Marcela Ruvalcaba
Specialist, Regulatory Affairs
Fresenius Kabi USA, LLC
Three Corporate Drive
Lake Zurich, IL 60047

January 18, 2023

Re: Docket No. FDA-2022-P-1656

Dear Ms. Ruvalcaba:

This letter responds to your citizen petition received on July 22, 2022 (Petition). You request that the Food and Drug Administration (FDA, Agency, or we) designate Fresenius Kabi USA, LLC's glycopyrrolate intramuscular, intravenous solution, 0.6 milligrams (mg)/3 milliliters (mL) (0.2 mg/mL) (the Fresenius glycopyrrolate product), approved under new drug application (NDA) 214919, a 505(b)(2) application, as therapeutically equivalent with an "AP" rating to Robinul (glycopyrrolate) injection, 0.2 mg/mL, approved under NDA 017558, held by Hikma Pharmaceuticals USA Inc.[1]

We have considered your Petition. For the reasons described below, your Petition is denied.

I. BACKGROUND

Therapeutically equivalent products are defined in the regulations as "approved drug products that are pharmaceutical equivalents for which bioequivalence has been demonstrated, and that can be expected to have the same clinical effect and safety profile when administered to patients under the conditions specified in the labeling."[2]

Pharmaceutical equivalents are:

> drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active drug ingredient, i.e., the same salt or ester of the same therapeutic moiety, or, in the case of modified-release dosage forms that require a reservoir or overage or such forms as prefilled syringes where residual volume may vary, that deliver identical amounts of the active drug ingredient over the identical dosing period; do not necessarily contain the same inactive ingredients; and meet the identical compendial or other applicable standard of identity, strength, quality, and purity,

[1] Petition at 1.

[2] See § 314.3(b) (21 CFR 314.3(b)).

> including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates. [3]

Bioequivalence is:

> the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study.[4]

Products classified as therapeutically equivalent can be substituted with the full expectation that the substituted product will have the same clinical effect and safety profile as the prescribed product when administered to patients under the conditions specified in the labeling.[5]

FDA's therapeutic equivalence (TE) evaluations for approved multisource prescription drug products are published in the Orange Book as TE Codes.[6] Only multisource prescription drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355) are evaluated for TE.[7] Drug products placed in the "Discontinued Drug Product List" section of the Orange Book do not have TE Codes.[8] Drug products are assigned an "A" as the first letter of their TE Code if they are products that FDA considers to be therapeutically equivalent to other pharmaceutically equivalent products. Drug products are assigned a "B" as the first letter of their TE Code if they are products that FDA, at this time, considers not to be therapeutically equivalent to other pharmaceutically equivalent products because actual or potential bioequivalence problems have not been resolved with adequate evidence of bioequivalence.[9]

TE Codes also include a second letter, which provides additional information on the basis of FDA's TE evaluations. The TE Code "AP," which your Petition requests be assigned to the

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[3] § CFR 314.3(b).

[4] § CFR 314.3(b).

[5] *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) (42nd Edition), available at https://www.fda.gov/media/71474/download, Preface, at viii. The Orange Book, available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book, identifies drug products approved under section 505 of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355), including drug products approved pursuant to 505(b)(1) NDAs, 505(b)(2) NDAs, and abbreviated new drug applications.

[6] Orange Book at iv and xii (stating that the term *multisource* generally is used to describe pharmaceutically equivalent drug products that are available from more than one manufacturer).

[7] Id. at xii.

[8] See Frequently Asked Questions on the Orange Book, available at https://www.fda.gov/drugs/drug-approvals-and-databases/approved-drug-products-therapeutic-equivalence-evaluations-orange-book. See also draft guidance for industry *Evaluation of Therapeutic Equivalence* (July 2022) at 8. When final, this guidance will represent the FDA's current thinking on this topic.

[9] Orange Book at xiii; see generally Orange Book at xii-xx.

Fresenius glycopyrrolate product, is assigned to therapeutically equivalent injectable aqueous solutions and, in certain instances, intravenous non-aqueous solutions.[10]

Drug products approved in 505(b)(2) applications generally do not have a TE Code assigned at the time of approval. The Orange Book preface acknowledges this:

> The coding system for therapeutic equivalence evaluations is designed to allow users to determine quickly whether the Agency has evaluated a particular approved prescription drug product (e.g., a particular strength of an approved drug that is not on the Discontinued Drug Product list) as therapeutically equivalent to other pharmaceutically equivalent products (first letter) and to provide additional information on the basis of FDA's evaluations (second letter). With some exceptions (e.g., therapeutic equivalence evaluations for certain 505(b)(2) applications), the therapeutic equivalence evaluation date is the same as the approval date.[11]

The differences between a product approved pursuant to a 505(b)(2) NDA and the listed drug it references may preclude a finding that the products are therapeutically equivalent, for example, if they are not pharmaceutically equivalent. In other cases, however, a drug product approved pursuant to a 505(b)(2) NDA and another listed drug may satisfy the TE criteria, and a finding by the Agency that the products have been demonstrated to be therapeutically equivalent may be appropriate.

II. DISCUSSION

In your Petition, you request that FDA designate the Fresenius glycopyrrolate product (approved under NDA 214919) as a therapeutic equivalent, with an "AP" rating, to Robinul (approved under NDA 017558).[12] You assert that the Fresenius glycopyrrolate product has the same active ingredients, conditions of use, dosage form, route of administration, strength, and indications and usage as Robinul.[13] Therefore, you request that the Agency designate the Fresenius glycopyrrolate product with an "AP" TE Code with respect to Robinul.[14]

Based on the information available to us, FDA has concluded that Robinul is no longer available for sale, and therefore, Robinul is in the Discontinued Drug Product List section of the Orange Book. As stated above, drug products placed in the Discontinued Drug Product List of the Orange Book do not have TE Codes. Consistent with this, a drug product that is on the Prescription Drug Product List (commonly referred to as "the Active Section" of the Orange Book) cannot have a TE Code with respect to a drug product in the Discontinued Drug Product List.

[10] Orange Book at xvi.

[11] Id. at xii-xiii.

[12] Petition at 1.

[13] Petition at 3.

[14] Petition at 3.

Because Robinul is on the Discontinued Drug Product List of the Orange Book, we decline to assign a TE Code of "AP" to the Fresenius glycopyrrolate product with respect to Robinul.[15] Therefore, your request is denied.

III. CONCLUSION

For the reasons described in this response, the Petition is denied.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
Date: 2023.01.18 10:13:44 -05'00'

Patrizia Cavazzoni, M.D.
Director
Center for Drug Evaluation and Research

[15] FDA declines at this time to further assess whether the Fresenius glycopyrrolate product otherwise could be considered therapeutically equivalent to Robinul.