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Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Human Services
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To Whom It May Concern:

Fresenius Kabi submits this petition pursuant to Section 505(q) of the Federal Food, Drug, and Cosmetic Act ("FDCA"), and in accordance with 21 C.F.R. §§ 10.20 and 10.30 to request that the Food and Drug Administration ("FDA") refuse to file or accept any Abbreviated New Drug Application ("ANDA") or 505(b)(2) new drug application ("NDA") for a levothyroxine sodium solution product for intravenous use that does not reference NDA No. 210362 for Levothyroxine Sodium Intravenous Solution. If an application to approve a solution product references any other product, including other lyophilized approved versions of levothyroxine, then any such application should be required to be refiled as a new ANDA or 505(b)(2) referencing NDA No. 210362 and certifying to the patents associated with that NDA.

This Citizen Petition pertains to Fresenius Kabi USA LLC's ("Fresenius Kabi") NDA No. 210632 for Levothyroxine Sodium Intravenous Solution, 20 mcg/mL, 40 mcg/mL, and 100 mcg/mL, which was approved April 11, 2019 pursuant to FDCA § 505(b)(2). We have become aware that Custopharm filed NDA No. 214253 pursuant to 21 C.F.R. § 505(b)(2) seeking approval to market a Levothyroxine Sodium Intravenous Solution 100 mcg/mL product, but that application improperly references Fresenius Kabi's Levothyroxine Sodium Powder NDA No. 202231 as the Reference Listed Drug ("RLD"). Custopharm and any other applicant seeking approval for a solution version of levothyroxine sodium should be required to reference the FDA-approved Fresenius Kabi solution product.

I. Action Requested

The undersigned requests that FDA:

(1) Refuse to file or approve any ANDA or 505(b)(2) application for Levothyroxine Sodium Intravenous Solution that does not reference the RLD approved in NDA No. 210632 and

(2) Require that any such pending applications be filed as a new ANDA or 505(b)(2) application and make all appropriate certifications with respect to the patents listed for NDA No. 210632.

II. Statement of Grounds

An application—whether it be a 505(b)(2) or ANDA—must reference the closest pharmaceutically equivalent approved product. Therefore, an applicant seeking approval for

a levothyroxine solution product should reference the approved solution product, not another approved powder product. As discussed further below, FDA's policy is that dry powders for reconstitution and sterile solutions ready for injection are not therapeutic equivalents. Allowing a levothyroxine solution application to reference the powder product instead of the approved solution product wastes FDA's resources and—as FDA has acknowledged in similar situations—is simply an attempt to circumvent the certification requirements of the Hatch-Waxman Act.

A levothyroxine solution product applicant that has improperly referenced the powder NDA cannot simply amend its application, but instead must file a new 505(b)(2) application or ANDA to change to the appropriate RLD; FDC Act § 505(b)(4)(A). That new application must contain the required certifications to the patents listed in connection with the solution NDA No. 210362.

A. Factual Background

FDA's "Approved Drug Products with Therapeutic Equivalence" (the "Orange Book") lists two types of intravenous levothyroxine sodium dosage forms: a powder dosage form and a liquid dosage form. Fresenius Kabi is the owner of the NDAs designated as RLD for both dosage forms.

Levothyroxine Sodium for Injection was a marketed unapproved drug used for treatment of myxedema coma and other forms of hypothyroidism in which oral levothyroxine administration is not feasible. FDA approved APP's NDA No. 202231 for Levothyroxine Sodium Intravenous Powder products, 100 mcg/vial, 200 mcg/vial, and 500 mcg/vial in June 2011. FDA designated the products approved under NDA No. 202231 as the RLD. Fresenius Kabi acquired APP and all its assets, including NDA No. 202231. Since approval of NDA No. 202231, FDA has approved three ANDAs that reference NDA No. 202231, all of which are Levothyroxine Powder products.

In connection with NDA No. 202231, Fresenius Kabi listed in the Orange Book three patents covering its Levothyroxine Sodium Intravenous Powder products, among others. The patents were listed in accordance with FDCA §505(b)(1) and expire in 2032.

In June 2018, Fresenius Kabi submitted NDA No. 210362 for Levothyroxine Sodium for injection 100 mcg/5 mL, 200 mcg/5 mL, and 500 mcg/5 mL Ready To Use (RTU) Liquid formulations under section 505(b)(2) for the treatment of myxedema coma. Because there was no approved Levothyroxine Liquid product, Fresenius Kabi referenced its NDA for the Powder product. As part of its review of Fresenius Kabi's solution NDA, FDA required Fresenius Kabi to provide information to bridge the proposed solution product and the approved Powder product. FDA approved NDA No. 210362 in April 2019 and designated the products approved therein as the RLD. To date, there are no other approved Levothyroxine Sodium solution products. NDA No. 210362 remains the reference listed drug for liquid solution products.

Pursuant to FDCA § 505(b)(1), Fresenius Kabi listed two patents in connection with the Solution NDA products. The patents listed in connection with the Solution NDA products expire

in 2036. These patents are not the same patents listed in connection with the Powder NDA products.

We are informed that Custopharm submitted a 505(b)(2) application seeking approval to market a Levothyroxine Solution product. Custopharm's 505(b)(2) application seeks approval for 100 mcg/mL Levothyroxine Solution product, which is one of the strengths of Fresenius Kabi's Solution NDA No. 210362. Instead of referencing the approved Levothyroxine Solution NDA No. 210362, which is a RLD, Custopharm referenced the Levothyroxine Powder NDA. On September 16, 2020, Custopharm sent a letter purportedly pursuant to 505(b)(3)(B)(i) (a "Paragraph IV Notice letter") to Fresenius Kabi informing Fresenius Kabi of its 505(b)(2) application. This notice was sent with regard to the Powder NDA 202231, indicating that Custopharm did not reference the appropriate RLD for Levothyroxine Solution or certify to the patents associated with that RLD.

B. The appropriate RLD is the one that is pharmaceutically equivalent.

FDA regulations and guidances instruct 505(b)(2) applicants and ANDA filers to reference the closest approved pharmaceutically equivalent product, both for ease of review and to ensure the applicant does not improperly bypass important statutory requirements. Here, as shown further below, the closest pharmaceutically equivalent product to a levothyroxine solution product is the product described in Fresenius Kabi's approved Solution NDA No. 210362 and not Fresenius Kabi's Powder NDA product No. 202231.

FDCA § 505(b)(2) permits the submission of an NDA where at least some of the information required for approval comes from studies not conducted by or for the applicant, and for which the applicant has not obtained a right of reference. A 505(b)(2) application enables the applicant to rely, in part, on FDA's previous findings of safety and efficacy for an approved drug product (and/or published literature) in support of its application for the marketing of a new drug. If a 505(b)(2) applicant is relying on FDA's previous findings of safety and efficacy for an approved drug product, the applicant must identify the application forming the basis for FDA's conclusions, or the reference listed drug ("RLD").[1] The regulations provide guidance on selecting the RLD:

> The listed drug(s) identified as relied upon **must** include a drug product approved in an NDA that:
>
> (A) Is **pharmaceutically equivalent** to the drug product for which the original 505(b)(2) application is submitted; and
>
> (B) Was approved before the original 505(b)(2) application was submitted.[2]

The regulations define "pharmaceutically equivalent" as "drug products in identical dosage forms and route(s) of administration that contain identical amounts of the identical active

[1] 21 C.F.R. § 314.54(a)(1)(iii).

[2] *Id.* (emphasis added).

drug ingredient,...that deliver identical amounts of the active drug ingredient over the identical dosing period;…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."[3] A pharmaceutically equivalent product is different from a product that is a "pharmaceutical alternative," which is a product that contains "the identical therapeutic moiety, or its precursor, but not necessarily in the same amount or dosage form…."[4]

FDA has clearly stated that "[i]f there is a listed drug that is the pharmaceutical equivalent to the drug proposed in the 505(b)(2) application, then that drug should be identified as the listed drug."[5] Selecting the closest pharmaceutically equivalent product avoids unnecessary duplication of research and review and "ensure[s] that the 505(b)(2) applicant (and FDA) can rely, to the maximum extent possible, on what is already known about a drug without having to re-prove (or re-review) what has already been determined."[6] Requiring an applicant to reference the closest pharmaceutical equivalent also prohibits applicants from abusing the regulatory process so as to potentially deprive an NDA holder of the protections afforded by the Hatch-Waxman Act and avoid having to certify against additional applicable patents.

Applicants that submit 505(b)(2) applications are required to certify to all patents that are listed in connection with the referenced pharmaceutically equivalent product.[7] If that certification is the so-called "Paragraph IV" certification[8], it has statutory implications: the filing of an application with a Paragraph IV certification is the jurisdictional basis for a lawsuit, the filing of which can result in a 30-month stay of approval of the application.[9] FDA has repeatedly refused to permit an applicant to use the 505(b)(2) process to circumvent certifying to the patents associated with a pharmaceutical equivalent. According to FDA, "if there is a listed drug that is the pharmaceutical equivalent of the drug proposed in the 505(b)(2) application, the 505(b)(2) application should provide patent certifications for the patents listed for the pharmaceutically equivalent drug."[10] FDA has stated that this policy "ensure[s] that the 505(b)(2) applicant does not use the 505(b)(2) process to end-run

[3] 21 C.F.R. § 314.3.

[4] *Id.*

[5] Draft Guidance for Industry, "Applications Covered by Section 505(b)(2)," at 8 (Oct. 1999) (hereinafter "1999 Guidance").

[6] FDA, Petition Response, Docket No. 2004P-0386, 9 (Nov. 30, 2004) ("Fenofibrate CP Response").

[7] 21 C.F.R. § 314.50(i)(C); 21 CFR § 314.54(a)(1)(vi).

[8] FDCA § 505(b)(2)(A)(iv).

[9] *Id.* at § 505(c)(3)(C).

[10] 1999 Guidance at 8; *see also* Fenofibrate CP at 9.

patent protections that would have applied had an ANDA been permitted."[11] For that reason, FDA has instructed that "if all the information relied on by FDA for approval…is contained in a single previously approved application and that application is a ***pharmaceutical equivalent***…to the product for which approval is sought, the 505(b)(2) applicant should certify only to the patents for that application."[12] In fact, "[t]his is the case ***even when another application also contains some or all of the same information***."[13]

The above approach to identify the correct RLD reflects a guiding principle in ensuring that the parallel structure and logic of the patent certification provisions in Sections 505(b)(2) and 505(j) in the Hatch-Waxman Amendments are interpreted faithfully. Therefore, a levothyroxine sodium solution application is not a pharmaceutical equivalent to the powder NDA; and therefore, should reference Fresenius Kabi's solution NDA No. 210632 to ensure the statutory safeguards for NDA holders are not abridged.

C. The appropriate RLD is the approved levothyroxine solution product, not levothyroxine powder.

As explained above, a 505(b)(2) applicant must reference the pharmaceutically equivalent product, and for a levothyroxine solution product the pharmaceutical equivalent to be referenced is the approved solution product (NDA No. 210632) and not the powder product.

The Orange Book addresses this issue directly:

> 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.[14]

Therapeutic equivalent products are defined as "pharmaceutical equivalents."[15] FDA has repeatedly explained that powder products and RTU solution products are not therapeutically equivalent under its analysis.

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[11] Fenofibrate CP at 9.

[12] *Id*. at 10. FDA provided the example that "if a tablet and a capsule are approved for the same moiety with patents listed for the tablet and none listed for the capsule, an ANDA applicant seeking approval for a tablet should cite the approved tablet as the reference listed drug." *Id*. at 9 n.13.

[13] *Id*. (emphasis added).

[14] *See* FDA, Approved Drug Products with Therapeutic Equivalence Evaluations, xvi (39th ed. 2019);

[15] 21 C.F.R. § 314.3(b).

The FDA's decision denying in part a Citizen Petition regarding zoledronic acid (Zometa) is an instructive example. Zoledronic acid was originally approved as a lyophilized powder, and then as an injectable solution as part of a supplement to the same NDA.[16] The powder version was withdrawn from the market, and therefore the petitioner sought to reference the marketed solution product in its ANDA for a lyophilized powder product.[17] FDA rejected the argument that the powder ANDA should be able to reference the approved liquid product and that the products be deemed "therapeutically equivalent," stating "the Zometa powder formulation would be considered to be a different dosage form than the Zometa solution formulation because a dry powder to be reconstituted for injection is a different dosage form than an injectable solution."[18] FDA determined that the powder zoledronic acid product was not withdrawn for safety reasons, and thus the appropriate reference product for the ANDA applicant was the powder lyophilized product and not the solution product. FDA stated "[i]f, as described in your petition, the proposed generic product is identical to the powder formulation, the discontinued powder formulation, and its labeling, would be the reference product."[19]

The situation here is virtually identical. Under the FDA's approach for classifying applications, Fresenius Kabi's levothyroxine powder and solution products are not therapeutically or pharmaceutically equivalent to each other.[20] There is an approved levothyroxine sodium solution RLD available. That product, and not the approved powder product, should be the RLD for any pending or future levothyroxine sodium solution application. In fact, as discussed further below, if the solution product that is subject to such an application is identical to the solution RLD, then the appropriate application should be an ANDA and not a 505(b)(2) application.

D. FDA has the authority to refuse to file a 505(b)(2) application that does not identify the appropriate RLD.

Because, as discussed above, FDCA requires a 505(b)(2) applicant to certify as to each patent for the RLD, a 505(b)(2) application that lacks accurate patent certifications is deficient "on its face" and thus meets the conditions for refusal to file under 21 C.F.R. § 314.101(d)(3). Here, the appropriate RLD for a levothyroxine sodium solution product is NDA No. 210362. FDA has ample authority to refuse to file any 505(b)(2) application for a levothyroxine sodium solution product that references the levothyroxine powder NDA. It should do so here.

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[16] FDA, Petition Response, Docket No. 2007P-0250, 1 (April 14, 2009) ("Zometa CP Response").

[17] *Id*. at 2-3.

[18] *Id*. at 3.

[19] *Id*.

[20] https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=202231.

E. FDA must require an applicant that has improperly identified an RLD to file a new application with appropriate certifications.

Applicants like Custopharm that reference the wrong levothyroxine RLD must file a new application to reference the correct product, and may be required to file an ANDA as opposed to a 505(b)(2) application. The FDCA provides that "[a]n applicant may not amend or supplement [a 505(b)(2) application] to seek approval of a drug that is a different drug than the drug identified in the application as submitted to the [FDA]."[21] Therefore, Custopharm cannot correct its error by simply amending its application but must instead file a new application for its solution product that references NDA No. 210623 and NDA No. 202231 and must certify to the patents listed in connection with both NDAs.[22]

If there is no substantive difference between Custopharm's product and the product of approved NDA No. 210623, then Custopharm's new application must be an ANDA and not a 505(b)(2) application. FDA will refuse to file a 505(b)(2) application when "NDA is submitted as a 505(b)(2) application for a drug that is a duplicate of a listed drug and is eligible for approval under section 505(j) of the Federal Food, Drug, and Cosmetic Act."[23]

III. Environmental Impact

Petitioner claims a categorical exclusion under 21 C.F.R. § 25.31.

IV. Economic Impact Statement

Petitioner will, upon request by the Commissioner, submit economic impact information, in accordance with 21 C.F.R. § 10.30(b).

V. Certification

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable

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[21] FDCA § 505(b)(4)(A).

[22] The new filing would have to certify to the patents listed for NDA No. 210632 ***and*** NDA 202231. "Where a 505(b)(2) application seeks to rely on the finding of safety or effectiveness for a listed drug that is a 505(b)(2) NDA which, itself, relied on a previous finding of safety and effectiveness, the 505(b)(2) applicant should certify to the patents of the 505(b)(2) NDA relied on, as well as to the patents of any underlying NDA on which that approved 505(b)(2) NDA relied for approval." Fenofibrate CP at 10 n.14. Fresenius Kabi's solution NDA No. 210632 initially relied on and referenced NDA 202231 because there was no approved solution product at the time. Therefore, reference to NDA 210632 means that the applicant must certify to the patents listed for both NDAs.

[23] 21 C.F.R. § 314.101(d)(9).

to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: September 16, 2020. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Fresenius Kabi USA LLC. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Sincerely,

Molly Ventrelli

Digitally signed by Molly Ventrelli
DN: c=US, st=Illinois, l=Lake Zurich, o=Fresenius Netcare, ou=IT, cn=Molly Ventrelli, email=Molly.Ventrelli@fresenius-kabi.com
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