U.S. FOOD & DRUG ADMINISTRATION

DEC 13 2019

Blessy Johns
Director, Regulatory Affairs
Aurobindo Pharma USA, Inc.
279 Princeton-Hightstown Road
East Windsor, NJ 08520

Re: Docket No. FDA-2019-P-1607

Dear Ms. Johns:

This letter responds to your citizen petition received on April 2, 2019 (Petition). In the Petition you request that the Food and Drug Administration (FDA or the Agency) designate phenoxybenzamine hydrochloride capsules, United States Pharmacopeia (USP), 10 milligrams (mg), approved under abbreviated new drug application (ANDA) 204522 held by Par Pharmaceutical Inc. (Par), as a reference standard 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, and FDA will identify ANDA 204522 for phenoxybenzamine hydrochloride capsules, USP, 10 mg, held by Par, as the new reference standard.

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of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act; (2) whose approval has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(6) of the FD&C Act; and (3) that has not been withdrawn from sale for what FDA has determined are

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

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 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, under FDA regulations, ANDA applicants must use in any in vivo bioequivalence study required for approval.[6] 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 phenoxybenzamine hydrochloride capsules, USP, 10 mg, approved under ANDA 204522, held by Par as a reference standard. You state that the current reference standard and RLD, Dibenzyline (phenoxybenzamine hydrochloride) Capsules, 10 mg (Dibenzyline), approved under NDA 008708 held by Concordia Pharmaceuticals Inc., is not available in the market, or is available in such limited quantities as to prevent an ANDA applicant from obtaining sufficient quantities to conduct in vivo bioequivalence testing (Petition at 1, 3).

We have examined the issues presented in your Petition and have determined that you have stated grounds for FDA to select phenoxybenzamine hydrochloride capsules, USP 10 mg, approved under ANDA 204522 held by Par, as a reference standard. We agree that Dibenzyline is no longer available in the market. In this instance, based on the available information, it is appropriate to select phenoxybenzamine hydrochloride capsules, USP 10 mg, approved under ANDA 204522, as the new reference standard because it is therapeutically equivalent to Dibenzyline (phenoxybenzamine hydrochloride) Capsules, 10 mg (Dibenzyline), approved under

[2] § 314.3(b) (21 CFR 314.3(b)).

[3] Id.

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

NDA 008708, and it is the current market leader as determined by FDA on the basis of commercial data.[10]

III. CONCLUSION

For the reasons described in this response, the Petition is granted, and FDA will identify ANDA 204522 for, phenoxybenzamine hydrochloride capsules, USP, 10 mg, held by Par, as the new reference standard in the Orange Book.

Sincerely,

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

[10] FDA will not approve any ANDA if the RLD has been voluntarily withdrawn from sale and the agency has not determined whether the withdrawal is for safety or effectiveness reasons. See § 314.161 (21 CFR 314.161). We also note that "[a]n abbreviated new drug application that refers to ... a listed drug that has been voluntarily withdrawn from sale in the United States must be accompanied by a petition seeking a determination whether the listed drug was withdrawn for safety or effectiveness reasons." See § 314.122 (21 CFR 314.122).