FDA U.S. FOOD & DRUG ADMINISTRATION

DEC 0 2 2016

Melissa Klesch
Baxter Healthcare Corporation
32650 N. Wilson Road, WG1-3
Round Lake, IL 60073

Re: Docket No. FDA-2016-P-1547

Dear Ms. Klesch:

This letter responds to your citizen petition received on June 8, 2016 (Petition), requesting that the Food and Drug Administration (FDA or Agency) designate levofloxacin injection in dextrose 5% in plastic container, approved under abbreviated new drug application (ANDA) 090343 held by ACS Dobfar, as a "reference listed drug" (RLD) 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.

## 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 that (1) has been approved under section 505(c) of the FD&C Act for safety and effectiveness or has been approved under section 505(j); (2) has not been withdrawn or suspended under section 505(e)(1) through (e)(5) or (j)(6) of the FD&C Act; and (3) has not been withdrawn from sale for what FDA has determined are reasons of safety or effectiveness.[2] Listed drug status is reflected by the drug product's identification as a drug with an effective approval in FDA's Orange

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

[2] § 314.3(b) (21 CFR 314.3(b)). The definition of *listed drug* in § 314.3(b) refers to section 505(j)(5) of the FD&C Act with respect to withdrawal or suspension of a drug product approved under section 505(j). We note that since this regulation was issued, paragraph (j)(5) was redesignated as paragraph (j)(6) (see section 119(b) of the Food and Drug Administration Modernization Act, Public Law 105-115).

Book.[3] An *RLD* is the listed drug identified by FDA as the drug product on which an ANDA applicant relies in seeking approval of its application.[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 to support approval.[5] Generally, the RLD will be the drug product selected by the Agency as the reference standard for conducting bioequivalence testing.[6] In certain circumstances, however, the Agency may designate a generic drug product as the reference standard for bioequivalence testing. For instance, if the RLD has been discontinued from marketing, FDA may designate a therapeutically equivalent[7] generic drug product as the reference standard.[8]

## II. DISCUSSION

In the Petition, you request that FDA designate levofloxacin injection in dextrose 5% in plastic container, approved under ANDA 090343 held by ACS Dobfar, as an additional "RLD" (Petition at 1). You state that while the product currently designated as the RLD is Levaquin (levofloxacin) Injection in Dextrose 5% in Plastic Container (held by Janssen Pharmaceuticals under NDA 020635), this product is not currently available for evaluation/comparison for development of a generic product, due to its market withdrawal (Petition at 1). You further state that there are generic products listed in the Orange Book with the same strengths, dosage form, and route of administration as the

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[3] § 314.3(b).

[4] Id.

[5] See Letter from Janet Woodcock, M.D., Director, Center for Drug Evaluation and Research, FDA to Paul A. Braier, Ph.D., Esq., Greenblum & Bernstein, P.L.C., Docket No. FDA-2014-P-0417 (Sept. 5, 2014) (Sept. 5, 2014, Petition Response).

[6] § 314.94(a)(3) (21 CFR 314.94(a)(3)).

[7] According to the Orange Book,

> FDA classifies as therapeutically equivalent those products that meet the following general criteria: (1) they are approved as safe and effective; (2) they are pharmaceutical equivalents in that they (a) contain identical amounts of the same active drug ingredient in the same dosage form and route of administration, and (b) meet compendial or other applicable standards of strength, quality, purity, and identity; (3) they are bioequivalent in that (a) they do not present a known or potential bioequivalence problem, and they meet an acceptable *in vitro* standard, or (b) if they do present such a known or potential problem, they are shown to meet an appropriate bioequivalence standard; (4) they are adequately labeled; (5) they are manufactured in compliance with Current Good Manufacturing Practice regulations.

Orange Book at vii, available at: http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/UCM071436.pdf.

[8] See Sept. 5, 2014, Petition Response.

RLD, including products approved under ANDA 090343 held by ACS Dobfar (Petition at 1).

As a preliminary matter, we note that an RLD generally is a drug product approved under section 505(c) of the FD&C Act based on full reports of investigations of safety and effectiveness. Accordingly, each of the strengths approved under Janssen Pharmaceuticals' NDA 020635 for Levaquin (levofloxacin) Injection in Dextrose 5% in Plastic Container (Eq 250 mg/50 mL (5 mg/mL), Eq 500 mg/100 mL (5 mg/mL), and Eq 750 mg/150 mL (5 mg/mL)) is an RLD and would be the basis for submission of an ANDA for the same strength of levofloxacin injection in dextrose 5% in plastic container. Because these RLDs have been moved to the Discontinued Drug Product List section of the Orange Book, and you are requesting that FDA designate a generic drug product as an RLD, we interpret your request as a request to designate a therapeutically equivalent product as a reference standard for a proposed generic drug product to use in conducting in vivo bioequivalence studies to support approval.

We have examined the issues presented in your Petition and have determined that you have stated grounds to designate each of the strengths of levofloxacin injection in dextrose 5% in plastic container (Eq 250 mg/50 mL (5 mg/mL), Eq 500 mg/100 mL (5 mg/mL), and Eq 750 mg/150 mL (5 mg/mL)), approved under ANDA 090343 held by ACS Dobfar, as a reference standard. The three strengths of Janssen Pharmaceuticals' Levaquin (levofloxacin) Injection in Dextrose 5% in Plastic Container (Eq 250 mg/50 mL (5 mg/mL), Eq 500 mg/100 mL (5 mg/mL), and Eq 750 mg/150 mL (5 mg/mL)) have been discontinued, and thus we have moved these strengths to the Discontinued Drug Product List section of the Orange Book.[9] When an RLD has been moved to the Discontinued Drug Product List section of the Orange Book, it is generally appropriate for FDA to designate a therapeutically equivalent product as a reference standard. In this instance, based on available information, it is appropriate to designate these three strengths of levofloxacin injection in dextrose 5% in plastic container (Eq 250 mg/50 mL (5 mg/mL), Eq 500 mg/100 mL (5 mg/mL), and Eq 750 mg/150 mL (5 mg/mL)), approved under ANDA 090343 held by ACS Dobfar, as reference standards because ANDA 090343 is the market leader as determined by FDA on the basis of commercial data.[10] Therefore, we will designate levofloxacin injection in dextrose 5% in plastic container, approved under ANDA 090343 (Eq 250 mg/50 mL (5 mg/mL), Eq 500 mg/100 mL (5 mg/mL), and Eq 750 mg/150 mL (5 mg/mL)), held by ACS Dobfar, as reference standards.

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[9] FDA has issued a Federal Register notice announcing its determination that Levaquin (levofloxacin) Injection in Dextrose 5% in Plastic Container (Eq 250 mg/50 mL (5 mg/mL), Eq 500 mg/100 mL (5 mg/mL), and Eq 750 mg/150 mL (5 mg/mL)) (NDA 020635) were not withdrawn from sale for reasons of safety or effectiveness. See 81 Fed. Reg. 81780 (Nov. 18, 2016).

[10] *See, e.g., Abbreviated New Drug Application Regulations, Final Rule*, 57 FR 17950, 17958 (April 28, 1992).

## III. CONCLUSION

For the reasons described in this response, the Petition is granted.

Sincerely,

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