

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

212849Orig1s000

OTHER ACTION LETTERS



NDA 212849

COMPLETE RESPONSE

Shandong Luye Pharmaceutical Co., Ltd.
Attention: Qi Cheng, PhD
Associate Director of Global Regulatory Affairs
502 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Dr. Cheng:

Please refer to your new drug application (NDA) dated March 28, 2019, received March 28, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Rykindo (risperidone) for extended-release injectable suspension.

We acknowledge receipt of your amendment dated August 19, 2021, which constituted a complete response to our January 28, 2020, 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.

CLINICAL AND CLINICAL PHARMACOLOGY

The January 28, 2020 complete response (CR) letter advised you to conduct a root-cause analysis that would adequately explain the origin of the concentration spikes observed in LY03004/CT-USA-102. We acknowledge that you have re-analyzed the pharmacokinetic (PK) samples of two patients (Subjects (b) (6)) and identified the presence of cocaine. We acknowledge your conclusion that high concentrations of LY03004 were not caused by unanticipated drug release related to the drug product quality but were most likely caused by the extrinsic factor cocaine (which you believe acted as a CYP2D6 inhibitor).

However, we disagree that concomitant use of cocaine adequately explains the high concentrations of LY03004. Labels for risperidone products, which are supported by clinical data, clearly indicate that risperidone concentrations increase less than ~80% in the presence of strong CYP2D6 inhibitors. The published literature consistently suggests that a ~40 to 75% increase in concentration occurs with the most potent CYP2D6 inhibitors, which aligns with language in approved labeling. Additionally, the concentrations are generally unchanged in extensive metabolizers (EMs) of CYP2D6 versus poor metabolizers (PMs) of CYP2D6, who are intrinsically devoid of CYP2D6

activity and thus reflect a drug interaction scenario via strong CYP2D6 inhibition. The extensive clinical data demonstrate that CYP2D6 inhibition cannot explain the significant extent of concentration spikes (i.e., unexplained intra-subject variability with 300 to 500% increase in concentration observed within a subject) for LY03004.

Most importantly, there is no available information indicating that cocaine may serve as a strong CYP2D6 inhibitor. Based on the available data, cocaine is either a non-inhibitor or at most a weak CYP2D6 inhibitor.

In addition, your other justifications and analyses did not provide any new information to explain the origin of the concentration spikes.

The safety issues with LY03004 remain and the potential for dose dumping cannot be ruled out based on your root-cause analysis.

To address this safety issue, you must provide us the following data in an NDA re-submission:

- Detailed study reports including all PK data (mean and individual subject data) for all the clinical trials that have been conducted outside of the United States with LY03004. This should include, but is not limited to, reports from studies conducted in China as well as in the European Union. Please ensure that the comprehensive data package includes a presentation of detailed PK data from all subjects (in relevant plots/figures/tables) to unequivocally rule out any incidence of dose dumping with LY03004. Additionally, include any/all other appropriate information (e.g., real world drug use data from China, ongoing studies, etc.) that you deem relevant to demonstrate the PK and safety of your product.
- In addition to the required safety update information described below, you must report adverse events of special interest (e.g., those related to warnings and precautions of the Listed Drug) that occurred in any clinical trials of LY03004 that you include in the resubmission. For any subject with concentration spikes or (suspected) dose-dumping events in clinical trials of LY03004, provide a summary of adverse events along with vital sign and electrocardiogram data.

PRODUCT QUALITY

Biopharmaceutics deficiency:

- The biowaiver request for the additional strengths (12.5 mg, 37.5 mg, and 50 mg strengths) cannot be granted at this time because of the continued clinical concerns related to results of the pivotal BE study. Therefore, satisfactory resolution of the clinical and clinical pharmacology concerns is required to establish the adequate BE between the proposed and Listed Drug products.

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)].³

CARTON AND CONTAINER LABELING

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

PROPRIETARY NAME

Please refer to correspondence dated, December 9, 2021, which addresses the proposed proprietary name, Rykindo. 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:

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>

- 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, contact Tiffanie Taylor, Regulatory Project Manager, at Tiffanie.Taylor@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
02/18/2022 11:33:40 AM



NDA 212849

COMPLETE RESPONSE

Shandong Luye Pharmaceutical Co., Ltd.
Attention: Li Wan, PhD, RAC
Director, Head of Global Regulatory Affairs
502 Carnegie Center, Suite 100
Princeton, NJ 08540

Dear Dr. Wan:

Please refer to your new drug application (NDA) dated and received March 28, 2019, and your amendments, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act for Rykindo (risperidone) for extended-release injectable suspension.

We also acknowledge receipt of your amendment dated November 22, 2019, which was not fully 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.

CLINICAL AND CLINICAL PHARMACOLOGY

Your NDA submission provides adequate pharmacokinetic bridging (via the bioequivalence at steady-state) to the listed drug, Risperdal CONSTA. However, FDA has concluded that there are potential safety issues with the proposed drug product. Three patients (subject numbers [REDACTED] (b) (6)) in Study LY03004/CT-USA-102 had unanticipated, unexplained, and abnormally high drug concentration spikes during the study. These unexplained spikes in drug concentration are concerning for patient safety because:

1. These unexplained spikes lead to concentrations of up to ~100 ng/mL (i.e., up to five times higher than average) in patients dosed with the lowest strength of the proposed product (25 mg). This suggests that exposures with concentrations up to ~200 ng/mL are possible when patients are dosed with the highest strength of the proposed product (50 mg). Those exposure levels would be significantly higher than the exposure range with the approved oral risperidone dose and could cause serious safety issues for patients.

2. These spikes were observed in approximately 6% of the patients dosed with the proposed product (i.e., 3 out of 51 patients in Study 102) in a well-controlled clinical trial. This could translate to a substantial number of patients with potentially very high and unsafe drug exposure if the product were to become commercially available.

To address this safety issue, you must:

1. Conduct a root-cause analysis to adequately explain the origin of the concentration spikes.
2. Determine how similar events would be prevented if the proposed product were to become commercially available.

PRODUCT QUALITY

The following product quality deficiencies will need to be adequately addressed before this application can be approved:

(b) (4)



(b) (4)

4. Biopharmaceutics deficiencies:

a. In vitro drug release acceptance criteria:

The following revisions are recommended for the acceptance criteria of the in vitro drug release test:

- i. Inclusion of an additional sampling time point at 72 hours to control the middle phase of the drug release profile, with acceptance criteria limits of (b) (4) (based on mean value $\pm 10\%$ of the bio-batch).
- ii. For the 56-hour time point, the proposed acceptance range is wider than the FDA's recommended (b) (4) range and is not acceptable. Therefore, we request that you revise the acceptance range for this sampling time point to (b) (4) (based on mean value $\pm 10\%$ of the bio-batch).

Please note that wider drug release acceptance criteria ranges may be accepted, if a justification based on clinical/PK data or data from an acceptable IVIVC/IVIVR model is provided. Refer to the Additional Biopharmaceutics Comments.

b. Bridging of clinical and commercial products:

The bridging between the proposed commercial drug product and the drug product used in the clinical-BE study has not been adequately established because of the following reasons:

- i. the differences between the commercial and clinical drug product-batches (microsphere) (b) (4)
- ii. although the similarity f_2 values indicate that the in vitro drug release profiles are similar, for extended release products it is required that the difference between the profiles at each sampling time point is $<15\%$. However, when the drug release profiles of the clinical and commercial batches are compared, the average differences in the cumulative percent of drug release from the microspheres at the 72 hours and 80 hours sampling time points, are greater than 15% , for 3 out of 7 commercial scale-up batches.

To support the bridging between the clinical and commercial drug products, address the following requests:

- i. Provide the details for all the changes made to the manufacturing process(es) during scale-up, explain why there are significant differences in (b) (4) between the clinical and commercial batches, and provide a justification with supporting data that the differences (b) (4) would not have an impact on the pharmacokinetics, efficacy, and safety of your drug product.
- ii. Provide a justification that the observed differences in the in vitro drug release at 72 hours and 80 hours time points for some commercial batches would not significantly impact the pharmacokinetics, efficacy, and safety of your proposed drug product.

As an alternative approach, consider developing an acceptable IVIVC/IVIVR model to support the bridging.

c. Biowaiver:

The biowaiver request for the additional strengths (12.5 mg, 37.5 mg, and 50 mg strengths) cannot be granted at this time because of the following:

- i. The unresolved clinical concerns related to the PK spikes observed in the pivotal BE study. Therefore, satisfactory resolution of the clinical and clinical pharmacology concerns is required to establish the adequate BE between the proposed and Listed Drug products. Note that an acceptable BA/BE study is required to support the biowaiver for the other proposed strengths not evaluated in an in vivo human clinical/PK study.
- ii. Lack of adequate in vitro drug release profile data to support the biowaiver request using the final to-be-marked drug product (both microsphere and diluent) and the same testing conditions including the same volume of dissolution medium. Therefore, we request that you provide the supporting in vitro drug release profile comparison data, i.e., n=12, and the samples be prepared for each strength per the proposed labeling instructions [using the equivalence of (b) (4) mg microspheres for 12.5 mg, 25 mg, 37.5 mg, and 50 mg strengths, respectively], and the resulting suspension sample volume be equivalent to that delivered to patients (i.e., approximately 2 mL), per Section 2.8 (b) (4). In addition, include the similarity profiles comparison values (using the f2 test or other appropriate statistical test), estimated by comparing the in vitro drug release profile of the bio-strength (used in acceptable PK study) vs. the drug release profiles of the other proposed strengths not evaluated in a clinical/PK study.

USE-RELATED RISK ANALYSIS

We refer to your Use-Related Risk Analysis (URRA) submitted on May 6, 2019 to NDA 212849 and your Information Request response sent on September 26, 2019 regarding loss of suspension of the microspheres in the syringe after reconstitution.

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

We note that your URRA is incomplete as it does not identify the risk of users failing to re-suspend the microspheres [REDACTED] (b) (4)

[REDACTED]. We consider these tasks to be critical tasks because a failure to perform them correctly may result in failure to administer the full labeled dose. Additionally, because these critical tasks need to be incorporated into the use sequence for the proposed product, we will need to evaluate the updated instructions for use and use-related risk analysis, as well as results from a human factors validation study that demonstrate that the proposed product can be used safely and effectively by the intended users for the intended use and use environments.

After resolving the Clinical, Clinical Pharmacology, and Product Quality deficiencies noted above, you must conduct a use-related risk analysis and determine whether a human factors validation study is necessary. Prior to conducting the human factors validation study, we recommend you submit your study protocol for feedback from the Agency before commencing your study. Please note we will need 60 days to review and provide comments on the HF validation study protocol. Plan your development program timeline accordingly. Note that submission of a protocol for review is not a requirement. If you decide not to submit a protocol, this approach carries some risk to you because prospective Agency review will not take place, but this is a decision for your company.

Please refer to our draft guidance entitled *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*¹ for the content of a human factors validation study protocol submission.

The requested information should be submitted to the IND. Place the requested information in eCTD Section 5.3.5.4 – Other Study reports and related information.

Guidance on human factors procedures to follow can be found in the following guidance documents²:

- *Applying Human Factors and Usability Engineering to Medical Devices*
- *Guidance on Safety Considerations for Product Design to Minimize Medication Errors*

¹ When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/RegulatoryInformation/Guidances/default.htm>

² 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>.

Note that we recently published three draft guidance documents that, while not yet finalized, might also be useful in understanding our current thinking and our approach to human factors for combination products, product design, and labeling³:

- *Human Factors Studies and Related Clinical Study Considerations in Combination Product Design and Development*
- *Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors*
- *Contents of a Complete Submission for Threshold Analyses and Human Factors Submissions to Drug and Biologic Applications*

FACILITY INSPECTIONS

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

ADDITIONAL COMMENTS

We have the following comments/recommendations that are not approvability issues:

1. We strongly suggest that you consider developing an in vitro-in vivo model to establish the correlation or relationship (IVIVC/IVIVR) between human PK data and the in vitro drug release data generated using the proposed in vitro drug release method (without reconstitution), which can be used to support postmarketing changes. This is recommended because:
 - a) The proposed in vitro drug release method does not reflect the clinical use of the proposed drug product (i.e., does not include the reconstitution step of the microspheres with the diluent to form the final drug product for intramuscular administration).
 - b) The proposed in vitro drug release method does not include individual drug release tests for each of the proposed strengths.
 - c) The quality and clinical risks associated with the in vitro and in vivo release of the drug from the product are considered high, because the proposed drug product is a reconstituted biodegradable polymeric parenteral microspheres product for intramuscular injection,

³ 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>.

- d) There are concerns with regard to the change (b) (4) during manufacturing scale-up and bridging of commercial batches, effectiveness of reconstitution, and un-resolved clinical safety concern related to the PK spikes observed in the pivotal BE study.
2. The effects of exercise and pressure on the PK profile of the proposed drug product in dogs were included in the NDA. We have concerns with regard to the reported increase on the in vitro drug release at elevated temperature and its impact on in vivo PK performance and safety. Therefore, we recommend that you investigate the effects of applied intermittent and continuous heat on the PK profile of the final to-be-marketed (reconstituted) drug product.

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 PLR Requirements for Prescribing Information¹ 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

PROPRIETARY NAME

Please refer to correspondence dated June 13, 2019, which addresses the proposed proprietary name, Rykindo. 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/product under consideration regardless of indication, dosage form, or dose level.

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

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² <https://www.fda.gov/drugs/labeling/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:
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- (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.
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- (8) Provide English translations of current approved foreign labeling not previously submitted.

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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, please contact CAPT Bill Bender, Senior Regulatory Project Manager, at (301) 796-2145 or via email at william.bender@fda.hhs.gov

Sincerely,

{See appended electronic signature page}

Tiffany R. Farchione, M.D.
Director (Acting)
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
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