DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave
Building 51
Silver Spring, MD 20993

NOV 1 2013

Joan Janulis, R.A.C.
Vice President
Lachman Consultant Services, Inc.
1600 Stewart Avenue
Westbury, NY 11590

Re: Docket No. FDA-2013-P-0493

Dear Ms. Janulis:

This letter responds to your citizen petition dated April 23, 2013, requesting that the Food and Drug Administration (FDA or the Agency) designate AK-Fluor® 25% (fluorescein sodium) Injection, equivalent to (eq.) 250 milligrams/milliliters (mg/mL) (new drug application (NDA) 022186), manufactured by Akorn, Inc. (Akorn), as a second reference listed drug (RLD) for fluorescein sodium injectable drug products. At this time, the only reference listed fluorescein sodium injectable drug product is Fluorescite 10% (fluorescein sodium) Injection eq. 100 mg/mL, manufactured by Alcon Pharms. Ltd. (Alcon). Thus, currently there is no RLD for a 25% dosage strength fluorescein sodium product. For the reasons stated below, your petition is granted.

I. BACKGROUND

A. Reference Listed Drugs

Section 505(j) of the Federal Food, Drug, and Cosmetic Act (the FD&C Act) (21 U.S.C. 355(j)) allows the marketing of generic versions of previously approved drug products when the generic drug product is the subject of an approved abbreviated new drug application (ANDA).[1] To obtain approval, the ANDA applicant must show, among other things, that with respect to a listed drug (i.e., a previously approved drug product), the generic drug product (1) has the same active ingredient(s) in the same strength, (2) has the same labeling (with certain permissible differences), and (3) is bioequivalent.[2]

A listed drug is a 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section 505(c) of the FD&C Act for safety and effectiveness, or under section 505(j) of the FD&C Act, that has not been withdrawn or suspended under section 505(e)(1) through (5) or (j)(5) of the FD&C Act, and that has not been withdrawn from sale for reasons of safety or effectiveness.[3] Listed drugs are

[1] The term *generic* is used in this petition response to refer to drug products for which approval is sought in an ANDA submitted under section 505(j) of the FD&C Act.

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

[3] See 21 CFR 314.3.

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]

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 reference listed drugs, 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 Fluorescein Sodium Injection

As described above, the Orange Book identifies drug products approved by FDA under the FD&C Act on the basis of safety and effectiveness.. 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 therapeutic equivalence evaluations of injectable 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

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

[5] See 21 CFR 314.3; see also 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 17950 at 17958.

[8] See the Orange Book Preface.

[9] Parenteral products that are pharmaceutically equivalent (i.e., have the same active ingredient, dosage form, strength, and route of administration) and have no known or suspected bioequivalence problems are considered to be therapeutically equivalent and are rated AP to each other.

(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 two active NDAs for fluorescein sodium injectable drug products:

Application No.	Applicant	Product(s)
NDA 022186	Akorn	AK-Fluor 10% (fluorescein sodium) Injection, eq. 100 mg/mL
		AK-Fluor 25% (fluorescein sodium) Injection, eq. 250 mg/mL
NDA 021980	Alcon	Fluorescite 10% Injection, eq. 100 mg/mL

Alcon's Fluorescite 10% (fluorescein sodium) Injection, eq. 100 mg/mL, is the only product designated as an RLD for fluorescein sodium injectable products.

II. DISCUSSION

In your petition, you note that there is no designated RLD for the 25% dosage strength of fluorescein sodium injection listed in the Orange Book. You state that unless FDA designates Akorn's AK-Fluor 25% drug product (NDA 022186) as an RLD, a generic applicant cannot submit an ANDA for that dosage strength of the product; thus, effectively shielding Akorn's AK-Fluor 25% (fluorescein sodium) Injection from generic competition.

We have examined the issues presented in your petition and determined that you have stated grounds establishing that it is in the public interest to allow the submission of ANDAs that cite AK-Fluor 25% (fluorescein sodium) Injection as the RLD. Therefore, consistent with the policy stated in the 1992 final rule, we will designate Akorn's AK-Fluor 25% (fluorescein sodium) Injection, eq. 250 mg/mL (NDA 022186), as an RLD.

III. CONCLUSION

For the reasons stated above, your petition is granted.

Sincerely,

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