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September 16, 2020

Re: Docket No. FDA-2019-P-4515

Dear Mr. Rosen:

This letter responds to your citizen petition received on September 26, 2019 (Petition), requesting that the Food and Drug Administration (FDA or Agency) designate propranolol hydrochloride tablets, 80 milligrams (mg), approved under abbreviated new drug application (ANDA) 070178 held by Watson Laboratories Inc. (Watson), as the new reference standard (RS) in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book).[1]

We have carefully considered the Petition. For the reasons described below, your Petition is granted.

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 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 the listed drug; and (2) is bioequivalent to the listed drug.

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of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act; (2) whose approval has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(6) of the FD&C Act; and (3) that has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness.[2] Listed drug status is evidenced by the drug product's identification in the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

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

[2] § 314.3(b) (21 CFR 314.3(b)).

[3] Id.

relies in seeking approval of its ANDA.[4] Generally, an RLD is a drug product approved in a new drug application (NDA) under section 505(c) of the FD&C Act.

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.[5] 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.[6] 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[7] generic drug product as the reference standard.[8]

II. DISCUSSION

In the Petition, you request that FDA designate propranolol hydrochloride tablets, 80 mg, approved under ANDA 070178 held by Watson as the new reference standard (Petition at 1). You state that the current reference standard is propranolol hydrochloride tablets, 80 mg, held by Impax Laboratories, Inc. (Impax), under ANDA 071976, and despite diligent efforts to obtain sufficient quantities of the current reference standard, samples are unavailable in the market to conduct the required studies (Petition at 1-2).

We have reviewed the information in the docket, regulatory filings for the current reference standard, and third-party commercial data regarding propranolol hydrochloride tablets, 80 mg. Based on this information, FDA concludes that the current reference standard, Impax's propranolol hydrochloride tablets, 80 mg, drug product is no longer available in the market. Therefore, we agree that you have stated grounds for selecting a new reference standard.[9]

In this instance, we have determined that it is appropriate to select ANDA 070178 held by Watson 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.

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[4] Id.

[5] Id.

[6] 21 CFR 314.94(a)(3).

[7] "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)).

[8] "Abbreviated New Drug Applications and 505(b)(2) Applications," 81 FR 69580, 69619 (Oct. 6, 2016).

[9] See 81 FR at 69619.

III. CONCLUSION

For the reasons described in this response, the Petition is granted.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
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