Ravi Rangasami
Director
Hibrow Healthcare LLC
601 Carlson Parkway, Suite 1050
Minnetonka, MN 55305

Re: Docket No. FDA-2019-P-4424

Dear Mr. Rangasami: May 7, 2020

This letter responds to your citizen petition received on September 23, 2019 (Petition), requesting that the Food and Drug Administration (FDA or Agency) designate either abbreviated new drug application (ANDA) 074721, held by Lannett Company, Inc. (Lannett), or ANDA 071918, held by Wockhardt Bio AG (Wockhardt), for doxepin hydrochloride oral concentrate, equivalent to (EQ) 10 milligrams (mg) base/milliliters (mL), as a reference standard in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).[1] You also request that FDA determine that "Doxepin Hydrochloride Oral Concentrate Eq 10 mg base/mL were not voluntarily withdrawn for safety and efficacy reasons" (Petition at 1).

We have carefully considered the Petition. For the reasons described below, your Petition is granted to the extent that it requests that FDA select a new reference standard. FDA selects ANDA 074721 for doxepin hydrochloride oral concentrate, EQ 10 mg base/mL, held by Lannett, as the new reference standard. Additionally, as your Petition notes, FDA has already determined that the reference listed drug Sinequan (doxepin hydrochloride) oral concentrate, EQ 10 mg base/mL, was not withdrawn from sale for reasons of safety or effectiveness (Petition at 1).[2]

I. BACKGROUND

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (21 U.S.C. 355(j)) allows the submission of an ANDA to market a generic version of a previously approved drug product. To obtain approval, the ANDA applicant generally must show, among other things, that the generic drug product (1) has the same active ingredient(s), dosage form, route of administration, strength, conditions of use, and, with certain exceptions, labeling as a listed drug; and (2) is bioequivalent to the listed drug.

[1] The Orange Book is available at http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm.

[2] See "Determination That INVERSINE (Mecamylamine Hydrochloride) Tablet and Six Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness," 76 FR 45267 (July 28, 2011). In your Petition, you specifically request that FDA determine "whether the applicant holder's decision to discontinue marketing, as approved under ANDA 071609, was for reason for safety or effectiveness" (Petition at 2). FDA is not required to make and does not routinely make such determinations as to reference standards approved in ANDAs. Because your proposed ANDA seeks to reference the RLD and as noted, that determination has already been made as to the RLD, no additional decisions regarding the reasons for withdrawal of the reference standard are relevant or required at this time. Accordingly, FDA denies this specific request.

A *listed drug* is a new drug product that (1) has been approved under section 505(c) of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act; (2) whose approval has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(6) of the FD&C Act; and (3) that has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness.[3] Listed drug status is evidenced by the drug product's identification in the current edition of FDA's Orange Book as an approved drug.[4] A *reference listed drug* (RLD) is the listed drug identified by FDA as the drug product on which an applicant relies in seeking approval of its ANDA.[5] Generally, an RLD is a drug product approved in a new drug application (NDA) under section 505(c) of the FD&C Act based on full reports of investigations of safety and effectiveness.

A *reference standard* is the drug product selected by FDA that an applicant seeking approval of an ANDA must use in conducting an in vivo bioequivalence study required for approval.[6] FDA generally selects a single reference standard that ANDA applicants must use in any in vivo bioequivalence testing required for approval. A single reference standard ensures the greatest level of consistency between a generic drug and its RLD and among generic drugs. Generally, the RLD will be the drug product selected by the Agency as the reference standard for conducting in vivo bioequivalence testing.[7] In certain circumstances, however, the Agency may select a generic drug product as the reference standard for bioequivalence testing. For instance, if the RLD has been discontinued from marketing, FDA may select a therapeutically equivalent[8] generic drug product as the reference standard.[9]

II. DISCUSSION

In the Petition, you request that FDA designate ANDA 074721 for doxepin hydrochloride oral concentrate, EQ 10 mg base/mL, held by Lannett, or ANDA 071918 for doxepin hydrochloride oral concentrate, EQ 10 mg base/mL, held by Wockhardt, as the reference standard (Petition at 2). You state that the current reference standard for doxepin hydrochloride oral concentrate, EQ 10 mg base/mL, approved under ANDA 071609, held by Teva Pharmaceuticals USA, is not available in the market (Petition at 1). You also request that FDA determine that "Doxepin Hydrochloride Oral Concentrate Eq 10 mg base/mL were not voluntarily withdrawn for safety and efficacy reasons" (Petition at 1).

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[3] § 314.3(b) (21 CFR 314.3(b)).

[4] Id.

[5] Id.

[6] Id.

[7] § 314.94(a)(3) (21 CFR 314.94(a)(3)).

[8] "*Therapeutic equivalents* are 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." § 314.3(b).

[9] See "Abbreviated New Drug Applications and 505(b)(2) Applications," 81 FR 69580 at 69619 (October 6, 2016).

As a preliminary matter, we note that an RLD generally is a drug product approved under section 505(c) of the FD&C Act, based on full reports of investigations of safety and effectiveness. Accordingly, NDA 017516, held by Pfizer Inc., for Sinequan (doxepin hydrochloride) oral concentrate, EQ 10 mg base/mL, is the RLD and would be the basis for submission of an ANDA for doxepin hydrochloride oral concentrate, EQ 10 mg base/mL. The RLD is no longer being marketed and thus has been moved to the Orange Book's "Discontinued Drug Product List." As noted above, FDA has already determined that Sinequan (doxepin hydrochloride) oral concentrate, EQ 10 mg base/mL, was not withdrawn from sale for reasons of safety or effectiveness.[10] Because the RLD appears in the "Discontinued Drug Product List" section of the Orange Book, and because you state that the current reference standard is not available in the market, you are requesting that FDA designate a different generic drug product as the reference standard.

We have reviewed the information submitted in the docket, regulatory filings for the current reference standard, ANDA 071609, and third-party commercial data regarding doxepin hydrochloride oral concentrate, EQ 10 mg base/mL. Based on the information available to us, FDA concludes that ANDA 071609, the current reference standard, is no longer marketed. Therefore, we agree that you have stated grounds for selecting a new reference standard.[11]

In this instance, we have determined that it is appropriate to select ANDA 074721 for doxepin hydrochloride oral concentrate, EQ 10 mg base/mL, held by Lannett, as the new reference standard. It is therapeutically equivalent to the RLD, and it is the current market leader as determined by FDA on the basis of commercial data.

III. CONCLUSION

For the reasons described in this response, the Petition is granted to the extent that it requests that FDA select ANDA 074721 for doxepin hydrochloride oral concentrate, EQ 10 mg base/mL, held by Lannett, as the new reference standard.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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Date: 2020.05.07 09:43:48 -04'00'

Janet Woodcock, M.D.
Director
Center for Drug Evaluation and Research

[10] See footnote 2, *supra*.,

[11] See "Abbreviated New Drug Applications and 505(b)(2) Applications" 81 FR 69580 at 69619 (October 6, 2016).