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BY ELECTRONIC SUBMISSION

Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Room 1061 (HFA-305)
Rockville, MD 20852

Citizen Petition

The undersigned submits this Citizen Petition pursuant to the Federal Food, Drug, and Cosmetic Act ("FDC Act") and in accordance with 21 C.F.R. §§ 10.25(a) and 10.30 to request that FDA amend the *Approved Drug Products with Therapeutic Equivalence Evaluations* ("Orange Book") to designate Docetaxel Injection, 20mg/ml, 80mg/4ml, and 160mg/8ml, approved under New Drug Application ("NDA") 205934 as an additional Reference Listed Drug ("RLD") and Reference Standard ("RS") because the labeling and formulation of the Docetaxel Injection approved under NDA 205934 differs from that of the existing RLDs.

I. ACTION REQUESTED

The undersigned respectfully requests that FDA designate NDA 205934 listed in the Orange Book for Docetaxel Injection, 20mg/ml, 80mg/4ml, and 160mg/8ml, as both an RLD and a RS for purposes of submitting an Abbreviated New Drug Application ("ANDA") for a generic version of the drug product.

II. STATEMENT OF GROUNDS

FDC Act § 505(j) allows the marketing of generic versions of previously approved drug products when the generic drug product is the subject of an ANDA. To obtain ANDA approval, the applicant must show, among other things, that with respect to a listed drug (i.e., a previously approved drug product), the generic drug product has the same active ingredient(s) in the same strength, dosage form and route of administration, has essentially identical labeling, and is bioequivalent.

A "listed drug" includes a new drug product that has an effective approval under FDC Act § 505(j), that has not been withdrawn or suspended under FDC Act §§ 505(e)(1) through (5) or (j)(5), and that has not been withdrawn from sale for reasons of safety or effectiveness. See 21 C.F.R. § 314.3. A listed drug, designated in FDA's Orange Book as "RLD," is the drug product on which an ANDA applicant should rely in seeking approval of an application.

FDA stated its policy for designating RLDs in the preamble to the Agency's 1992 final ANDA Regulations. Specifically, in response to comments asking FDA to explain how the Agency determines which drugs should be RLDs, FDA stated:

> FDA will designate [RLDs]. Generally, the [RLD] will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the [RLD] generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a [RLD], it should consult FDA.

FDA, Final Rule, ANDA Regulations, 57 Fed. Reg. 17,950, 17,958 (Apr. 28, 1992). In addition, FDA states in the preface to the Orange Book that:

> [I]n some instances when a listed drug is not designated as a [RLD], such listed drug may be shielded from generic competition. If FDA has not designated a [RLD] for a drug product the applicant intends to duplicate, the potential applicant may ask FDA to designate a reference listed drug for that drug product.

Orange Book, Preface, at x (40th ed. 2020). FDA guidance directs potential ANDA applicants to petition FDA to rely on a different RLD:

> If FDA has designated a listed drug as an RLD, but the potential applicant intends to refer to a different listed drug that is a pharmaceutical equivalent to the drug designated as an RLD, the potential applicant may submit a citizen petition under 21 CFR 10.25(a) and 10.30 to request that FDA designate that different listed drug as an additional RLD.

FDA, Draft Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions (Jan. 2017).

Similarly, a "reference standard," designated as "RS" in the Orange Book, is the product that an ANDA applicant must use to conduct in vivo bioequivalence testing required

for approval. Generally, FDA selects a single RS, which is usually the same as the RLD. FDA may select a new RS to further the submission and evaluation of generic drug applications. In determining whether to select a new RS, FDA will consider the marketing status of the RLD, the impact a new RS could have on preventing shortages, and the quantity of the current RS in distribution. See FDA, Draft Guidance for Industry, Referencing Approved Drug Products in ANDA Submissions, at 8-9 (Jan. 2017). A potential ANDA applicant may request FDA to select a new RS when another may be more appropriate or if there is no RS in the "Active Section" of the Orange Book. Requests for changes to FDA's selection of the RS because the applicant believes another RS is more appropriate requires the submission of a Citizen Petition to request that FDA select a different listed drug as an additional RS. See id. at 9.

Currently, there are two RLDs listed in the Orange Book for Docetaxel Injection 20 mg/mL: One-Vial Taxotere® (docetaxel) Injection, sponsored by Sanofi-Aventis U.S. LLC, which is approved by the FDA under NDA 20449, and Docetaxel Injection sponsored by Accord Healthcare and approved under NDA 201195. These products are both comprised of 395 mg dehydrated alcohol solution, requiring the inclusion of the following Warning and Precaution related to alcohol:

> Alcohol content: The alcohol content in a dose of Docetaxel Injection may affect the central nervous system. This may include impairment of a patient's ability to drive or use machines immediately after infusion

One-Vial Taxotere Prescribing Information § 5.13, NDA 20449 (May 2020); Docetaxel Injection Prescribing Information § 5.13, NDA 201195 (July 2020). The same warning can be found in the labeling for both RLDs.

Importantly, not all approved Docetaxel Injection products contain alcohol. NDA 205934, sponsored by Teikoku Pharma, contains no alcohol and was submitted through the 505(b)(2) pathway precisely because of "the lack of alcohol as an excipient." Summary Review, NDA 205934 (Dec. 22, 2015). Because of the proposed formulation differences, "the applicant proposed to omit the warning and precaution regarding alcohol content from the package insert." *Id.* FDA approved NDA 205934 without the alcohol warning in December 2015. The non-alcohol formulation is intended for patients who are more sensitive to alcohol. Clinical Pharmacology and Biopharmaceutics Review, NDA 205934 (Dec. 22, 2015). Identified in the Orange Book as "therapeutically equivalent" to the existing RLDs, FDA did not select NDA 205934 as an additional RLD.

Although NDA 205934 is considered "therapeutically equivalent" to them, NDA 205934 is different enough from the two identified RLDs that its sponsor sought approval through the 505(b)(2) pathway. The only difference between the products is the inactive ingredient, suggesting that Teikoku Pharma submitted a 505(b)(2) rather than an ANDA because FDA determined that the excipients substituted for alcohol were "non-exception"

excipients and the proposed drug product did not meet the requirement that "a drug product intended for parenteral use must contain the same active or inactive concentration as" the RLD under 21 C.F.R. § 314.94(a)(9)(iii). It follows that another ANDA applicant seeking approval of a non-alcohol version relying on the currently listed RLDs would not be able to meet that requirement either. But, from a process perspective and an access perspective, it makes little sense to subject products that cannot be quantitatively and qualitatively the same as the RLD to the more expensive and time-consuming 505(b)(2) pathway (that NDA 205934 was subject to) when FDA has already approved a product that ***can*** be used as the basis for an ANDA submission if FDA were to designate it as an RLD. Indeed, the purpose of the ANDA pathway is to allow putative generic sponsors to rely on FDA's findings of safety and effectiveness for identical products, and that is exactly what identifying NDA 205934 as an RLD would facilitate.

Though the formulation differences between the alcohol and non-alcohol Docetaxel Injection versions is limited to excipients, the excipient change has the effect of changing the degradation products of the reaction products of the active ingredient. As explained in FDA's guidance document ANDAs: Impurities in Drug Products (Nov. 2010), FDA expects that, when the acceptance criterion for a specified degradation product does not exist in the U.S. Pharmacopeia ("USP"), the acceptance criterion for that degradation product is qualified based on similarity to the RLD. FDA, Guidance for Industry, ANDAs: Impurities in Drug Products, 3 (Nov. 2010). "A degradation product present in the generic drug product is considered qualified if the amount of identified degradation product in the generic drug product is similar to the levels observed in the RLD." *Id*. at 5. In this instance, where no USP acceptance criterion exists for a degradation product not observed in the alcohol-based RLD, an ANDA sponsor would be required to qualify the degradation product by way of comparison to the RLD. However, the impurity profile pattern is different between the alcohol-based RLD and the non-alcohol-based formulation; this different degradation product renders comparison between the products challenging, if not impossible. Identifying NDA 205934 as an additional RLD would also address this issue, facilitating generic approval of a non-alcohol-based formulation.

There is, therefore, a sound basis for selecting NDA 205934 as a new RLD and RS. As the Agency notes in the Orange Book Preface, a listed drug not designated as an RLD or RS can be shielded from generic competition. Such is the case here for NDA 205934. Because the labeling, and formulation impurities of the Docetaxel Injection approved under NDA 205934 differ from the RLD, it currently faces no competition, and, without the identification of NDA 205934 as an RLD, no generic versions can come to market under the

ANDA pathway.[1] As such, in an effort to introduce competition to the market for the non-alcohol formulation, Docetaxel Injection, 20mg/ml, 80mg/4ml, and 160mg/8ml, approved under NDA 205934, should be identified as the RLD. It follows therefore that identification of that RLD as an RS for purposes of bioequivalence testing is appropriate. Further, the expansion of potential competition to generic non-alcohol formulations of this product would benefit the alcohol sensitive patient population. Accordingly, the undersigned requests that FDA designate in the Orange Book the Docetaxel Injection drug product approved under NDA 205934 as both an RLD and RS.

III. ENVIRONMENTAL IMPACT

An environmental assessment report on the action requested in this petition is not required under 21 C.F.R. § 25.31.

IV. ECONOMIC IMPACT

In accordance with 21 C.F.R. § 10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of the petition. Petitioner hereby commits to promptly provide this information, if so requested.

V. CERTIFICATION

The undersigned certifies that, to the best knowledge and belief of the undersigned, this petition includes all information and views on which the petition relies, and that it includes representative data and information known to the petitioner which is unfavorable to the petition.

Sincerely,

/s/ Sara Koblitz

Sara W. Koblitz

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[1] Notably, because a different excipient or impurity profile is not considered a "route of administration, dosage form, [or] strength," the submission of a suitability petition, permitting changes to ANDA labeling under 21 C.F.R. § 314.127(a)(7), is not permissible under 21 C.F.R. § 314.93(b).