Blessy Johns
US Agent for Aurobindo Pharma Limited
279 Princeton-Hightstown Road
East Windsor, NJ 08520

September 8, 2020

Re: Docket No. FDA-2019-P-5237

Dear Ms. Johns:

This letter responds to your citizen petition received on November 5, 2019 (Petition), requesting that the Food and Drug Administration (FDA or the Agency) select a new reference standard for Augmentin XR (amoxicillin and clavulanate potassium) extended-release tablets 1000 milligrams (mg)/ 62.5 mg, approved under new drug application (NDA) 050785 held by Neopharma Inc. (Neopharma), 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. FDA will select abbreviated new drug application (ANDA) 090227 held by Sandoz Inc. (Sandoz), 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of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act; (2) whose approval has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(6) of the FD&C Act; and (3) that has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness.[2] Listed drug status is evidenced by the drug product's

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

[2] § 314.3(b) (21 CFR 314.3(b)).

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.

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 Petition states that although not listed as discontinued in the Orange Book, the quantity of the reference standard, Augmentin XR, 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 statement of non-availability of samples received from a distributor indicates that the current reference standard is unavailable. We note that the Petition includes an attachment containing a table titled "Amoxicillin and Clavulanate Potassium Extended Release Tablets 1000 mg/ 62.5 mg – US Market Data" indicating that Sandoz had the highest market share (at 100 percent) as of June 2019 and an emailed statement of non-availability for Augmentin XR from a third-party source, Symbio Generrics (I) Pvt. Limited. Accordingly, the Petition requests that FDA select amoxicillin and clavulanate potassium extended-release tablets, 1000 mg/ 62.5 mg, approved under ANDA 090227 held by Sandoz, as the reference standard.[10]

We have reviewed the information in the docket, regulatory filings for the current reference standard, Augmentin XR, and third-party commercial data regarding Augmentin XR. Based on the information available to us, FDA concludes that Augmentin XR is not available in the

[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).

[9] Petition at 1.

[10] Petition at 1-3.

market. 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 090227 for amoxicillin and clavulanate potassium extended-release tablets, 1000 mg/ 62.5 mg, held by Sandoz, as the new reference standard. NDA 050785 and ANDA 090227 are currently the only two approved applications for amoxicillin and clavulanate potassium extended-release tablets, 1,000 mg/ 62.5 mg. ANDA 090227 is therapeutically equivalent to the RLD, and it is the current market leader as determined by FDA on the basis of commercial data. Therefore, ANDA 090227 will be identified as the new reference standard in the Orange Book.[12]

## III. CONCLUSION

For the reasons described in this response, your Petition is granted, and FDA will select ANDA 090227 for amoxicillin and clavulanate potassium extended-release tablets, 1000 mg/ 62.5 mg, as the new reference standard in the Orange Book.

Sincerely,

Douglas C. Throckmorton -S

Digitally signed by Douglas C. Throckmorton -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300121270, cn=Douglas C. Throckmorton -S
Date: 2020.09.03 21:41:51 -04'00'

Patrizia Cavazzoni, M.D.
Acting Director
Center for Drug Evaluation and Research

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

[12] We note that FDA will not approve any ANDA that uses the reference standard to demonstrate bioequivalence until FDA determines that the RLD was not withdrawn for safety or effectiveness reasons. See § 314.161(a)(1) (21 CFR 314.161(a)(1)); § 314.122(c) (21 CFR 314.122(c)); § 314.127(a)(11) (21 CFR 314.127(a)(11)).