March 26, 2020

Jayant Muley
General Manager, Regulatory Affairs
Encube Ethicals Private Limited
Unit 24, Steelmade Industrial Estate
Marol village, Andheri (E)
Mumbai, Maharashtra
India 400059

Re: Docket No. FDA-2019-P-2074

Dear Mr. Muley:

This letter responds to your citizen petition received on April 30, 2019 (Petition), requesting that the Food and Drug Administration (FDA or Agency) designate fluorouracil topical solution, 5%, approved under abbreviated new drug application (ANDA) 076526 fluorouracil topical solution, 5%, held by Taro Pharmaceutical Industries Ltd. (Taro), 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 to the extent that it requests that FDA select ANDA 076526 for fluorouracil topical solution, 5%, held by Taro, as a 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. [2]

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of the FD&C Act for safety and effectiveness or under section 505(j) of the FD&C Act; (2) whose approval has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(6) of the FD&C Act; and (3) that has not been withdrawn from sale for what FDA has determined are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

[2] See Section 505(j)(2) of the FD&C Act, §314.94 (21 CFR 314.94); see also §314.93 (21 CFR 314.93).

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 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.[6] FDA generally selects a single reference standard that ANDA applicants must use in any in vivo bioequivalence study required for approval.[7] 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.[8] 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[9] generic drug product as the reference standard.[10] FDA understands that even where an in vivo bioequivalence study is not required, a reference standard may also be useful for other purposes, such as product development.

II. DISCUSSION

In the Petition, you request that FDA designate fluorouracil topical solution, 5%, approved under ANDA 076526, held by Taro, as a reference standard (Petition at 1, 2). You state that the current reference standard and RLD, Efudex (Fluorouracil Topical Solution) 5% (Efudex), approved under NDA 016831 held by Valeant Pharmaceuticals International (Valeant),[11] 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, 2).

[3] § 314.3(b) (21 CFR 314.3(b)).

[4] Id.

[5] Id.

[6] Id.

[7] Id.

[8] § 314.94(a)(3) (21 CFR 314.94(a)(3)).

[9] "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)).

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

[11] Petitioner refers to the NDA holder as Valeant Pharmaceuticals International (Valeant) in the Petition, and Valeant was the named holder of NDA 016831 in Orange Book until recently. Valeant now operates under the name Bausch Health, and The Orange Book has been updated to reflect this.

We have reviewed the information in the docket, regulatory filings for the current RLD/reference standard, and third party commercial data regarding fluorouracil topical solution, 5%. Based on this, and other information available to the Agency, FDA concludes that the RLD/reference standard Efudex, fluorouracil topical solution, 5%, is unavailable in the market. Accordingly, FDA agrees that you have stated grounds for the Agency to identify a new reference standard.

In this instance, we have determined that it is appropriate to select ANDA 076526 , as the new reference standard for fluorouracil topical solution, 5%, because it is therapeutically equivalent to Efudex (Fluorouracil Topical Solution), 5%, approved under NDA 016831, and it is the current market leader as determined by FDA on the basis of commercial data.[12]

III. CONCLUSION

For the reasons described in this response, the Petition is granted to the extent that it requests that FDA select ANDA 076526 for, fluorouracil topical solution, 5%, held by Taro, as a reference standard.

Sincerely,

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

[12] 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).