Molly Ventrelli
Senior Vice President, Regulatory Affairs
Fresenius Kabi USA LLC
Three Corporate Drive
Lake Zurich, IL 60047

May 17, 2021

Re: Docket No. FDA-2020-P-2133

Dear Ms. Ventrelli:

This letter responds to your citizen petition received on October 26, 2020 (Petition). In the Petition, you request that the Food and Drug Administration (FDA, the Agency, or we): (1) refuse to file or approve any abbreviated new drug application (ANDA) or 505(b)(2) new drug application (NDA) for levothyroxine sodium intravenous solution that does not rely upon the listed drug approved under NDA 210632; and (2) require that any such pending application be filed as a new ANDA or 505(b)(2) application and make all appropriate patent certifications with respect to the patents listed for NDA 210632.
FDA has carefully considered the information submitted in the Petition and other relevant information available to the Agency. Based on our review of these materials and for the reasons described below, the Petition is denied in all respects.[1]

I. FACTUAL BACKGROUND

A. Levothyroxine Sodium Products for Intravenous Use

Levothyroxine sodium for intravenous use is indicated for the treatment of myxedema coma. FDA's "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") lists two types of intravenous levothyroxine sodium dosage forms: a powder dosage form and a solution dosage form. Fresenius Kabi USA LLC ("Fresenius") is the application holder of approved 505(b)(2) NDAs for both dosage forms. Levothyroxine sodium intravenous powder (NDA 202231), 100 mcg/vial, 200 mcg/vial, and 500 mcg/vial, was approved June 24, 2011. Levothyroxine sodium intravenous solution (NDA 210632), 100 mcg/5 mL (20 mcg/mL), 200 mcg/5 mL (40 mcg/mL), and 500 mcg/5 mL (100 mcg/mL), was approved April 11, 2019. The products approved under NDA 202231 and NDA 210632 are designated as RLDs in the Orange Book.

As of the date of this response, three patents are listed in the Orange Book for Fresenius's NDA 202231: U.S. Patent Nos. 9,006,289; 9,168,238; and 9,168,239. All three of these patents currently expire in 2032. Two patents are listed in the Orange Book for Fresenius's NDA 210632: U.S. Patent Nos. 9,782,376 and 10,398,669. Both of these patents currently expire in 2036.

On July 17, 2020, Custopharm Inc. ("Custopharm") submitted NDA 214253 under the pathway described in section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) for levothyroxine sodium intravenous solution, 100 mcg/mL (100 mcg/mL), for the treatment of myxedema coma. Custopharm

[1] Today FDA has approved Custopharm Inc.'s NDA 214253 for levothyroxine sodium intravenous solution, 100 mcg/mL (100 mcg/mL).

stated that it relies upon NDA 202231 (levothyroxine sodium intravenous powder). On September 16, 2020, Custopharm sent paragraph IV notice under section 505(b)(3) to Fresenius informing Fresenius of its application and intent to rely on NDA 202231. (*See also* Petition at 3).

B. Fresenius's Citizen Petition

On October 26, 2020, you submitted your Petition requesting that FDA refuse to file or approve any ANDA or 505(b)(2) application for levothyroxine sodium intravenous solution that does not reference NDA 210632. Your Petition also requests that the Agency require any pending applications to be re-filed as new ANDAs or 505(b)(2) applications and make appropriate certifications to the patents listed for NDA 210632.

In support of your Petition, you argue that both 505(b)(2) applications and ANDAs are required to reference the "closest pharmaceutically equivalent product." (Petition at 3). You assert that a levothyroxine sodium solution product is not pharmaceutically equivalent to a levothyroxine sodium powder product. (Petition at 5). You state that allowing an application for a levothyroxine sodium solution product to reference a powder product when there has already been an approved solution product is a waste of FDA resources and an attempt to circumvent the requirements of the Hatch-Waxman Amendments. (Petition at 2, 4-5). As such, you request that FDA require any ANDA or 505(b)(2) applicant for a levothyroxine sodium intravenous solution product that relies on a levothyroxine sodium intravenous powder product to file a new 505(b)(2) application or ANDA and make the appropriate patent certifications in the new application. (Petition at 6-7).

II. LEGAL AND REGULATORY BACKGROUND

A. 505(j) Applications

The Drug Price Competition and Patent Term Restoration Act of 1984 (Public Law 98-417) (the Hatch-Waxman Amendments) amended the FD&C Act to add, among other things, section 505(j) (21 U.S.C. 355(j)), which established an abbreviated approval pathway for generic drugs. To obtain approval, an ANDA applicant is not required to submit evidence to establish the clinical safety and effectiveness of the drug product; instead, an ANDA relies on FDA's previous finding that the reference listed drug (RLD) is safe and effective.[2] The ANDA applicant must identify the listed drug on which it seeks to rely and, with certain limited exceptions, a drug product described in an ANDA must contain the same active ingredient, route of administration, dosage form, strength, and (with certain permissible differences) labeling as the RLD.[3]

B. 505(b)(2) Applications

Section 505(b)(2) was also enacted as part of the Hatch-Waxman Amendments. Section 505(b)(2) of the

[2] An *RLD* is the "listed drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its ANDA." 21 CFR 314.3(b). RLDs are identified in the Orange Book.

[3] Section 505(j)(2)(A) and (j)(4) of the FD&C Act; see also 21 CFR 314.94(a).

FD&C Act describes an application that contains full reports of investigations of safety and effectiveness, 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 or use (i.e., published literature or the Agency's finding of safety and/or effectiveness for one or more listed drugs).[4] A 505(b)(2) applicant may rely on FDA's finding of safety and effectiveness for a listed drug only to the extent that the proposed product in the 505(b)(2) application shares characteristics (e.g., active ingredient, dosage form, route of administration, strength, indication, conditions of use) in common with the listed drug(s). The 505(b)(2) application must include sufficient data to support any differences between the proposed drug and the listed drug(s) and demonstrate that the proposed drug product meets the statutory approval standard for safety and effectiveness. The 505(b)(2) pathway permits sponsors to rely on what is already known about a drug, thereby avoiding unnecessary duplication of human or animal studies and conserving resources.

A sponsor interested in submitting a 505(b)(2) application that relies upon FDA's finding of safety and/or effectiveness for one or more listed drugs[5] should determine which listed drug(s) is most appropriate for its development program, and must establish that such reliance is scientifically appropriate.[6]

C. Identifying a Listed Drug in a 505(b)(2) Application

A 505(b)(2) application must identify the listed drug or drugs on which it seeks to rely. Once a listed drug has been identified, the 505(b)(2) applicant need only provide sufficient information to support any change from the listed drug (21 CFR 314.54(a)). If FDA has approved one or more pharmaceutically equivalent products in one or more NDAs before the date of the submission of the original 505(b)(2) application,[7] the 505(b)(2) applicant must identify one such pharmaceutically equivalent product as a listed drug (or an additional listed drug) relied upon but need not provide a scientific bridge to that product unless it is scientifically necessary to support approval.[8] For each listed drug relied upon, the applicant must submit an appropriate patent certification or statement for each patent listing.[9]

Pharmaceutical equivalents are defined in 21 CFR 314.3 as:

> 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

[4] A 505(b)(2) application differs from a stand-alone NDA in which the full reports of investigations of safety and effectiveness were conducted by or for the applicant or for which the applicant has a right of reference or use.

[5] For example, in certain cases, a sponsor may rely on FDA's finding of safety and/or effectiveness for different listed drugs to support different aspects of its development program.

[6] See FDA Response to Sanzo, Chasnow, Lawton, and Rakoczy (October 14, 2003) at 12. This joint response was previously assigned Docket Nos. 2001P-0323, 2002P-0047, and 2003P-0408, but as a result of FDA's transition to its new docketing system (Regulations.gov) in 2008, these numbers were combined to Docket No. FDA-2003-P-0274.

[7] *See* 21 CFR 314.3(b) (defining "original application").

[8] *See* 21 CFR 314.50(i)(1)(i)(C), 314.54(a)(1)(iii) and (vi), and 314.125(b)(19).

[9] 21 CFR 314.54(a)(1)(vi).

> 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.[10]

FDA regulations establish that FDA may refuse to file 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).[11]

D. Patent Listing and Patent Certification Requirements

Section 505(b)(1)(A)(viii) of the FD&C Act requires the applicant for an NDA to file with the application "the patent number and expiration date of each patent for which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug, and that (I) claims the drug for which the applicant submitted the application and is a drug substance (active ingredient) patent or a drug product (formulation or composition) patent; or (II) claims a method of using such drug for which approval is sought or has been granted in the application" (*see also* 21 CFR 314.53 and section 505(c)(2) of the FD&C Act). This requirement applies to both stand-alone NDAs and 505(b)(2) applications. Upon approval of an application under section 505(c) of the FD&C Act, FDA publishes the patent information provided by the drug product's application holder in the Orange Book.

An ANDA applicant must provide in its ANDA information related to any patents listed for the RLD. In particular, the ANDA applicant generally must submit to FDA one of four specified certifications regarding the patents for the RLD under section 505(j)(2)(A)(vii) of the FD&C Act.[12]

Section 505(b)(2) of the FD&C Act provides that:

> An application submitted under paragraph (1) for a drug for which the investigations described in clause (A)) . . . and relied upon by the applicant for approval of the application were not conducted by or for the applicant and for which the applicant has not obtained a right of reference or use from the person by or for whom the investigations were conducted shall also include--
>
> > (A)) a certification . . . with respect to each patent which claims the drug for which such investigations were conducted or which claims a use for such drug for which the applicant is seeking approval under this subsection and for which information is required to be filed under paragraph (1) or subsection (c)--

[10] 21 CFR 314.3(b).

[11] 21 CFR 314.101(d)(9).

[12] The FD&C Act describes only one circumstance in which an ANDA applicant need not certify to a timely listed patent that claims a method of using the listed drug. Specifically, when a patent is listed only for a method of use, an ANDA applicant seeking to omit that approved method of use from the generic drug's labeling can submit a "section viii statement," acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval. *See* section 505(j)(2)(A)(viii) of the FD&C Act. *See also* 21 CFR 314.94(a)(12)(iii).

Section 505(b)(2) of the FD&C Act.

With respect to each patent listed for the listed drug relied upon, the 505(b)(2) applicant must make one of the following certifications:

> (i) that such patent information has not been filed,
> (ii) that such patent has expired,
> (iii) he date on which such patent will expire, or
> (iv) hat such patent is invalid or will not be infringed by the manufacture, use, or sale of the new drug for which the application is submitted.

Section 505(b)(2)(A) of the FD&C Act.[13]

If an applicant wishes to challenge the validity of the listed patent, or to claim that the listed patent would not be infringed by the product proposed in the 505(b)(2) application, the applicant must submit a paragraph IV certification to FDA. The applicant must also provide a notice to the NDA holder and the patent owner stating that the application has been submitted and explaining the factual and legal basis for the applicant's opinion that the patent is invalid or not infringed (section 505(b)(3) of the FD&C Act). Once the NDA holder and patent owner have received notice, they have 45 days within which to sue the applicant for patent infringement to trigger a 30-month stay on FDA approval of the proposed drug (section 505(c)(3)(C) of the FD&C Act). FDA may approve the proposed drug before the 30-month period expires if a court finds the patent invalid or not infringed, the parties enter and the court signs a settlement agreement stating that the patent is invalid or not infringed, or the court shortens the period because the parties fail to cooperate in expediting the litigation (section 505(c)(3)(C) of the FD&C Act).

III. DISCUSSION

A. Custopharm's Levothyroxine Sodium Intravenous Solution Product is Not Pharmaceutically Equivalent to Any Product Approved Under NDA 210632

Your Petition requests that the Agency refuse to approve any 505(b)(2) NDA for a levothyroxine sodium intravenous solution product that does not rely on NDA 210632 (levothyroxine sodium intravenous solution). Specifically, you assert that a 505(b)(2) applicant seeking to market a levothyroxine sodium solution product must identify the solution product approved under NDA 210632 as a listed drug relied upon because the two products are pharmaceutically equivalent. (Petition at 3). Furthermore, you assert, "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. [210632]." (Petition at 3). Additionally, you assert that the product approved under NDA 210632 is the "closest pharmaceutically equivalent product" and that 505(b)(2) NDA applicants are required to reference the "closest approved pharmaceutically equivalent product." (Petition at 3). You assert that Custopharm's application improperly

[13] As with ANDAs, when a patent is listed only for a method of use, a 505(b)(2) applicant seeking to omit that approved method of use from its proposed drug's labeling can submit a statement acknowledging that a given method-of-use patent has been listed, but stating that the patent at issue does not claim a use for which the applicant seeks approval. *See* section 505(b)(2)(B) of the FD&C Act. *See also* 21 CFR 314.50(i)(1)(iii).

relies upon only the levothyroxine sodium intravenous powder approved under NDA 202231, because Custopharm's proposed product is pharmaceutically equivalent to a product approved under NDA 210632 but not to any product approved under NDA 202231.

FDA Response

We agree that in a 505(b)(2) application, the applicant would be required to identify one pharmaceutically equivalent product as a listed drug relied upon if a pharmaceutically equivalent product had been approved before the original 505(b)(2) application was submitted.[14] However, we disagree that Custopharm's levothyroxine sodium intravenous solution product (NDA 214253), 100 mcg/mL (100 mcg/mL), is pharmaceutically equivalent to any of Fresenius's levothyroxine sodium intravenous solution products (NDA 210632), 100 mcg/5 mL (20 mcg/mL), 200 mcg/5 mL (40 mcg/mL), and 500 mcg/5 mL (100 mcg/mL).

We determined whether Custopharm's levothyroxine sodium intravenous solution product (NDA 214253) and any of Fresenius's levothyroxine sodium intravenous solution products (NDA 210632) meet the definition of pharmaceutical equivalents under 21 CFR 314.3 by considering, generally, the active ingredient, route of administration, dosage form, and strength. Custopharm's and Fresenius's products contain levothyroxine sodium as the active ingredient. Additionally, each of the products has the same route of administration and dosage form, as each is a solution for intravenous injection. However, as discussed further below, Custopharm's levothyroxine sodium intravenous solution product (NDA 214253), 100 mcg/mL (100 mcg/mL), does not have the same strength as any of Fresenius's levothyroxine sodium intravenous solution products (NDA 210632), 100 mcg/5 mL (20 mcg/mL), 200 mcg/5 mL (40 mcg/mL), and 500 mcg/5 mL (100 mcg/mL).

Under 21 CFR 314.3, strength is defined as:

> the amount of drug substance contained in, delivered, or deliverable from a drug product, which includes: (1)(i) The total quantity of drug substance in mass or units of activity in a dosage unit or container closure (e.g., weight/unit dose, weight/volume or weight/weight in a container closure, or units/volume or units/weight in a container closure); and/or, as applicable. (ii) The concentration of the drug substance in mass or units of activity per unit volume or mass (e.g., weight/weight, weight/volume, or units/volume); or (2) Such other criteria the Agency establishes for determining the amount of drug substance contained in, delivered, or deliverable from a drug product if the weights and measures described in paragraph (i) of this definition do not apply (e.g., certain drug-device combination products for which the amount of drug substance is emitted per use or unit time).[15]

The criteria in both paragraphs (1)(i) and (ii) of the definition (i.e., the total quantity of drug substance in mass or units of activity in a dosage unit or container closure and the concentration of the drug substance in mass per unit volume) are applicable to levothyroxine sodium intravenous solution. "FDA has a longstanding history of considering a difference in the total quantity of a drug substance of a parenteral

[14] *See* 21 CFR 314.54(a)(1)(iii).

[15] 21 CFR 314.3(b).

product (*e.g.*, a single or multiple dose vial) or a difference in the concentration of a parenteral product to be a difference in the 'strength' of the product for purposes of section 505(j)(2)(A)(iii) of the FD&C Act."[16] The strength of a parenteral drug product is determined by both the total quantity of drug substance and the concentration of the drug substance.[17] This policy is also aligned with the current Orange Book practice to display, for parenteral drug products, both total drug content per container and concentration of the drug in terms of mass per volume.[18]

Fresenius's levothyroxine sodium intravenous solution, 500 mcg/5 mL (100 mcg/mL), does not have the same strength as Custopharm's levothyroxine sodium intravenous solution (NDA 214253), 100 mcg/mL (100 mcg/mL). Fresenius's product contains 500 mcg levothyroxine sodium in the total quantity per unit and has a concentration of 100 mcg/mL. However, Custopharm's product contains 100 mcg in the total quantity per unit and has a concentration of 100 mcg/mL. Thus, the products differ in total drug content. Fresenius's levothyroxine sodium intravenous solution, 100 mcg/5 mL (20 mcg/mL), does not have the same strength as Custopharm's levothyroxine sodium intravenous solution (NDA 214253), 100 mcg/mL (100 mcg/mL). Fresenius's product contains 100 mcg levothyroxine sodium in the total quantity per unit and has a concentration of 20 mcg/mL. However, Custopharm's product contains 100 mcg in the total quantity per unit but has a concentration of 100 mcg/mL. Thus, the products differ in concentration. Finally, Fresenius's levothyroxine sodium intravenous solution, 200 mcg/5 mL (40 mcg/mL), does not have the same strength as Custopharm's levothyroxine sodium intravenous solution (NDA 214253), 100 mcg/mL (100 mcg/mL). Fresenius's product contains 200 mcg levothyroxine sodium in the total quantity per unit and has a concentration of 40 mcg/mL. However, Custopharm's product contains 100 mcg in the total quantity per unit and has a concentration of 100 mcg/mL. Thus, the products differ in total drug content and concentration.

Accordingly, under the definition of "pharmaceutical equivalents" in 21 CFR 314.3(b), Custopharm's levothyroxine sodium intravenous solution product (NDA 214253), 100 mcg/mL (100 mcg/mL), is not pharmaceutically equivalent to any of Fresenius's levothyroxine sodium intravenous solution products (NDA 210632), 100 mcg/5 mL (20 mcg/mL), 200 mcg/5 mL (40 mcg/mL), and 500 mcg/5 mL (100 mcg/mL). Therefore, Custopharm is not required under FDA's regulations to identify a product approved under NDA 210632 as a listed drug relied upon.[19] Thus, FDA rejects your argument that the Agency must refuse to approve this 505(b)(2) application because it does not rely upon NDA 210632.[20]

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[16] Abbreviated New Drug Applications and 505(b)(2) Applications (80 FR 6802, 6816 (Feb. 5, 2015)). These considerations are also applicable to products approved under section 505(c) of the FD&C Act.

[17] *Id.*

[18] *See* Orange Book, Preface, at xvii (41st ed. 2021) ("[T]he strength of parenteral drug products generally is identified by both the total drug content and the concentration of drug substance in a container approved by FDA.").

[19] *See, e.g.*, 21 CFR 314.54(a)(1)(iii).

[20] To the extent that your Petition could be read to argue that a 505(b)(2) applicant must identify the closest pharmaceutical alternative as a listed drug relied upon where no pharmaceutical equivalent to the proposed drug product has been approved, we disagree. Neither the FD&C Act nor FDA's regulations require that a 505(b)(2) applicant identify the closest pharmaceutical alternative.

B. 505(b)(2) Application Filing

In your Petition, you note that the FD&C Act requires a 505(b)(2) applicant to certify as to each patent listed for a listed drug relied upon. You argue that an application that does not include all such patent certifications meets the conditions for refusing to file under 21 CFR 314.101(d)(3). (Petition at 6). You further argue that because Custopharm submitted its 505(b)(2) application referencing NDA 202231, and not NDA 210632, FDA should have refused to file the application.[21]

FDA Response

FDA may refuse to file a 505(b)(2) application that does not on its face contain required information (see 21 CFR 314.101(d)(3)). We do not agree, however, that we should refuse to file Custopharm's 505(b)(2) application for its levothyroxine sodium intravenous solution product because it does not cite a product approved under NDA 210632 as a listed drug relied upon. As explained above, Custopharm's levothyroxine sodium intravenous solution product is not pharmaceutically equivalent to any product approved under NDA 210632 and therefore, Custopharm is not obligated to identify a product approved under NDA 210632 as a listed drug relied upon. If there are no pharmaceutically equivalent drug products approved prior to the submission of its original 505(b)(2) application, Custopharm is obligated only to identify any listed drug relied upon in its drug development program and provide the relevant patent certifications for any such listed drug.

Furthermore, a 505(b)(2) applicant's failure to identify a listed drug, or identification of a listed drug that does not provide adequate support for its proposed product, generally would not be grounds for refusing to file an application. Rather, this would be a review issue that could preclude approval if the application were not amended to cite reliance on an appropriate listed drug or to include the data needed to meet the approval standard.

C. ANDA Receipt and Approval

Your Petition requests that the Agency refuse to file or approve any ANDA for a levothyroxine sodium intravenous solution product that does not rely on NDA 210632 (levothyroxine sodium intravenous solution).

FDA Response

As noted above, the products approved under both Fresenius's NDA 202231 and NDA 210632 currently are designated as RLDs in the Orange Book. The RLD is the listed drug to which an ANDA applicant must show its proposed generic drug is the same with respect to active ingredient(s), dosage form, route of administration, strength, labeling, and conditions of use, among other characteristics. FDA evaluates each

[21] You also assert that, if Custopharm's proposed product is a duplicate of a product approved under NDA 210632 and therefore eligible for approval under section 505(j) of the FD&C Act, that would be a basis for refusing to file Custopharm's 505(b)(2) NDA and Custopharm would be required to submit its application as an ANDA. (Petition at 6-7). FDA has determined, however, that Custopharm's product is not a duplicate of a listed drug (including any product approved under NDA 210632). Accordingly, Custopharm's application was properly filed as a 505(b)(2) NDA.

submitted ANDA individually to determine whether the ANDA can be received. The receipt of an ANDA means that FDA made a threshold determination that the ANDA is a substantially complete application, that is, an ANDA that on its face is sufficiently complete to permit a substantive review.[22] Sufficiently complete means that the ANDA contains all the information required under section 505(j)(2)(A) of the FD&C Act and does not contain a deficiency described in 21 CFR 314.101(d) and (e).[23]

Our regulations at 21 CFR 314.101 provide the regulatory authority by which FDA may in certain cases, and will in others, refuse to receive an ANDA that does not satisfy the criteria for a threshold determination that the application is substantially complete.[24]

FDA's decision to receive or refuse to receive a specific ANDA application, or to approve or not approve a specific application, will be based on the particular facts that are applicable to that application at the time of the decision.

IV. CONCLUSION

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

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300121270, cn=Douglas C. Throckmorton -S
Date: 2021.05.17 14:38:56 -04'00'

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

[22] *See* 21 CFR 314.101(b)(1) and 314.3(b).

[23] 21 CFR 314.3(b).

[24] *See* 21 CFR 314.101(d)-(e).