Blessy Johns
US Agent for Aurobindo Pharma Limited
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Janelle Delk
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IQVIA RDS Inc.
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DEC 19 2019

Re: Docket Nos. FDA-2018-P-1892 and FDA-2019-P-4101

Dear Ms. Johns and Ms. Delk:

This letter responds to your citizen petitions received on May 15, 2018, (Aurobindo Petition) and August 30, 2019 (IQVIA Petition) (collectively, Petitions), requesting that the Food and Drug Administration (FDA or the Agency) select a new reference standard for Bentyl (dicyclomine hydrochloride) tablets, 20 milligrams (mg), approved under new drug application (NDA) 007409 held by Allergan Sales LLC (Allergan), in the *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).[1]

We have carefully considered the Petitions. For the reasons described below, your Petitions are granted. FDA will identify abbreviated new drug application (ANDA) 085223 held by Watson Laboratories Inc., as the new reference standard for this drug product.

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of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act; (2) whose approval has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(6) of the FD&C Act; and (3) that has not been withdrawn from sale for what FDA has determined are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

The Aurobindo Petition states that although not listed as discontinued in the Orange Book, the quantity of the reference standard, Bentyl, is so limited that a potential ANDA applicant is not able to obtain sufficient quantities to conduct required bioequivalence testing.[9] It further states that a non-availability statement received from the distributor indicates that the current reference standard is unavailable. Accordingly, the Aurobindo Petition requests that FDA select dicyclomine hydrochloride tablets, 20 mg, approved under ANDA 085223 held by Watson Laboratories Inc., or a suitable alternative, as the reference standard.[10]

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[2] § 314.3(b) (21 CFR 314.3(b)).

[3] Id.

[4] Id.

[5] Id.

[6] § 314.94(a)(3) (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] See preamble to the final rule, "Abbreviated New Drug Applications and 505(b)(2) Applications," 81 FR 69580, 69619 (Oct. 6, 2016) (Preamble to Final Rule).

[9] Aurobindo Petition at 1.

[10] Id.

The IQVIA Petition states that the current reference standard is not available on the market.[11] It notes that although Bentyl is not listed as discontinued in the Orange Book, the product is currently unavailable for sale according to the FDA's website on drug shortages.[12] As a result, the IQVIA Petition states that IQVIA's client is unable to proceed with the development of a generic product.[13] It requests that FDA select a suitable alternative reference standard. We note that the IQVIA Petition includes a table titled "Market Share Snapshot from January 2018 – March 2019" indicating that "Mylan Pharmaceuticals, Inc." had the highest market share during that time period but does not identify a preferred ANDA to be selected as a new reference standard.

We have reviewed the information in the docket, regulatory filings for Bentyl and commercial data regarding Bentyl and dicyclomine hydrochloride tablets. Based on this and other information available to the Agency, FDA concludes that Bentyl is unavailable in the market. Accordingly, FDA agrees that the Aurobindo Petition and the IQVIA Petition have stated grounds for the Agency to identify a new reference standard.[14]

In this instance, based on the available information, we have determined that it is appropriate to select ANDA 085223 for dicyclomine hydrochloride tablets, 20 mg, held by Watson Laboratories Inc., as the new reference standard because it is the current market leader as determined by FDA based on commercial data, and is therapeutically equivalent to the current reference standard (as indicated by the AB therapeutic equivalence code in the Orange Book). Therefore, ANDA 085223 will be identified as the new reference standard in the Orange Book. [15]

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[11] IQVIA Petition at 1.

[12] IQVIA Petition at 2. See FDA Drug Shortages database located at https://www.accessdata.fda.gov/scripts/drugshortages/default.cfm.

[13] IQVIA Petition at 1.

[14] See preamble to the final rule, "Abbreviated New Drug Applications and 505(b)(2) Applications," 81 FR 69580, 69619 (Oct. 6, 2016).

[15] We note that FDA will not approve any ANDA if the reference listed drug 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).

III. CONCLUSION

For the reasons described in this response, your Petitions are granted, and FDA will identify ANDA 085223 for dicyclomine hydrochloride tablets, 20 mg, as the new reference standard in the Orange Book.

Sincerely,

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