CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

214919Orig1s000

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

NDA 214919

REFUSAL TO FILE

Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

Attention: Marcela Ruvalcaba
Associate Specialist, Regulatory Affairs

Dear Ms. Ruvalcaba:

Please refer to your new drug application (NDA) dated and received December 30, 2020, submitted pursuant to section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FDCA), for glycopyrrolate injection, USP.

After a preliminary review, we find your application is not sufficiently complete to permit a substantive review. Therefore, we are refusing to file this application under 21 CFR 314.101(d) for the following reasons:

CMC

1. The leachables study as provided is not reviewable due to a lack of information on methodology, sample preparation, and interpretable data. Presenting data solely as chromatograms without supporting information including retention times and peak integrations, does not allow for a quantitative analysis of the data. The sample preparation for the semi-volatile analysis suggests that the standard concentration does not match what is labeled on the chromatograms, and the standard concentrations presented are significantly higher than the analytical evaluation threshold.

To address the deficiency:

1. Any peaks detected should be presented in numerical format with retention time and peak integration/area values. Chromatograms may be provided, but the data should be quantitatively analyzed.

2. Methodology including instrument methods and sample preparation should be provided for all leachables methods which must be fully validated analytical methods.

Nonclinical

1. Your NDA does not contain any nonclinical information in Module 2. We note that you are relying on the Agency's previous findings of nonclinical pharmacology, safety pharmacology, pharmacokinetic/toxicokinetic data, repeat-dose toxicity,

genotoxicity, and reproductive and developmental toxicity from ROBINUL® (NDA 017558), which should be included in your summary.

To address the deficiency:

Provide a summary of the data from the Reference Drug (ROBINUL® NDA 017558), for which you are relying, as a Nonclinical Written Summary in Module 2.

2. Your NDA includes incomplete leachable data. In general, leachable studies should evaluate at least three batches of your to-be-marketed drug product for leachables and include assessments at multiple timepoints over the course of stability (e.g., early, middle, and late) in order to identify trends in leachable levels over time and account for batch to batch variability. We note that you have conducted leachable assessment on one batch of product at 32 months stability.

To address the deficiency:

You should provide additional leachable data from three batches at multiple timepoints during stability to identify trends over time. If higher levels of leachables are observed in your trend analysis compared to the levels predicted by the 32-month data, revise the toxicological risk assessments accordingly to reflect the highest predicted level over the proposed shelf-life.

In general, any leachable exceeding 5 mcg/day should be evaluated for safety. The leachable data should be accompanied by an adequate toxicological risk assessment. The final safety assessment should be based on your evaluation of leachables from at least three batches of your drug product tested at multiple timepoints over the course of your stability studies, as discussed above. The approach for toxicological evaluation of the safety of leachables should be based on good scientific principles and take into account the specific container closure system, drug product formulation, dosage form, route of administration, and dose regimen (chronic or short-term dosing). The safety assessment should be specifically discussed in Module 2.6.6.8 (Toxicology Written Summary/Other Toxicity) of the NDA submission. The risk assessment should be based on the maximum level of each leachable detected in long-term stability samples that include any intended secondary container closure system(s) unless otherwise justified. Include copies of all referenced studies upon which a safety assessment is based. In addition, consider the following points as you prepare your toxicological risk assessment:

a. If you employ a Permissible Daily Exposure (PDE) assessment as described in ICH Q3C, provide justification for all safety factors employed.

b. Published literature submitted to support the safety of any compound rarely provides adequate detail of the study design and study results to permit a thorough independent evaluation of the data. Summary reviews,

(e.g., BIBRA, CIR, HERA), although potentially useful to identify original source material, are not acceptable as the source material is not provided and the conclusions cannot be independently verified. Submission of any published study reports should be accompanied by a detailed comparison to modern toxicology study endpoints and any shortcomings of the study should be discussed and justification should be provided to support your assertion that these data are adequate to support the safety of your container closure system.

c. Safety justifications based on analogous compounds are also not acceptable unless you can provide adequate data to support your conclusions that a risk assessment based on one compound can be logically interpolated to represent an adequate safety evaluation for your leachable/extractable. This should include a detailed understanding of the absorption, distribution, metabolism, and elimination of the compounds and an adequate scientific bridge to interpolate a NOAEL for the extractable/leachable compound.

3. Although your label is in the PLLR general format, you have not yet submitted a review and summary of the existing literature.

To address the deficiency:

Submit a review and summary of the available published literature regarding drug use in pregnant and lactating women, a review and summary of reports from your pharmacovigilance database, and an interim or final report of an ongoing or closed pregnancy registry (if applicable), which should be located in Module 1. Refer to the draft guidance for industry: *Pregnancy, Lactation, and Reproductive Potential: Labeling for Human Prescription Drug and Biological Products – Content and Format.*[1] Copies of all cited references should be included in the Module 4 (nonclinical) or Module 5 (clinical). Update, as necessary, your proposed language for Section 8 of the labeling. Refer to the information on the final rule and links to the FDA draft guidance document.[2] As the package insert language has significantly changed as a result of the PLLR conversion, you should annotate the changes with justifications for the changes and provide a side by side comparison with the Referenced Drug.

Clinical

4. Your submission does not contain an Integrated Summary of Safety (ISS) and an Integrated Summary of Effectiveness (ISE) documents in Module 5. In certain instances, Module 2 Summaries of Clinical Safety and Clinical Efficacy may be appropriate alternatives to the ISS and the ISE, respectively. However, your application also does not contain Module 2 summaries. We understand that you

[1] https://www.fda.gov/media/90160/download
[2] http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/Labeling/ucm093307.htm

intend to rely on both safety and efficacy information established by the Agency for ROBINUL®. However, you must still submit an analysis of all available safety information regarding the clinical use of glycopyrrolate. The safety information must include the following:

a. A benefit-risk analysis for the intended use of your product.
b. An analysis and discussion of major safety results, including non-fatal serious adverse events and adverse events of special interest.
c. A FAERS search from the most recently approved ROBINUL® label to the time of your NDA submission.
d. A review of the worldwide published literature to identify new potential safety concerns that have not been incorporated into the most recently approved labeling of glycopyrrolate.

While not issues related to our refusal to file this application, you should address the following issues if the application is resubmitted.

Drug Product:

1. Regarding your extractable and leachable study reports, the extractable report did not contain information about the analytical methods used in the study. The leachables study did not report any detected leachables. While theoretically possible, this is extremely unlikely, particularly given the quantities of extractables detected. Additionally, a validation report for the leachable analytical methods was not provided, and samples were only tested at a single timepoint.

Submit the following:

a. Analytical methods used in the extractables testing should be provided, including information about sample preparation, solvents/reagents, instrumentation, and instrument methods. We refer you to USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems.

b. A validation report for the analytical methods used in the leachable analysis. For more information, refer to FDA guidance for industry: *Q2B Validation of Analytical Procedures*.[3]

c. Samples of drug product placed on stability for leachables testing should be tested at multiple timepoints throughout the duration of the study. Refer to FDA guidance for industry: *Q1A(R2) Stability Testing for New Drug Substances and Products.*[4]

d. All leachables that are detected should be reported, and those that are over the analytical evaluation threshold should be quantified and identified. We refer you

[3] https://www.fda.gov/media/71725/download
[4] https://www.fda.gov/media/71707/download

to USP <1663> Assessment of Extractables Associated with Pharmaceutical Packaging/Delivery Systems and USP <1664> Assessment of Leachables Associated with Pharmaceutical Packaging/Delivery Systems.

Biopharmaceutics:

2. We acknowledge that you submitted a biowaiver request for your proposed drug product; however, you did not provide sufficient data to support the biowaiver request. In your submission, you should provide the following:

   a. Comparative physicochemical property data, such as pH and osmolarity of your proposed drug product and the Listed Drug (LD) for at least 3 batches each drug product. The measurements should be done in triplicate for each batch tested.

   b. Justification that any differences between your proposed drug and the LD do not affect the in vivo performance of glycopyrrolate.

3. In Module 1.12.15 Request for Waiver for In-Vivo Studies, you stated "Per 21 CFR 314.94 (a)(9)(iii), a preservative is considered to be an exception excipient. The information provided in this application confirms that there is no impact to the safety or efficacy of the proposed drug product". However, the information about the preservative (i.e., Benzyl Alcohol) could not be located in the submission. If you believe you have provided it in the submission, specify its location. Otherwise, provide a scientific justification.

Microbiology:

4. We acknowledge the container closure integrity test (CCIT) that was provided in Section 3.2.P.2 in the Pharmaceutical Development document on page 48 of 52. However, the information that was provided is incomplete. Therefore, provide the following information for the 1% methylene blue dye ingress CCIT: positive controls, negative controls, number of test units, vacuum and pressure limits and exposure time, and the limit of detection. If any of this information is provided in a DMF, provide the submission, submission date, section, document, and page numbers that contain the relevant information.

5. We acknowledge that the drug product will be [(b) (4)] as stated in Section 3.2.P.3.3 in the Description of the Manufacturing Process and Process Controls document. However, the [(b) (4)] that will be used to [(b) (4)] the subject drug product was not named in the submission and the letter of authorization (LOA) for DMF [(b) (4)] does not state where the relevant information is located. Therefore, state the [(b) (4)] that will be used for [(b) (4)] the drug product and the location in the DMF for the [(b) (4)] design and controls, initial validation studies [(b) (4)], and current requalification studies that validate the [(b) (4)] process for

the subject drug product including submission, submission date, section, document, and page numbers.

6. We acknowledge the endotoxins method suitability studies that were provided in Section 3.2.P.5.3 in the Endotoxin (b) (4)-VAL-5375-MVS document. In the endotoxins suitability study, the maximum valid dilution (MVD) was stated to be 11,110 and the commercial test dilution is 1:100. However, the endotoxins specification is (b) (4) EU/mg, the drug product concentration is 0.2 mg/mL, and the cartridge sensitivity ranges from 0.01 EU/mL to 1 EU/mL which yields MVDs ranging from 3,500 to 35, depending on the cartridge sensitivity. Therefore, provide an explanation for the reported MVD of 11,110 or update the MVD to 3,500 to 35 and clarify the commercial testing dilution.

7. We acknowledge that the endotoxins specification of NMT (b) (4) EU/mg as stated in Section 3.2.P.5.1. However, the maximum endotoxins exposure for adult and pediatric patients exceeds the USP <85> limit of NMT 5 EU/kg/hour. The maximum dose for an adult patient based on the intraoperative indication (0.1 mg/2 minutes) is 3 mg/hour; therefore, the following calculation can be applied: (b) (4). The maximum dose for a pediatric patient based on the intraoperative indication (0.004 mg/kg/2 minutes) is 0.12 mg/kg/hour; therefore, the following calculation can be applied: (b) (4). Revise the endotoxins specification such that the maximum endotoxins exposure does not exceed 5 EU/kg/hour for both adult and pediatric patients per USP <85>. If applicable, provide updated endotoxins method suitability per USP <85>.

Nonclinical

8. Provide a side-by-side comparison of the proposed drug formulation to the reference drug (ROBINUL®). Include in your side-by-side comparison the physicochemical properties (e.g., osmolality, pH). If there is a significant change of any physicochemical property between your product and the reference drug, provide justification to support that there will be no impact on safety of the drug product. A safety justification for a change in physiochemical properties of the drug product should focus on the impact on blood compatibility and local tissue effects.

CDRH

9. In your stability program (ICH Q1), the essential performance requirements (EPRs) (dose accuracy (expelled volume), break loose, and glide force) of the combination product should be verified to ensure that the device EPRs are maintained at expiry. At the accelerated storage condition, a minimum of three timepoints, including initial and final time points (e.g., 0, 3, 6 months) is recommended.

10. It is noted that you provided a shipping study of a previously launched product (3 mL Simplist® Neostigmine) in lieu of the to be marketed combination product, in which EPRs were evaluated. You also stated that the only difference is the

[redacted](b) (4). However, it is not clear if you had taken into consideration other factors that may impact the EPRs (e.g., siliconization). Therefore, in your re-submission, provide a shipping documentation for the final finished product to demonstrate that the device EPRs are met after shipping. It is the expectation that the sample size tested meets a 95% confidence and 95% reliability. For a smaller sample size, you may analyze the data using variable testing. If you provide variable testing, you should provide mean, standard deviation, USL/LSL, Kact (calculated from data), acceptance criteria (k-value, confidence/reliability), graph, and min and max.

Please note that this filing review represents a preliminary review of the application and is not indicative of deficiencies that would be identified if we performed a complete review.

We will refund 75% of the total user fee submitted with the application.

Within 30 days of the date of this letter, you may request in writing a Type A meeting about our refusal to file the application. A meeting package should be submitted with this Type A meeting request. To file this application over FDA's protest, you must avail yourself of this meeting.

If, after the meeting, you still do not agree with our conclusions, you may request that the application be filed over protest. In that case, the filing date will be 60 days after the date you requested the meeting. The application will be considered a new original application for user fee purposes, and you must remit the appropriate fee. If you choose to file over protest, FDA will generally not review any amendments to the application and will generally not issue information requests during the review cycle. Resubmission goals will not apply to any resubmission of this application.

If you have any questions, call Allison Meyer, Senior Regulatory Health Project Manager at (301)796-1258.

Sincerely,
{See appended electronic signature page}

Rigoberto Roca, MD
Director
Division of Anesthesiology, Addiction Medicine
and Pain Medicine
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/

RIGOBERTO A ROCA
02/25/2021 09:36:32 AM