U.S. FOOD & DRUG ADMINISTRATION

NOV 26 2019

Timothy H. Kratz
George J. Barry III
Kratz & Barry LLP
1050 Crown Pointe Parkway, Suite 500
Atlanta, GA 30338

Kwok Hang Wu
Yiling Pharmaceutical Ltd.
5348 Vegas Drive
Las Vegas, NV 89108

Re: Docket Nos. FDA-2018-P-1263; FDA-2018-P-2901; and FDA-2019-P-2407

Dear Messrs. Kratz, Barry, and Wu:

This letter responds to Citizen Petition FDA-2018-P-1263, received on March 26, 2018; Citizen Petition FDA-2018-P-2901, received on July 26, 2018; and Citizen Petition FDA-2019-P-2407, received on May 15, 2019 (collectively referred to as Petitions). Petition FDA-2018-P-1263 (the First Rubicon Petition), submitted on behalf of Rubicon Research Private Limited (Rubicon), requests that the Food and Drug Administration (FDA or Agency) select a new reference standard in the *Approved Drug Products With Therapeutic Equivalence Evaluations* (the Orange Book) for diclofenac sodium delayed-release tablets, 25 milligrams (mg) and 50 mg, for purposes of submitting an abbreviated new drug application (ANDA).[1] Petition FDA-2018-P-2901 (the Yiling Petition), submitted on behalf of Yiling Pharmaceutical Ltd. (Yiling), requests that FDA select a new reference standard for diclofenac sodium delayed-release tablets, 25 mg, 50 mg, and 75 mg.[2] Petition FDA-2019-P-2407 (the Second Rubicon Petition), submitted on behalf of Rubicon, requests that FDA select a new reference standard for diclofenac sodium delayed-release tablets, 75 mg.

We have carefully considered your Petitions, including the Supplement to the First Rubicon Petition, dated May 30, 2018. For the reasons described below, your Petitions are granted.

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

[2] The Yiling Petition alternately mentions "75g, 50mg and 25mg" and "75mg, 50mg and 25mg" (Petition at 1). Because there is no approved product for 75 gram (g) diclofenac sodium delayed-release tablets listed in FDA's Orange Book, we interpret your request as directed to 75 mg, 50 mg, and 25 mg diclofenac sodium delayed-release tablets.

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

## 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 under section 505(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 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.[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]

---

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

## II. DISCUSSION

Currently, the Prescription Drug Product List (Active Section) of the Orange Book lists as reference standards diclofenac sodium delayed-release tablets, 25 mg and 50 mg, approved under ANDA 074376 held by CASI Pharmaceuticals Inc. (CASI), and diclofenac sodium delayed-release tablets, 75 mg, approved under ANDA 074394 held by CASI. The Discontinued Drug Product List of the Orange Book also currently lists as the RLD Voltaren (diclofenac sodium) delayed-release tablets, 25 mg, 50 mg, and 75 mg, approved under NDA 019201 held by Novartis.[10]

The First Rubicon Petition requests that FDA select diclofenac sodium delayed-release tablets, 25 mg and 50 mg, marketed under ANDA 090066 held by Unique Pharmaceutical Laboratories (Unique), as a new reference standard (First Rubicon Petition at 2). The First Rubicon Petition states that Rubicon has not been able to obtain sufficient quantities of the current reference standard, diclofenac sodium delayed-release tablets, 25 mg and 50 mg, approved under ANDA 074376 held by CASI (Supplement to First Rubicon Petition at 1-2).

The Second Rubicon Petition requests that FDA select diclofenac sodium delayed-release tablets, 75 mg, marketed under ANDA 077863 held by Unique, as a new reference standard (Second Rubicon Petition at 2). The Second Rubicon Petition states that Rubicon has concluded that the current reference standard, diclofenac sodium delayed-release tablets, 75 mg, approved under ANDA 074394, is not available on the market (Second Rubicon Petition at 2).

The Yiling Petition requests that FDA select a new reference standard for diclofenac sodium delayed-release tablets, 25 mg, 50 mg, and 75 mg. The Yiling Petition states that the current reference standard, diclofenac sodium delayed-release tablets, 50 mg, approved under ANDA 074376 held by CASI, has been discontinued and is unavailable on the market (Yiling Petition at 3-4).[11] The Yiling Petition further states that although the current reference standard, diclofenac sodium delayed-release tablets, 75 mg, approved under ANDA 074394 held by CASI, "is still available on the market . . . its manufacturing has also been stopped" (Yiling Petition at 4). The Yiling Petition does not specify which drug product should be selected as the new reference standard.

We have reviewed the information in the dockets, regulatory filings for the current reference standards, and third-party commercial data regarding diclofenac sodium

[10] FDA concluded that Novartis's NDA 019201 for Voltaren was not discontinued or withdrawn from sale for safety or effectiveness reasons. See *Determination That Protamine Sulfate Injection and 26 Other Drug Products Were Not Withdrawn From Sale for Reasons of Safety or Effectiveness,* 72 FR 28982 (May 23, 2007); *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).

[11] The Yiling Petition does not state whether Yiling has been able to obtain the current reference standard diclofenac sodium delayed-release tablets, 25 mg, approved under ANDA 074376 held by CASI.

delayed-release tablets. Based on this information, FDA concludes that the current reference standards for diclofenac sodium delayed-release tablets (ANDA 074376 held by CASI for 25 mg and 50 mg; and ANDA 074394 held by CASI for 75 mg) are unavailable in the market. Accordingly, FDA has determined it is appropriate for the Agency to identify a new reference standard.[12]

In this instance, we have determined that it is appropriate to select Unique's ANDA 090066 as the new reference standard for diclofenac sodium delayed-release tablets, 25 mg and 50 mg, and Unique's ANDA 077863 as the new reference standard for diclofenac sodium delayed-release tablets, 75 mg, because these are the current market leaders as determined by FDA based on commercial data.

## III. CONCLUSION

For the reasons described in this response, your Petitions are granted.

Sincerely,

Patricia Cavazzoni -s/-

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

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