

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

214835Orig1s000

OTHER ACTION LETTERS



NDA 214835

COMPLETE RESPONSE

Laboratorios Farmacéuticos ROVI, S.A.
c/o PharmaLex
Attention: Anna Perelka
Associate Director, Regulatory Affairs
1700 District Avenue, Suite 100
Burlington, MA 01803

Dear Anna Perelka:

Please refer to your new drug application (NDA) dated and received November 24, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Risvan (risperidone ISM) intramuscular injectable suspension.

We acknowledge receipt of your amendment dated January 27, 2023, which constituted a complete response to our July 15, 2022, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

FACILITY INSPECTIONS

Following pre-approval inspection of the Laboratorios Farmacéuticos ROVI, S.A. (FEI: 3010705046) manufacturing facility listed in this application, FDA conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI)—a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.³

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d):

(b) (4)

(b) (4)

PROPRIETARY NAME

Please refer to correspondence dated, April 19, 2023, which addresses the proposed proprietary name, Risvan. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

1. Describe in detail any significant changes or findings in the safety profile.

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

2. When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
3. Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
4. Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
5. Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
6. Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
7. Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.
8. Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within 1 year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, please email Simran Parihar, PharmD, at simran.parihar@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Bernard Fischer, MD
Deputy Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

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/

BERNARD A FISCHER
07/27/2023 02:23:23 PM



NDA 214835

COMPLETE RESPONSE

Laboratorios Farmaceuticos Rovi, S.A.
c/o PharmaLex
Attention: Nick Palmer
Senior Manager, Consulting and Scientific Affairs
1700 District Avenue, Suite 100
Burlington, MA 01803

Dear Mr. Palmer:

Please refer to your new drug application (NDA) dated and received November 24, 2020, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Risvan (risperidone ISM) intramuscular injectable suspension.

We acknowledge receipt of your amendment dated January 18, 2022, which constituted a complete response to our September 24, 2021, action letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

PRODUCT QUALITY

Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission and a deficiency letter was sent to the DMF holder on July 15, 2022. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

FACILITY INSPECTIONS

During a recent inspection of the (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

During a recent inspection of the Laboratorios Farmacéuticos ROVI, S.A. (FEI: 3010705046) manufacturing facility for this application, our field investigator conveyed

deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

MICROBIOLOGY

Sterile Drug Substance Risperidone

The referenced DMF (b) (4) for sterile drug substance risperidone has been reviewed and determined to be inadequate. The DMF holder has been notified.

Solvent DMSO

We acknowledge the new validation study plan provided on pages 56-57 of 76 (1.11.4 *Multiple Information Amendment*, Seq-0038) regarding the (b) (4)

(b) (4) You indicate that the new validation study runs will be performed March 1 to May 31, 2022. Provide the (b) (4) validation study summary and data demonstrating a minimum of (b) (4) log of endotoxin reduction.

Sterile excipient PLGA

We acknowledge the responses provided on pages 57-68 of 76 (1.11.4 *Multiple Information Amendment*, Seq-0038) regarding the (b) (4) validation of the excipient PLGA. Address the following issues:

- a. You indicate that the (b) (4) based validation studies (verification cycles of sterilizing capacity) were performed using (b) (4). Note that the microbiological efficacy studies should be performed using a dose of \leq the minimum dose specified for the production sterilization process. If you decide to choose the (b) (4) based validation strategy, provide three validation studies and data using a dose of \leq the minimum specified production dose demonstrating a minimum sterility assurance level of (b) (4). Requalification should be also performed using a dose of \leq the minimum specified production dose. Alternatively, provide data for validation studies using the (b) (4) approach with (b) (4) dose audits per (b) (4).
- b. Page 61 of 76 indicates (b) (4) growth in the first "revalidation" batch performed in 2015 with the treatment No. 15T02296T. Additionally, the maximum dose for the first batch of 2020 "revalidation" with the treatment No. 20T01769T, (b) (4), exceeds the maximum dose of (b) (4). Provide a summary of investigations, the root cause identified, potential impact on routine production, and corrective and preventative actions.
- c. Page 66 of 76 indicates that the (b) (4)

(b) (4)

- d. Pages 67-68 of 76 provide requalification data from the 03SEP2019 run (study code: UDMI-PVP-18-018/00). However, exposed (b) (4) results after incubation are not provided and should be described. Specify the positive (b) (4) control result.

HUMAN FACTORS

We acknowledge your response to our complete response letter dated September 24, 2021, and your response to our information request dated September 10, 2021. These submissions addressed some of our Human Factors concerns; however, our review of the instructions for use identified an area of vulnerability that may lead to medication errors. We note that two participants in your HF validation study had difficulty injecting the full dose due to the viscosity of the medication. Additionally, we note that your root cause analysis states that the proposed product requires the user to maintain the force for a longer time to inject the medication.

Furthermore, in your response dated September 10, 2021, although your IFU states: "THICK MEDICATION. MAKE SURE TO FULLY INJECT," and "The injection time is longer than usual due to the viscosity of the medication," it does not explicitly instruct the user to inject the medication slowly and steadily. Revise the IFU to include instructions for users to inject the medication slowly and steadily.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

If you revise labeling, use the SRPI checklist to ensure that the Prescribing Information conforms with format items in regulations and guidances. Your response must include updated content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at FDA.gov.³

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

³ <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>

CARTON AND CONTAINER LABELING

We reserve comment on the proposed labeling until the application is otherwise adequate.

MEDICATION GUIDE

Add the following bolded statement or appropriate alternative to the carton and container labeling per 21 CFR 208.24(d):

(b) (4)

(b) (4)

PROPRIETARY NAME

Please refer to correspondence dated, April 12, 2022, which addresses the proposed proprietary name, Risvan. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the product under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.

- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each subject who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.
- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this product. Include an updated estimate of use for product marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, contact Eugene Lee, Regulatory Project Manager, at C.Eugene.Lee@fda.hhs.gov.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

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/

TIFFANY R FARCHIONE
07/15/2022 05:47:51 PM



NDA 214835

COMPLETE RESPONSE

Laboratorios Farmaceuticos Rovi, S.A.
c/o PharmaLex
Attention: Nick Palmer
Senior Manager, Consulting and Scientific Affairs
1700 District Avenue, Suite 100
Burlington, MA 01803

Dear Mr. Palmer:

Please refer to your new drug application (NDA) dated and received January 8, 2021, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for risperidone extended-release injectable suspension.

We also acknowledge receipt of your amendments dated September 10, 2021, and September 23, 2021, which were not reviewed for this action. You may incorporate applicable sections of the amendment by specific reference as part of your response to the deficiencies cited in this letter.

We have completed our review of this application, as amended, and have determined that we cannot approve this application in its present form. We have described our reasons for this action below and, where possible, our recommendations to address these issues.

OPHTHALMOLOGY

On August 21, 2021, we sent an information request with several questions about your ophthalmologic examination data. On September 1, 2021, we received your response to our questions (eCTD #0032). In your response, you committed to perform a full data re-check and re-analyses of ophthalmologic findings and submit a response no earlier than October 15, 2021. Of the six ophthalmologic questions in our August 21, 2021, information request, you must fully address questions 1, 2, 4, 5, and 6 in (or prior to) your NDA resubmission.

HUMAN FACTORS

The results of your human factors (HF) validation study indicated the need for further revisions to your user interface in order to mitigate residual risk.

In particular, we are concerned that your intended users may have difficulty injecting the full dose of medication due to the viscosity of the product, as evidenced by use difficulties and use errors in your human factors validation study.

We sent an information request on August 20, 2021, for you to provide data or information (for example, anthropometry or other data) to support that the intended users will be able to reliably deliver the full dose of medication, and that the injection rate used in the glide force testing is representative of actual use. We have received a response to this information request; however, the additional information will not be reviewed at this time. Therefore, we cannot conclude that the proposed product user interface supports safe and effective use by the intended users, for the intended use, and in the intended use environment.

We recommend you provide data or information to support that the intended users will be able to reliably and effectively deliver the full dose of medication. If you are unable to provide such data or information, we recommend you redesign the product to ensure that it supports use by the intended users, for the intended uses, and in the intended use environments. Any product redesign will require an additional human factors validation study to demonstrate that the design mitigations were effective.

Additionally, we recommend you take additional measures to ensure that the finger flange remains in place during injection and does not interfere with the operation of the syringe.

PRODUCT QUALITY

Drug Product

1. Due to intra- and inter-batch dissolution result variability attributed to (b) (4) we recommend developing a test to directly monitor (b) (4) molecular weight and (b) (4). Propose a limit and provide a justification for the proposed limit.
2. In a response to an information request dated July 30, 2021, you provided additional information supporting the omission of (b) (4) and (b) (4) testing on the drug product. However, no data for the drug product was included, specifically during long-term storage (controlled room temperature). Provide data demonstrating that (b) (4) remains unchanged on stability of the drug product (e.g., (b) (4) result from drug product registration stability batches stored for 12 months under long-term conditions).
3. In a response to an information request dated August 6, 2021, you provided additional dissolution profiles predictions using drug product with inherent viscosity of (b) (4). The model predicts that drug product with this viscosity (b) (4) would likely meet the proposed specifications (b) (4) probability). Therefore, the model cannot be used to support the currently proposed limits as it does not discriminate between failing and passing product. As such, tighten the inherent viscosity specifications (both raw material and sterilized material).

4. We remind you of the following outstanding information requests:
- a. You previously committed to establishing direct PLGA testing on non-reconstituted drug-product in your response to information request dated May 21, 2021.
 - b. Perform a thermal cycling study to determine acceptable temperature/humidity excursions of the powder syringe (risperidone and PLGA) to ensure short term freeze/thaw conditions do not adversely impact the drug product.

Biopharmaceutics

1. The provided in vitro drug release testing (IVRT) data from the clinical and registration batches show high inter-batch and intra-batch variabilities. The observed high variabilities could come from inconsistent drug product quality, dissolution method, analytical method/assay, or other sources. You have not provided adequate information/data to confirm and address the source(s) of this variability. We recommend that you investigate and identify the source(s) of the observed variability and provide data supporting the findings.
2. The proposed wide dissolution acceptance criteria ranges are permissive and unacceptable. Please note that, in general, the selection of the dissolution acceptance criteria ranges is based on mean target value \pm (b) (4)% and $>$ (b) (4)% for the last specification time-point. Wider specification ranges may be acceptable if they are supported by an established "safe space" based on an approved IVVC model, PBBM, etc. For an established safe space, the acceptable dissolution specifications should ensure bioequivalence/clinical relevance of future batches with dissolution profiles falling between the identified extreme ranges within the limits.

Microbiology

Your application referenced the Drug Master File (DMF) (b) (4). This DMF was found inadequate to support your submission. Deficiencies were sent to the DMF holder on May 11, 2021. These deficiencies must be adequately addressed before this application can be approved. As part of your response to this letter, include the date the DMF holder amended their DMF to address the deficiencies.

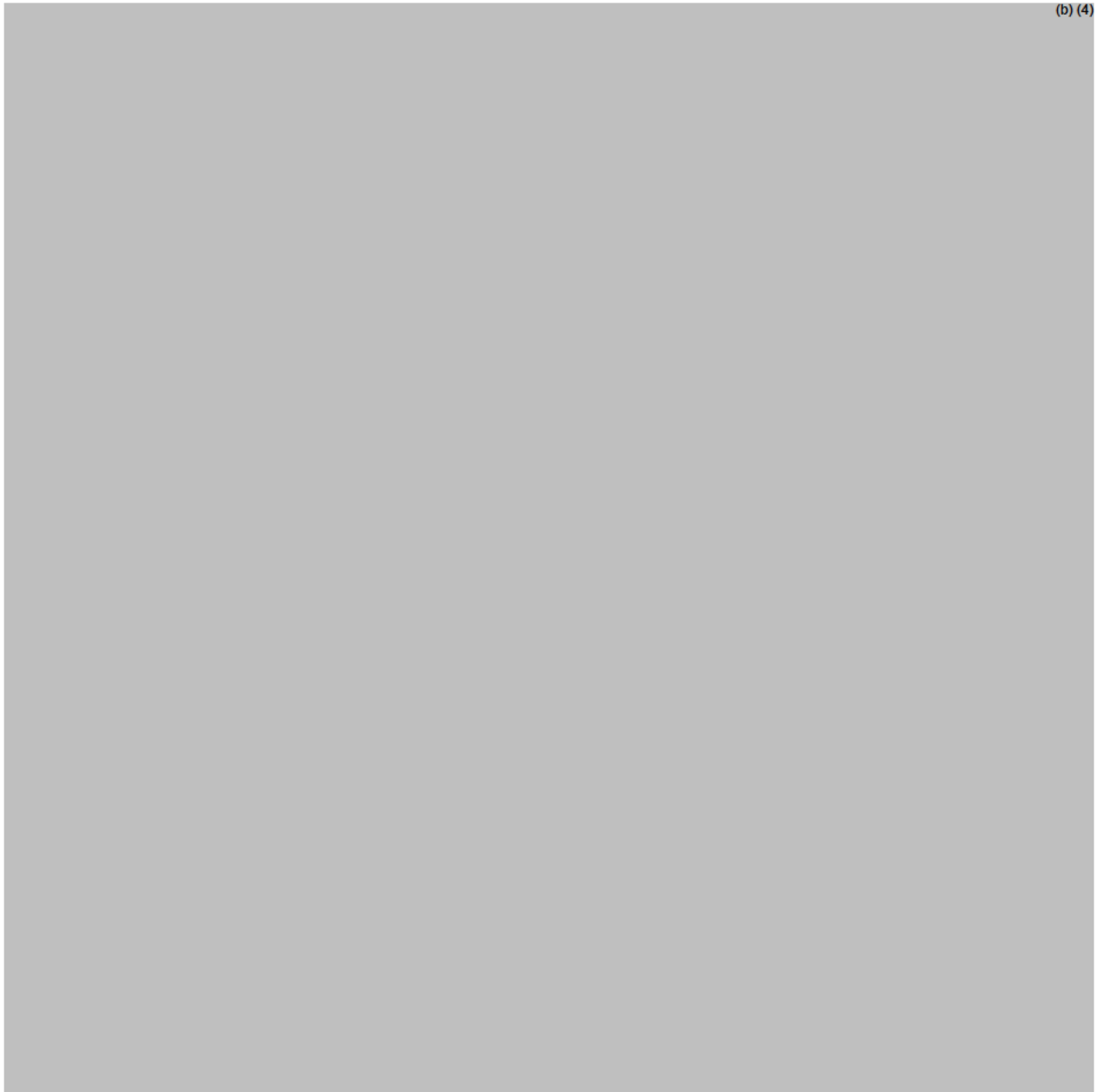
Powder prefilled syringe (Risperidone+PLGA)

1. We acknowledge the provided container closure integrity validation reports for the drug product and the diluent DMSO (UDMI-IVP-21-013/00 and UDMI-IVP-21-014/00) by microbial immersion method in 1.11.1 (Seq-0023). It is noted that the syringes were exposed to the vacuum condition but not a pressure condition. Note that the additional (b) (4) vacuum process is not considered the pressure condition. The microbial immersion container closure integrity test should be conducted using pressure and vacuum conditions. These conditions may be necessary to ensure that debris, dried product, and/or particulate matter are completely removed from potential leak paths. Commit to

using both vacuum and pressure conditions for future container closure integrity testing by microbial immersion.

2. We acknowledge the provided information regarding the 2015 qualification summary and 2019 requalification runs for (b) (4) process of (b) (4) (b) (4) and (b) (4) in (b) (4) on pages 5-30 of 132 (1.11.1 Response, Seq-0013) and the validation reports UDMI-IC-16-023/01, UDMI-IVP-19-017/00 (1.11.1, Seq-0013), and ICO-ROV-SM-7710.1505 (1.11.1, Seq-0014).

Address the following issues:



(b) (4)

3

FACILITY INSPECTIONS

During a recent inspection of the [REDACTED] (b) (4) manufacturing facility for this application, our field investigator conveyed deficiencies to the representative of the facility. Satisfactory resolution of these deficiencies is required before this application may be approved.

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

In addition to responding to the deficiencies presented above, please note and acknowledge the following comment in your response. Inspections of the following facilities:

- Rovi Pharma Industrial Services SA (FEI: 3007512884; Spain)
- (b) (4)
- Rovi Pharma Industrial Services SA (FEI: 3002989591; Spain)

are required before this application can be approved. FDA must assess the ability of these facilities to conduct the listed manufacturing operations in compliance with CGMP. Due to restrictions on travel, we were unable to complete inspections during the current review cycle for your application. You may respond to deficiencies in this Complete Response Letter while the travel restrictions remain in effect. However, even if these deficiencies are addressed, the application cannot be approved until the required FDA inspections are completed and any findings are assessed with regard to our application. We will continue to monitor the public health situation as well as travel restrictions. We are actively working to define an approach for scheduling outstanding inspections once safe travel may resume and based on public health need and other factors.

Because approval of your application requires inspections that cannot be completed in a timely manner due to COVID-19 travel restrictions, the FDA has made an initial determination that the amendment to your application in response to this complete response letter will be received as an amendment as described in the 2020 Guidance for Industry Review Timelines for Applicant Responses to Complete Response Letters When a Facility Assessment Is Needed During the COVID-19 Public Health Emergency.

For more information, please see the FDA guidances related to COVID 19. These guidances can be found at: <https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-related-guidance-documents-industry-fda-staff-and-otherstakeholders>.

PRESCRIBING INFORMATION

We reserve comment on the proposed labeling until the application is otherwise adequate. We encourage you to review the labeling review resources on the Prescription Drug Labeling Resources¹ and Pregnancy and Lactation Labeling Final Rule² websites, including regulations and related guidance documents and the Selected Requirements for Prescribing Information (SRPI) – a checklist of important format items from labeling regulations and guidances.

¹ <https://www.fda.gov/drugs/laws-acts-and-rules/prescription-drug-labeling-resources>

² <https://www.fda.gov/drugs/labeling-information-drug-products/pregnancy-and-lactation-labeling-drugs-final-rule>

CARTON AND CONTAINER LABELING

Submit draft carton and container labeling based on our proposed revisions dated September 17, 2021.

PROPRIETARY NAME

Please refer to correspondence dated, August 29, 2021 which addresses the proposed proprietary name, Risvan. This name was found acceptable pending approval of the application in the current review cycle. Please resubmit the proposed proprietary name when you respond to the application deficiencies.

SAFETY UPDATE

When you respond to the above deficiencies, include a safety update as described at 21 CFR 314.50(d)(5)(vi)(b). The safety update should include data from all nonclinical and clinical studies/trials of the drug under consideration regardless of indication, dosage form, or dose level.

- (1) Describe in detail any significant changes or findings in the safety profile.
- (2) When assembling the sections describing discontinuations due to adverse events, serious adverse events, and common adverse events, incorporate new safety data as follows:
 - Present new safety data from the studies/clinical trials for the proposed indication using the same format as in the original submission.
 - Present tabulations of the new safety data combined with the original application data.
 - Include tables that compare frequencies of adverse events in the original application with the retabulated frequencies described in the bullet above.
 - For indications other than the proposed indication, provide separate tables for the frequencies of adverse events occurring in clinical trials.
- (3) Present a retabulation of the reasons for premature trial discontinuation by incorporating the drop-outs from the newly completed trials. Describe any new trends or patterns identified.
- (4) Provide case report forms and narrative summaries for each patient who died during a clinical trial or who did not complete a trial because of an adverse event. In addition, provide narrative summaries for serious adverse events.

- (5) Describe any information that suggests a substantial change in the incidence of common, but less serious, adverse events between the new data and the original application data.
- (6) Provide updated exposure information for the clinical studies/trials (e.g., number of subjects, person time).
- (7) Provide a summary of worldwide experience on the safety of this drug. Include an updated estimate of use for drug marketed in other countries.
- (8) Provide English translations of current approved foreign labeling not previously submitted.

OTHER

Within one year after the date of this letter, you are required to resubmit or take other actions available under 21 CFR 314.110. If you do not take one of these actions, we may consider your lack of response a request to withdraw the application under 21 CFR 314.65. You may also request an extension of time in which to resubmit the application.

A resubmission must fully address all the deficiencies listed in this letter and should be clearly marked with "**RESUBMISSION**" in large font, bolded type at the beginning of the cover letter of the submission. The cover letter should clearly state that you consider this resubmission a complete response to the deficiencies outlined in this letter. A partial response to this letter will not be processed as a resubmission and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss what steps you need to take before the application may be approved. If you wish to have such a meeting, submit your meeting request as described in the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products*.

The drug product may not be legally marketed until you have been notified in writing that this application is approved.

If you have any questions, call Latrice Wilson, Senior Regulatory Project Manager, at (240) 402-5317.

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, MD
Director
Division of Psychiatry
Office of Neuroscience
Center for Drug Evaluation and Research

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/

TIFFANY R FARCHIONE
09/24/2021 01:21:11 PM