DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

DEC 20 2013

Kurt R. Karst
Hyman, Phelps & McNamara, P.C.
700 Thirteenth St., NW
Suite 1200
Washington, DC 20005

Re: Docket Nos. FDA-2013-P-0848 and FDA-2013-P-0849

Dear Mr. Karst:

This letter responds to the two citizen petitions you submitted on July 11, 2013, in the dockets noted above. The petition in Docket No. FDA-2013-P-0848 (Oxacillin Petition) requests that the Food and Drug Administration (FDA or the Agency) designate abbreviated new drug application (ANDA) 062737 (ADD-Vantage Oxacillin), held by Sandoz, Inc., as an additional reference listed drug (RLD) for oxacillin sodium injection, 1 gram (g) and 2 g. The petition in Docket No. FDA-2013-P-0849 (Ampicillin Petition) requests that FDA designate ANDA 062738 (ADD-Vantage Ampicillin), held by Sandoz, Inc., as an additional RLD for ampicillin sodium injection, 1 g and 2 g. You state that you have made these requests so that ANDAs may be submitted for generic versions of these drug products.

We have carefully considered your petitions and other information available to us. Because both petitions raise similar issues, we are consolidating our response. For the reasons stated below, the petitions are granted.

I. BACKGROUND

A. Reference Listed Drugs

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)[1] allows the marketing of generic versions of previously approved drug products when the generic drug product is the subject of an approved ANDA. To obtain approval, an ANDA applicant must demonstrate, among other things, that with respect to a listed drug (i.e., a previously approved drug product), the generic drug product is bioequivalent and has the same active ingredient, conditions of use, route(s) of administration, dosage form, strength, and labeling (with certain permissible differences), unless a petition for certain changes is approved by the Secretary.[2]

[1] Section 505 of the FD&C Act appears in the United States Code at 21 U.S.C. 355.

[2] See sections 505(j)(2)(A), (j)(2)(C), and (j)(4) of the FD&C Act.

A *listed drug* is a new drug product that has an effective approval under section 505(c) of the FD&C Act for safety and effectiveness or under section 505(j), that has not been withdrawn or suspended under sections 505(e)(1) through (5) or (j)(5) of the FD&C Act, and that has not been withdrawn from sale for reasons of safety or effectiveness.[3] Listed drugs are identified as drugs with an effective approval in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the Orange Book).[4] 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.[5]

As you note in your petitions, our policy on the designation of RLDs is stated in the preamble to the 1992 final rule establishing the requirements for ANDAs.[6] In response to comments asking us to explain how we determine which drugs should be RLDs, we stated: [7]

> FDA will designate all reference listed drugs. Generally, the reference listed drug will be the NDA drug product for a single source drug product. For multiple source NDA drug products or multiple source drug products without an NDA, the reference listed drug generally will be the market leader as determined by FDA on the basis of commercial data. FDA recognizes that, for multiple source products, a product not designated as the listed drug and not shown bioequivalent to the listed drug may be shielded from direct generic competition. If an applicant believes that there are sound reasons for designating another drug as a reference listed drug, it should consult FDA.

B. Orange Book Listings for Oxacillin Sodium Injection, 1 g and 2 g, and Ampicillin Sodium Injection, 1 g and 2 g

As described above, the Orange Book identifies drug products approved on the basis of safety and effectiveness by FDA under the FD&C Act. The Orange Book also contains therapeutic equivalence evaluations for approved multisource prescription drug products. These evaluations have been prepared to serve as public information and advice to state health agencies, prescribers, and pharmacists to promote public education in the area of drug product selection and to foster containment of health care costs.[8] With respect to

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[3] See 21 CFR 314.3.

[4] See id. The Orange Book is available at http://www.fda.gov/Drugs/default.htm.

[5] See the Orange Book Preface available at http://www.fda.gov/Drugs/DevelopmentApprovalProcess/ucm079068.htm.

[6] See 57 FR 17950 (April 28, 1992).

[7] See 57 FR at 17958.

[8] See the Orange Book Preface.

therapeutic equivalence evaluations of parenteral products,[9] the Orange Book Preface explains:

> It should be noted that even though injectable (parenteral) products under a specific listing may be evaluated as therapeutically equivalent, there may be important differences among the products in the general category, *Injectable; Injection*. For example, some injectable products that are rated therapeutically equivalent are labeled for different routes of administration. In addition, some products evaluated as therapeutically equivalent may have different preservatives or no preservatives at all. Injectable products available as dry powders for reconstitution, concentrated sterile solutions for dilution, or sterile solutions ready for injection are pharmaceutical alternative drug products. They are not rated as therapeutically equivalent (AP) to each other even if these pharmaceutical alternative drug products are designed to produce the same concentration prior to injection and are similarly labeled. Consistent with accepted professional practice, it is the responsibility of the prescriber, dispenser, or individual administering the product to be familiar with a product's labeling to assure that it is given only by the route(s) of administration stated in the labeling.

The Orange Book identifies the following drug product as the RLD for oxacillin sodium injection, 1 g and 2 g:

Application Type and Number	**Drug Name**	**Strengths**	**Routes of Administration**	**Whether AP-rated to ADD-Vantage Oxacillin**
ANDA 061490	Oxacillin sodium	1 g and 2 g	Intramuscular (IM) and intravenous (IV)	Yes

The Orange Book identifies the following drug product as the RLD for ampicillin sodium injection, 1 g and 2 g:

Application Type and Number	**Drug Name**	**Strengths**	**Routes of Administration**	**Whether AP-rated to ADD-Vantage Ampicillin**
ANDA 061395	Ampicillin sodium	1 g and 2 g	IM and IV	Yes

II. DISCUSSION

In the Oxacillin Petition, you state that the currently designated RLD for oxacillin sodium injection, 1 g and 2 g, is ANDA 061490, which is in a glass flip-top vial approved for both IM and IV administration (Oxacillin Petition at 2). You state that ADD-Vantage

[9] Parenteral products that are pharmaceutically equivalent and have no known or suspected bioequivalence problems are considered to be therapeutically equivalent and are rated AP to each other.

Oxacillin is bioequivalent to ANDA 061490 but uses the ADD-Vantage container/closure system and is approved for IV administration only. Given the difference in container/closure and route of administration, you state that ADD-Vantage Oxacillin should also be designated as an RLD to allow generic competition against that product (Oxacillin Petition at 3).

In the Ampicillin Petition, you present a similar argument. You note that the current RLD for ampicillin sodium injection, 1 g and 2 g, is ANDA 061395, which is in a glass flip-top vial approved for IM and IV administration (Ampicillin Petition at 2). You state that ADD-Vantage Ampicillin is bioequivalent to ANDA 061395 but uses the ADD-Vantage container/closure system and is approved for IV administration only. In light of the difference in container/closure and route of administration, you state that ADD-Vantage Ampicillin should also be designated as an RLD to allow generic competition against that product (Ampicillin Petition at 3).

We have examined the issues presented in both petitions and have determined that you have stated grounds establishing that it is in the public interest to allow the submission of ANDAs that cite ADD-Vantage Oxacillin or ADD-Vantage Ampicillin as the RLD. Even though both products are rated as therapeutically equivalent to currently designated RLDs, the products could nonetheless be shielded from direct generic competition because, unlike the current RLDs, they are approved for IV administration only and use the unique ADD-Vantage container/closure system.[10] Therefore, consistent with the policy stated in the 1992 final rule, we will designate ADD-Vantage Oxacillin and ADD-Vantage Ampicillin as RLDs for oxacillin sodium injection, 1 g and 2 g, and ampicillin sodium injection, 1 g and 2 g, respectively.

III. CONCLUSION

For the reasons stated above, your petitions are granted.

Sincerely,

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

[10] Generic drug products are not required to use the same container/closure as the RLD on which they are based. Generic drug products are, however, required to have the same labeling as the RLD (with certain permissible differences). In some cases, use of a unique container/closure system for a drug product may require specialized instructions in the labeling. If an RLD uses such a container/closure, then it may also be necessary for a generic version of that product to use the same container/closure system to ensure that the labeling is the same for both products. Likewise, if an RLD uses a conventional container, a generic version could not use a unique container/closure system that would require specialized instructions in the labeling.