stability studies appears reasonable. We recommend that during the thermal cycling study, the drug product be tested in accordance with the drug product release specification at the end of each thermal cycle. You should also generate short-term stability data that capture the potential worst-case storage conditions of the battlefield (such as at freezing temperatures and at temperatures higher than 40^{o}C). In the NDA submission, you should provide adequate justification to support the selection of the proposed stability orientations (i.e., horizontal and upright). See the responses to Questions 11a, 11c, and 11f for additional comments on the proposed long-term and accelerated stability approaches.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 11c: Does the Agency agree that the data referenced in part (b) above will support a shelf-life of (b) (4) months at the time of filing?

FDA Response to Question 11c:

We cannot comment on the acceptability of the proposed shelf-life until all of the data submitted to the NDA are reviewed. Generally, per ICH Q1E, in order to extrapolate an expiry, at least 12 months of long-term data are required. When less data are provided, the expiry is based on the amount of data submitted.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 11d: Does the Agency agree with the justification for photostability studies not being required?

FDA Response to Question 11d:

The justification provided in the meeting package appears reasonable to support your proposal not to conduct photostability studies of the drug product. Note that the acceptability of your photostability proposal will ultimately be determined at the time of the NDA review.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 11e: Does the Agency agree that Rafa has provided sufficient stability data and commitments to continue gathering stability data to support FDA approval of this critically important, lifesaving medical countermeasure?

FDA Response to Question 11e:

The adequacy of your stability data and post-approval stability commitment will be determined at the time of NDA submission, when all of the data can be evaluated in their entirety.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

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.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 12: Rafa has comparability data to establish a bridge between Midazolam Injection and Seizalam in support of the 505(b)(2) application and a waiver to file the NDA without clinical data. Does the Agency agree?

FDA Response to Question 12:

We agree that your future midazolam injection 505(b)(2) NDA may be filed without safety and efficacy data, provided that the comparative physicochemical data are assessed and found to be acceptable for establishing the bridge during the NDA review cycle. Based on our previous advice, however, the comparative physicochemical properties of the listed drug and the proposed drug product will be supportive of the scientific bridge but not definitive or pivotal. Rather, results of the ongoing relative bioavailability study will be definitive in establishing the scientific bridge between the proposed drug product and the listed drug.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 13a: Does the Agency agree with the approach to monitoring the impurity?

FDA Response to Question 13a:

Acceptability of the proposed impurity monitoring approach will be determined at the time of the NDA review

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

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:

(b) (4)

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.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

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.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

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.

Rafa Response:

No comments.

Meeting Discussion:

No discussion.

Question 17: Does the Agency agree with the approach for leachables testing, including providing only the 6-month data with the original NDA submission, then 12-month data during review of the NDA, and finally 24-month data post-approval?

FDA Response to Question 17:

Your proposal to submit 6-month leachable stability with the original NDA might be acceptable provided that the 12-month leachable stability data are submitted within 60 days of the NDA submission. If leachables stability data are not collected for the initial (time zero) and 3-month time-points, then we recommend that you include an 18-month time-point in your leachables testing protocol.

Rafa Response:

No comments.

Meeting Discussion:

No discussion

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)

(b) (4)

Rafa Response:

No comments.

Meeting Discussion:

No discussion

2.3. Clinical

Question 19: Does the Agency agree that the Phase 1 study (Protocol RLM-559-01, v2) can be the sole clinical study to support reliance upon the Agency's previous finding of safety and effectiveness of Seizalam?

FDA Response to Question 19:

If you are able to successfully establish bioequivalence between your proposed product (midazolam autoinjector) and Seizalam in your proposed Phase 1 study RLM-559-01, those study results could support reliance upon the Agency's previous finding of the safety and effectiveness of Seizalam. However, we note that the acceptability of the study results will be a matter of review when they are submitted as part of your NDA submission.

Rafa Response:

No comments.

Meeting Discussion:

No discussion

Question 20a: 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 Response to Question 20a:

We acknowledge that your August 2, 2021 submission includes your use-related risk analysis (URRA), Comparative Analyses, and Question 20a, and Question 20b. We will provide written responses to Question 20a and Question 20b as soon as our review of your August 2, 2021, submission is completed.

Rafa Response:

No comments.

Meeting Discussion:

No discussion

Question 20b: 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 Response to Question 20b:

See the response to Question 20a.

Rafa Response:

No comments.

Meeting Discussion:

No discussion

Additional Comments: Combination Product

1. Combination products are subject to the current good manufacturing practices (CGMP) requirements applicable to each constituent part (drug, device, biological product) of the combination product. For further information on 21 CFR Part 4, the final rule is accessible at https://www.federalregister.gov/articles/2013/01/22/2013-01068/current-good-manufacturing-practice-requirements-for-combination-products. Also, *Guidance for Industry and FDA Staff: Current Good Manufacturing Practice Requirements for Combination Products* (Jan. 2017), is accessible at https://www.fda.gov/media/90425/download.

2. For location of information on the device constituent part, see the FDA eCTD Technical Conformance Guide: Technical Specifications Document: "Guidance for Industry *Providing Regulatory Submissions in Electronic Format —Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications" July 2020* accessible at http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/ElectronicSubmissions/UCM465411.pdf.

Rafa Response:

No comments.

Meeting Discussion:

No discussion

Additional Comments: Controlled Substances Staff

Although formal studies of abuse potential and dependence are not required for your proposed 505(b)(2) clinical development program, we recommend the following:

> Monitor for the occurrence of abuse-related adverse events (AEs) in any clinical studies conducted with your proposed product (e.g., bioavailability/bioequivalence studies). We refer you to guidance for industry, Assessment of Abuse Potential of Drugs, available at: http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf for a list of abuse-related terms for which to monitor and for additional details regarding the documentation of abuse-related AEs.
>
> The incidence of abuse-related AEs in comparison to placebo in trials should be reported by study, population, and dose and should be displayed in tabular format, including study number, type of study, and subject ID number. Also provide narratives, case description and details. Tables should be created for abuse-related higher level MedDRA terms, even if there were few patients or subjects who experienced a particular AE. Narratives describing these events should be provided in tabular form and should include the timing of the event in relation to drug administration, duration, severity; indicate if more than one event was observed simultaneously, and if other drugs were taken by subjects at the time of the event. In addition, if available, you should provide pharmacokinetic measures for subjects reporting the event to determine if there is a correlation between the onset of the event and drug exposure.

Rafa Response:

Rafa thanks the FDA Controlled Substances Staff for their additional comments on abuse potential.

Boxed warnings for risks from abuse, misuse, and addiction and dependence and withdrawal reactions are included in the current labeling for Seizalam and draft labeling for Rafa's Midazolam Injection and described in the Investigator's Brochure (IB) for Rafa's Midazolam Injection. Please note that Midazolam is intended for a

single administration on the battlefield rather than repeated or chronic administration. The Seizalam labeling and Midazolam Injection IB were provided to the Investigator of Rafa's ongoing Phase 1 bioavailability (BA)/ pharmacokinetic (PK) study (Protocol RLM-559-01, v2; NCT04679623) to facilitate his understanding of the rationale for protocol features, such as monitoring procedures, and clinical management of study participants. Participants are being monitored for AEs and serious AEs after 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). All safety data are being recorded in the eCRF. Therefore, the Investigator is informed of the risks of abuse-related AEs and appropriate safety monitoring is being performed.

Separate monitoring procedures for abuse-related AEs were not prospectively defined in the protocol for the ongoing Phase 1 study. Therefore, Rafa plans to analyze the database of AEs from the eCRFs for the abuse-related AE terms and verbatim terms, words, and phrases from a patient or observer listed in the Guidance for Industry, "Assessment of Abuse Potential of Drugs," January 2017 ("Abuse Potential Guidance"). No abuse- related AEs have been noted so far. As the Phase 1 study is not a placebo-controlled trial, incidence of abuse-related AEs compared with placebo cannot be provided. However, Rafa will report any abuse-related AEs for Midazolam Injection and Seizalam (active comparator) in tabular format using higher- level MedDRA terms with subject ID number. Rafa will also provide narratives of any abuse-related AEs in tabular format with the suggested case descriptions, PK measures, and any other relevant details per the Controlled Substances Staff additional comment and the Abuse Potential Guidance.

Does the Agency agree that the approach to monitoring for the occurrence and reporting of abuse-related AEs in Rafa's Phase 1 BA/PK study of Midazolam Injection, 10 mg is acceptable?

Meeting Discussion:

Given that the Phase 1 BA/PK study was already initiated and is nearly completed, we agree the proposed approach to monitor and report the abuse-related AEs.

The applicant should monitor for possible cases of abuse (subjects taking the drug for non-therapeutic purposes, e.g., for psychoactive effects such as high or euphoria) in all clinical studies. Additionally, the applicant should look for drug accountability discrepancies (e.g., missing medication, loss of drug, or non-compliance cases in which more investigational drug was used as compared to expected use). Towards this end, the applicant should:

a. Train investigators to capture cases of abuse, misuse, and addiction and to monitor for drug accountability discrepancies before starting trials. In addition, instruct investigators to obtain more information and

explanations from the subjects when there are drug accountability discrepancies.

b. Provide data in tabular form for all reports of abuse, overuse, and lost/stolen/missing or unaccounted-for product that occurred in clinical studies (Phase 1, 2 and 3). These data should include study number and type of study, subject ID number, narratives, case description, and other available details.
c. Provide narratives for cases where the patients dropped out from studies for reasons that might be coded as “protocol violation,” “lack of efficacy” (to eliminate the possibility of aberrant behavior in patients who drop out of the study supposedly due to lack of efficacy), “lost to follow up,” “noncompliance to study medication or procedures,” “over compliance,” or for “other.” Case reports should be provided separately.
d. Report any use of the investigational formulation by individuals other than the patients (family member, health care practitioner, etc.).
e. Report any instances of drug accountability discrepancies that may have occurred at the study site level and identify the origin of the discrepancy and individuals involved.

Rafa Response:

As noted in the response to Additional Comment 1 above, monitoring for abuse-related AEs was not prospectively defined in the protocol, although the Investigator is informed of the risks of abuse and study subjects are being monitored for AEs throughout the 30-hour monitoring period post- injection and at each visit. Concomitant medications are also assessed at each visit, which can help to identify any changes in medications or controlled substances taken. Please note that study subjects should not be able to self-administer the drug for non-therapeutic purposes because access to the drug is restricted to certain site staff for administration to subjects at the study site. Also, an exclusion criterion for the protocol is “Has a current or history of drug and /or alcohol abuse.”

Regarding a), drug accountability responsibilities were prospectively defined in Protocol RLM-559- 01, v2. Investigator responsibilities for storage and dispensing of product supplies include that the Investigator or Investigator’s pharmacist must assure the study monitor that adequate and accurate written records show receipt and disposition of all product supplies, including dates, serial or lot numbers, quantities received, and each quantity dispensed, administered, or used, with identification of each subject and that the purpose and reasons are given in written records for product disposal (e.g., the amount contaminated, broken, or lost) and the quantity that was returned to the sponsor. As Sponsor, Rafa will examine pharmacy records for documentation of quantity and date of receipt of investigational drug, dispensation, and accountability data for product administration to each subject, loss of materials, contamination, and unused supplies. Investigational product

accountability is being reviewed and confirmed at Interim Monitoring Visits and there have been no issues so far.

Please note that subjects are being dosed at the site and subjects do not take investigational product with them from the site. Thus far, there have been several monitoring visits that have accounted for the study products, and there are no accountability issues at this time. The site maintains continuous drug product accountability. Every time study product is issued to a subject, it is accounted for on a real-time basis, and drug accountability is reviewed at every other monitoring visit.

Regarding b) through e), Rafa agrees to provide the data on abuse, overuse, lost/stolen/missing, or unaccounted product; narratives on drop-outs and separate case reports; and reports of any use of study product by individuals other than study subjects; and reports of any drug accountability discrepancies as specified by the Controlled Substances Staff Additional Comment 2 b) through e).

Does the Agency agree that the approach to monitoring for possible cases of abuse misuse, and addiction and to monitoring for drug accountability discrepancies in Rafa's Phase 1 BA/PK study of Midazolam Injection, 10 mg is acceptable?

Meeting Discussion:

Yes, we agree with the proposed approach.

As per 21 CFR 314.50(d)(5)(vii), at the time of submission of your NDA, you need to provide all information related to abuse of the drug, a proposal for scheduling, and any information on any studies related to overdosage. Therefore, your NDA submission should include a proposal for scheduling of midazolam, which may be that it appropriately remain as a schedule IV-controlled substance or that it may be more appropriately controlled in another schedule.

Rafa Response:

No comments.

Meeting Discussion:

No discussion

3.0 ADDITIONAL INFORMATION

PROSPECTIVE ASSESSMENTS OF SUICIDAL IDEATION AND BEHAVIOR IN CLINICAL PROTOCOLS

Treatment-emergent suicidal ideation and behavior have been identified as a concern for a number of drugs and drug classes. For example, meta-analyses of clinical trial data for both antiepileptic drugs and antidepressants have demonstrated that these drugs increase the risk of suicidal ideation and behavior. Spontaneous reports have led to similar concerns with other drugs as well, e.g., isotretinoin and other tretinoins, beta blockers, reserpine, smoking cessation drugs, and drugs for weight loss. Because of these concerns, a prospective assessment for suicidal ideation and behavior should be included, when appropriate and feasible, in clinical trials involving all drugs and biological products for neurological indications. These assessments should generally be included in every clinical protocol, at every visit, and in every phase of development, with the exception of single-dose trials in healthy volunteers. These assessments should be conducted whether or not a particular product is known or suspected to be associated with treatment-emergent suicidal ideation and behavior. A sponsor considering the omission of the assessment of suicidal ideation and behavior from a particular clinical protocol should prospectively discuss this omission with the Division of Neurology 2.

Rafa Response:

Rafa appreciates the FDA's additional information regarding prospective assessments of suicidal ideation and behavior in clinical protocols. As described in the Clinical Information Amendment submitted to IND 147559 on June 3, 2021 (SN0007) and as denoted in Section III, C3 of the FDA's draft Guidance, "Suicidal Ideation and Behavior: Prospective Assessment of Occurrence in Clinical Trials," August 2012, "it is reasonable to omit such assessments from single-dose trials in healthy volunteers." Since single-dose trials in healthy volunteers may omit prospective assessments of suicidal ideation and behavior per the Guidance, such assessments are not indicated for Rafa's Phase 1 BA/PK study (RLM-559-01, v2.) because it is a single-dose, cross-over study in healthy volunteers.

In this Phase 1 trial, a single 10-mg dose of the two study drugs (the investigational product Midazolam Injection and the listed drug Seizalam) are administered by intramuscular injection to healthy adult volunteers separated by a two-week washout period. Such cross-over studies are considered single-dose and the two-week washout period is considered adequate for a 10-mg intramuscular dose of midazolam for this type of study based on FDA draft Guidance, "Bioequivalence Studies with Pharmacokinetic Endpoints for Drugs Submitted Under an ANDA," December 2013. The adequacy of the washout period, which exceeds the five half- lives recommended by the Bioequivalence Guidance, is described in Comment #1 of the Clinical Information Amendment submitted to IND 147559 on 14 April 2021.

Further support that monitoring for suicidal ideation and behavior is not indicated for this clinical study includes:

- Midazolam Injection, 10 mg is proposed as a single-dose, emergency-use product.
- RLM-559-01 exclusion criteria include, but are not limited, to neurologic disease, psychiatric disease, and history of drug and/or alcohol abuse.
- Subjects in Study RLM-559-01 will be under continuous observation through 30 hours post- dose onsite and at the other monitoring visits 14 days post-dose, allowing for careful monitoring of any adverse events, such as treatment-emergent suicidal ideation and behavior.
- The Investigator's Brochure for Midazolam Injection, 10 mg provided to the Investigator includes the risk of suicidal ideation (0.2% of participants in study NCT00809146, Table 5 in the Investigator's brochure for Midazolam Injection, 10 mg).
- The most up-to-date labeling for Seizalam, Seizalam Labeling (02/2021), lists suicidal ideation and behavior as serious adverse reactions that have been reported with benzodiazepine abuse/misuse in Section 9.2 and includes suicidality as an acute withdrawal symptom associated with benzodiazepines in Section 9.3. This labeling was provided to the Investigator with a note regarding these updates.
- The Investigator's Brochure for Midazolam Injection, 10 mg provided to the Investigator includes risks of abuse, misuse, addiction, physical dependence, and withdrawal as well as potential suicidal ideation and behavior with benzodiazepine abuse/misuse and suicidality as an acute withdrawal symptom associated with benzodiazepines.

Does the Agency agree it is reasonable to omit prospective assessments of suicidal ideation and behavior from Rafa's Phase 1 BA/PK study of Midazolam Injection, 10 mg, which is a single- dose, cross-over study in healthy volunteers?

Meeting Discussion:

The Agency agreed that prospective assessments of suicidal ideation and behavior could be omitted from this single-dose, cross-over study in healthy volunteers.

PREA REQUIREMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients (which includes new salts and new fixed combinations), new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because none of the criteria apply at this time to your application, you are exempt from these requirements. Please include a statement that confirms this finding, along with a reference to this communication, as part of the pediatric section (1.9 for eCTD submissions) of your application. If there are any changes to your development plans that would cause your application to trigger PREA, your exempt status would change.

PRESCRIBING INFORMATION

In your application, you must submit proposed prescribing information (PI) that conforms to the content and format regulations found at 21 CFR 201.56(a) and (d) and 201.57 including the Pregnancy and Lactation Labeling Rule (PLLR) (for applications submitted on or after June 30, 2015). As you develop your proposed PI, we encourage you to review the labeling review resources on the PLR Requirements for Prescribing Information[3] and Pregnancy and Lactation Labeling Final Rule[4] websites, which include:

- The Final Rule (Physician Labeling Rule) on the content and format of the PI for human drug and biological products.
- The Final Rule (Pregnancy and Lactation Labeling Rule) on the content and format of information related to pregnancy, lactation, and females and males of reproductive potential.
- Regulations and related guidance documents.
- A sample tool illustrating the format for Highlights and Contents, and
- The Selected Requirements for Prescribing Information (SRPI) − a checklist of important format items from labeling regulations and guidances.
- FDA's established pharmacologic class (EPC) text phrases for inclusion in the Highlights Indications and Usage heading.

Pursuant to the PLLR, you should include the following information with your application to support the changes in the Pregnancy, Lactation, and Females and Males of Reproductive Potential subsections of labeling. The application should include a review and summary of the available published literature regarding the drug's use in pregnant and lactating women and the effects of the drug on male and female fertility (include search parameters and a copy of each reference publication), a cumulative review and summary of relevant cases reported in your pharmacovigilance database (from the time of product development to present), a summary of drug utilization rates amongst females of reproductive potential (e.g., aged 15 to 44 years) calculated cumulatively since initial approval, and an interim report of an ongoing pregnancy registry or a final report on a closed pregnancy registry. If you believe the information is not applicable, provide justification. Otherwise, this information should be located in Module 1. Refer to

[3] https://www.fda.gov/drugs/laws-acts-and-rules/plr-requirements-prescribing-information
[4] https://www.fda.gov/drugs/labeling/pregnancy-and-lactation-labeling-drugs-final-rule

the draft guidance for industry Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.

Prior to submission of your proposed PI, use the SRPI checklist to ensure conformance with the format items in regulations and guidances.

Rafa Response:

Rafa thanks the Agency for the comments on the Pregnancy and Lactation Labeling Rule. The proposed labeling for Rafa's Midazolam Injection, 10 mg will be based upon the labeling for the listed drug, Seizalam, with no changes proposed in the Pregnancy and Lactation subsections of the Seizalam labeling. The proposed labeling for Midazolam Injection includes the same descriptions of nonclinical studies related to pregnancy, lactation, and fertility contained in the Seizalam labeling. The Seizalam labeling does not include a Females and Males of Reproductive Potential subsection, so this subsection is not planned for the Midazolam Injection, 10 mg labeling. There are no recommendations or requirements in the Seizalam labeling for pregnancy testing and/or contraception before, during, or after drug therapy, nor does the Seizalam labeling include human and/or animal data suggesting drug-associated effects on fertility and/or pre-implantation loss effects. Therefore, as the pregnancy testing, contraception, and infertility headings are inapplicable, the Females and Males of Reproductive Potential subsection should be omitted per the FDA Draft Guidance, "Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format," July 2020 ("PLLR Guidance").

Rafa is not planning to include a literature review/summary regarding the drug's use in pregnancy or lactation or on fertility, data on pharmacovigilance, drug utilization rates amongst females of reproductive potential, or reports of pregnancy registries, which are not applicable because Rafa is not submitting a PLR/PLLR labeling conversion as a prior approval supplement as outlined in Section V.B. of the PLLR Guidance, so these requirements are not applicable.

Does the Agency agree with the approach to the Pregnancy and Lactation subsections of, and the omission of the Females and Males of Reproductive Potential subsection from, the labeling for Midazolam Injection, 10 mg?

Does the Agency agree that the literature, pharmacovigilance, and drug utilization reviews/summaries and report of pregnancy registries described in Section V.B. of the PLLR Guidance are not applicable to Rafa's NDA for Midazolam Injection, 10 mg?

Meeting Discussion:

The Agency noted that, unless new information regarding reproductive potential or the need for pregnancy testing/contraception has become available regarding midazolam

use since the 2018 approval of the listed drug (Seizalam), we would not anticipate a difference between the Rafa Midazolam Injection PI and the Seizalam PI with respect to a *Females and Males of Reproductive Potential* subsection (8.3).

The Agency also noted the labeling regulation that states that the labeling must be updated when new information becomes available that causes the labeling to become inaccurate, false, or misleading [21 CFR 201.56(a)(2)]. The Agency explained that this applies to applications submitted under 505(b)(2) if there is new information available that is not included in the listed drug labeling. The Agency advised that, to ensure that the PLLR portion is up to date, the applicant should complete a review (e.g., from the published literature, from the pregnancy registry dated from the 2018 Seizalam approval, and from Rafa's study database) to ensure that no new information would necessitate labeling revisions. The Agency clarified that applicant does not need to assess the literature prior to 2018, because this information would have been reviewed previously at the time of approval of the listed drug.

SUBMISSION FORMAT REQUIREMENTS

The Electronic Common Technical Document (eCTD) is CDER and CBER's standard format for electronic regulatory submissions. The following submission types: **NDA, ANDA, BLA, Master File** (except Type III) and **Commercial INDs** must be submitted in eCTD format. Submissions that do not adhere to the requirements stated in the eCTD Guidance will be subject to rejection. For more information, please visit FDA.gov.[5]

The FDA Electronic Submissions Gateway (ESG) is the central transmission point for sending information electronically to the FDA and enables the secure submission of regulatory information for review. Submissions less than 10 GB must be submitted via the ESG. For submissions that are greater than 10 GB, refer to the FDA technical specification *Specification for Transmitting Electronic Submissions using eCTD Specifications*. For additional information, see FDA.gov.[6]

SECURE EMAIL COMMUNICATIONS

Secure email is required for all email communications from FDA when confidential information (e.g., trade secrets, manufacturing, or patient information) is included in the message. To receive email communications from FDA that include confidential information (e.g., information requests, labeling revisions, courtesy copies of letters), you must establish secure email. To establish secure email with FDA, send an email request to SecureEmail@fda.hhs.gov. Please note that secure email may not be used for formal regulatory submissions to applications (except for 7-day safety reports for INDs not in eCTD format).

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[5] http://www.fda.gov/ectd
[6] http://www.fda.gov/ForIndustry/ElectronicSubmissionsGateway

505(b)(2) REGULATORY PATHWAY

The Division recommends that sponsors considering the submission of an application through the 505(b)(2) pathway consult the Agency's regulations at 21 CFR 314.54, and the draft guidance for industry *Applications Covered by Section 505(b)(2)* (October 1999).[7] In addition, FDA has explained the background and applicability of section 505(b)(2) in its October 14, 2003, response to a number of citizen petitions that had challenged the Agency's interpretation of this statutory provision (see Docket FDA-2003-P-0274-0015, available at Regulations.gov.[8]

If you intend to submit a 505(b)(2) application that relies for approval on FDA's finding of safety and/or effectiveness for one or more listed drugs, you must establish that such reliance is scientifically appropriate, and must submit data necessary to support any aspects of the proposed drug product that represent modifications to the listed drug(s). You should establish a "bridge" (e.g., via comparative bioavailability data) between your proposed drug product and each listed drug upon which you propose to rely to demonstrate that such reliance is scientifically justified.

If you intend to rely on literature or other studies for which you have no right of reference but that are necessary for approval, you also must establish that reliance on the studies described in the literature or on the other studies is scientifically appropriate. You should include a copy of such published literature in the 505(b)(2) application and identify any listed drug(s) described in the published literature (e.g., by trade name(s)).

If you intend to rely on the Agency's finding of safety and/or effectiveness for a listed drug(s) or published literature describing a listed drug(s) (which is considered to be reliance on FDA's finding of safety and/or effectiveness for the listed drug(s)), you should identify the listed drug(s) in accordance with the Agency's regulations at 21 CFR 314.54. It should be noted that 21 CFR 314.54 requires identification of the "listed drug for which FDA has made a finding of safety and effectiveness," and thus an applicant may only rely upon a listed drug that was approved in an NDA under section 505(c) of the FD&C Act. The regulatory requirements for a 505(b)(2) application (including, but not limited to, an appropriate patent certification or statement) apply to each listed drug upon which a sponsor relies.

If FDA has approved one or more pharmaceutically equivalent products in one or more NDA(s) before the date of submission of the original 505(b)(2) application, you must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon (see 21 CFR 314.50(i)(1)(i)(C), 314.54, and 314.125(b)(19); see also 21 CFR 314.101(d)(9)). If you identify a listed drug solely to comply with this regulatory requirement, you must provide an appropriate patent certification or statement for any patents that are listed in the Orange Book for the pharmaceutically

[7] We update guidances periodically. For the most recent version of a guidance, check the FDA Guidance Documents Database https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.
[8] http://www.regulations.gov

equivalent product, but you are not required to establish a "bridge" to justify the scientific appropriateness of reliance on the pharmaceutically equivalent product if it is scientifically unnecessary to support approval.

If you propose to rely on FDA's finding of safety and/or effectiveness for a listed drug that has been discontinued from marketing, the acceptability of this approach will be contingent on FDA's consideration of whether the drug was discontinued for reasons of safety or effectiveness.

We encourage you to identify each section of your proposed 505(b)(2) application that is supported by reliance on FDA's finding of safety and/or effectiveness for a listed drug(s) or on published literature (see table below). In your 505(b)(2) application, we encourage you to clearly identify (for each section of the application, including the labeling): (1) the information for the proposed drug product that is provided by reliance on FDA's finding of safety and/or effectiveness for the listed drug or by reliance on published literature; (2) the "bridge" that supports the scientific appropriateness of such reliance; and (3) the specific name (e.g., proprietary name) of each listed drug named in any published literature on which your marketing application relies for approval. If you are proposing to rely on published literature, include copies of the article(s) in your submission.

In addition to identifying the source of supporting information in your annotated labeling, we encourage you to include in your marketing application a summary of the information that supports the application in a table similar to the one below.

List the information essential to the approval of the proposed drug that is provided by reliance on the FDA's previous finding of safety and effectiveness for a listed drug or by reliance on published literature	
Source of information (e.g., published literature, name of listed drug)	Information Provided (e.g., specific sections of the 505(b)(2) application or labeling)
(1) Example: Published literature	*Nonclinical toxicology*
(2) Example: NDA XXXXXX "TRADENAME"	*Previous finding of effectiveness for indication A*
(3) Example: NDA YYYYYY "TRADENAME"	*Previous finding of safety for Carcinogenicity, labeling section B*
(4)	

Please be advised that circumstances could change that would render a 505(b)(2) application for this product no longer appropriate. For example, if a pharmaceutically equivalent product were approved before your application is submitted, such that your proposed product would be a “duplicate” of a listed drug and eligible for approval under section 505(j) of the FD&C Act, then it is FDA’s policy to refuse to file your application as a 505(b)(2) application (21 CFR 314.101(d)(9)). In such a case, the appropriate submission would be an Abbreviated New Drug Application (ANDA) that cites the duplicate product as the reference listed drug.

4.0 ISSUES REQUIRING FURTHER DISCUSSION

None.

5.0 ACTION ITEMS

None.

6.0 ATTACHMENTS AND HANDOUTS

None.

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/

NICHOLAS A KOZAUER
09/13/2021 10:04:48 AM