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

August 16, 2023

Re: Docket No. FDA-2020-P-1246

Dear Ms. Kannan:

This letter responds to your citizen petition received on April 2, 2020 (Petition). In the Petition, you request that the Food and Drug Administration (FDA or the Agency) designate Fresenius Kabi USA, LLC's acetaminophen intravenous solution, 1 gram (g)/100 milliliters (mL) (10 milligrams (mg)/mL) (the Fresenius acetaminophen product), approved under new drug application (NDA) 204767, a 505(b)(2) application, as therapeutically equivalent with an "AP" rating to Ofirmev (acetaminophen) intravenous solution, 1 g/100 mL (10 mg/mL), approved under NDA 022450, held by Mallinckrodt Hospital Products IP Ltd.

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."[1]

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, including potency and, where applicable, content uniformity, disintegration times, and/or dissolution rates.[2]

[1] See § 314.3(b) (21 CFR 314.3(b)).

[2] § 314.3(b).

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.[3]

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.[4]

FDA's therapeutic equivalence (TE) evaluations for approved multisource prescription drug products are published in the Orange Book as TE Codes.[5] 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.[6] Drug products placed in the "Discontinued Drug Product List" section of the Orange Book do not have TE Codes.[7] 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.[8]

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 Fresenius acetaminophen product, is assigned to injectable aqueous and, in certain instances, intravenous non-aqueous solutions, as the Orange Book explains:

> It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences

[3] § 314.3(b).

[4] *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) (43rd 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 (ANDAs).

[5] 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).

[6] Id. at xii.

[7] 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.

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

> among the products in the general category, Injectable; Injection. For example, historically some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are pharmaceutical alternative drug products. They are not rated as therapeutically equivalent (AP) to each other even if these pharmaceutical alternative drug products are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to assure that it is given only by the route(s) of administration stated in the labeling.[9]

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 prescription drug 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.[10]

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 acetaminophen product (approved under NDA 204767) as a therapeutic equivalent, with an "AP" rating, to Ofirmev (approved under NDA 022450).[11] You assert that the Fresenius acetaminophen product is therapeutically equivalent and pharmaceutically equivalent to Ofirmev, and that the Fresenius acetaminophen product is expected to have the same clinical effect and safety profile as Ofirmev.[12] Therefore, you request that the Agency designate the Fresenius acetaminophen product with an "AP" TE Code with respect to Ofirmev.[13]

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[9] Id. at xiii and xvi.

[10] Id. at xii-xiii.

[11] Petition at 1.

[12] Id.

[13] Id. at 3.

Based on the information available to us, FDA has concluded that Ofirmev is no longer available for sale, and therefore, Ofirmev 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. Accordingly, 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.

Because Ofirmev is on the Discontinued Drug Product List of the Orange Book, we decline to assign a TE Code of "AP" to the Fresenius acetaminophen product with respect to Ofirmev.[14] 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: 2023.08.16 10:57:12

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

[14] FDA declines at this time to further assess whether the Fresenius acetaminophen product otherwise could be considered therapeutically equivalent to Ofirmev.