DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Rockville MD 20857

FEB 27 2014

Edward J. Pardon
Merchant & Gould
10 East Doty Street, Suite 600
Madison, WI 53703-3376

Re: Docket No. FDA-2013-P-0203

Dear Mr. Pardon:

This letter responds to your citizen petition that we received on February 19, 2013 (Petition), submitted on behalf of an unnamed client. You ask the Food and Drug Administration (FDA) to consider the petitioner's proposed formulation of voriconazole for injection 200 milligrams (mg)/vial as appropriate for submission as an abbreviated new drug application (ANDA) under section 505(j) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), even though the proposed formulation contains an inactive ingredient that differs from the reference listed drug (RLD) by means other than a different preservative, buffer, or antioxidant. You therefore ask that FDA refrain from enforcing its so-called "exception excipient" regulations to permit a "non-exception excipient" change from the RLD. For the reasons discussed below, your Petition is denied.

I. BACKGROUND

A. Voriconazole

Vfend I.V. (voriconazole) for Injection, 200 mg/vial, approved under new drug application (NDA) 021267, is a parenteral drug product intended for intravenous administration. It is supplied in a single-use vial as a sterile lyophilized powder equivalent to 200 mg of voriconazole (the active ingredient) and 3,200 mg of sulfobutyl ether β-cyclodextrin sodium (SBEβCD) (an inactive ingredient). Voriconazole is a broad spectrum triazole antifungal agent indicated for the treatment of invasive aspergillosis; candidemia (nonneutropenics) and disseminated candidiasis in skin, abdomen, kidney, bladder wall, and wounds; esophageal candidiasis; and serious infections caused by *Scedosporium apiospermum* and *Fusarium* spp., including *Fusarium solani*, in patients intolerant of, or refractory to, other therapy.

B. ANDAs — Legal and Regulatory Background

The Drug Price Competition and Patent Term Restoration Act of 1984 (the Hatch-Waxman Amendments) created section 505(j) of the FD&C Act (21 U.S.C. 355(j)),

which established the current ANDA approval process. An ANDA applicant does not have to submit clinical studies to demonstrate the safety and effectiveness of a drug product. Instead, an ANDA applicant relies on FDA's previous finding that the RLD is safe and effective.[1] To rely on FDA's previous finding of safety and effectiveness, an ANDA applicant must demonstrate, among other things, that its drug product is bioequivalent to the RLD as required by section 505(j)(2)(A)(iv) of the FD&C Act. In addition, an ANDA applicant must provide sufficient information to show that the generic drug product has the same active ingredient(s), dosage form, route of administration, and strength as the RLD (section 505(j)(2)(A)(iii) and (j)(4)). An ANDA applicant must also demonstrate that its product has (with certain permissible differences) the same labeling as the RLD (section 505(j)(2)(A) and (j)(4)). The Agency must approve an ANDA unless it finds, among other things, the ANDA applicant has not provided sufficient evidence of the foregoing, or if the methods used in, or the facilities and controls used for, the manufacture, processing, and packing of the drug are inadequate to assure and preserve its identity, strength, quality, and purity (section 505(j)(4) of the FD&C Act).

The scientific premise underlying the Hatch-Waxman Amendments is that when certain aspects of the drug products (e.g., active ingredient(s), strength, dosage form, route of administration) are the same, the products may be substituted for each other.[2]

C. ANDAs for Parenteral Drug Products

Section 505(j)(4)(H) of the FD&C Act provides that FDA shall approve an ANDA for a drug unless, among other things, "information submitted in the application or any other information available to the Secretary shows that (i) the inactive ingredients of the drug are unsafe for use under the conditions prescribed, recommended, or suggested in the labeling proposed for the drug, or (ii) the composition of the drugs is unsafe under such conditions because of the type or quantity of inactive ingredients included or the manner in which the inactive ingredients are included." Consistent with the statute, FDA has issued implementing regulations on inactive ingredients in products proposed in ANDAs. In general, an ANDA may have different inactive ingredients from the RLD as long as the ANDA demonstrates that the different inactive ingredients do not affect the safety or efficacy of the proposed drug product (21 CFR 314.94(a)(9)(ii)). However, for ANDAs for parenteral drug products, the only differences in inactive ingredients that are routinely permitted are changes in a preservative, a buffer, or an antioxidant. FDA's regulation at § 314.94(a)(9)(iii) concerning the content and format of an ANDA states the following:

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[1] A reference listed drug or RLD is "the listed [i.e., approved] drug identified by FDA as the drug product upon which an applicant relies in seeking approval of its abbreviated application" (21 CFR 314.3). RLDs are identified in FDA's *Approved Drug Products With Therapeutic Equivalence Evaluations* (generally known as the "Orange Book"), 33rd edition.

[2] FDA classifies as therapeutic equivalents products that (1) are approved as safe and effective; (2) 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) are bioequivalent; (4) are adequately labeled; and (5) are manufactured in compliance with Current Good Manufacturing Practice regulations. Orange Book at vii.

> Generally, a drug product intended for parenteral use shall contain the same inactive ingredients and in the same concentration as the reference listed drug identified by the applicant. . . . However, an applicant may seek approval of a drug product that differs from the reference listed drug in preservative, buffer, or antioxidant provided that the applicant identifies and characterizes the differences and provides information demonstrating that the differences do not affect the safety or efficacy of the proposed drug product.

The corresponding provision that addresses the refusal to approve an ANDA, 21 CFR 314.127(a)(8)(ii)(B), provides the following:

> FDA will consider an active ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the [ANDA] unless it contains the same inactive ingredients, other than preservatives, buffers, and antioxidants, in the same concentration as the listed drug, and if it differs from the listed drug in a preservative, buffer, or antioxidant, the application contains sufficient information to demonstrate that the difference does not affect the safety or efficacy of the drug product.

These provisions require ANDAs for parenteral products to contain the same inactive ingredients, in the same concentrations, as the reference listed drug with the exception of preservatives, buffers, and antioxidants (so-called "exception excipients"). They also require applicants to demonstrate that any differences in the stated exception excipients do not affect the safety or efficacy of the drug product.

In addition, an applicant may request that FDA waive certain regulatory requirements for drug applications, including ANDAs. The Agency may waive certain regulatory requirements in part 314 (21 CFR part 314) pertaining to ANDAs if the Agency finds that the applicant's compliance with the regulatory requirement is unnecessary for the Agency to evaluate the application or compliance cannot be achieved, the applicant's alternative submission satisfies the requirement, or the applicant's submission otherwise justifies the waiver (§§ 314.99(b) and 314.90). As explained more below, in the past, the Agency has waived the inactive ingredient sameness requirements in very limited circumstances (not applicable here) as long as the statutory standard for safety of inactive ingredients and other requirements for approval were met.

II. DISCUSSION

In the Petition, you ask FDA to waive the application of the inactive ingredient requirements using the general waiver authority in §§ 314.90 and 314.99. Specifically, you request that FDA consider the petitioner's proposed formulation as appropriate for submission as an ANDA, even though the proposed formulation contains a different inactive ingredient that is not an exception excipient under § 314.94(a)(9)(iii) (i.e., preservative, buffer, or antioxidant) (Petition at 1). According to the Petition, the proposed product contains a different solubilizing agent than the solubilizing agent in the RLD: hydroxypropyl b-cyclodextrin (HPβCD) instead of SBEβCD. You state that the proposed product is otherwise identical to the RLD, containing the same active ingredient in the same quantity, same route of administration, dosage form, strength, and conditions

of use (Petition at 5). You explain that in this instance, compliance with the inactive ingredient sameness requirement is unnecessary because HPβCD is from the same group of compounds as SBEβCD (Petition at 8) and the petitioner's submission otherwise justifies a waiver of the inactive ingredient sameness requirement because there are sufficient data demonstrating that the proposed product is as safe and effective as the RLD formulation (Petition at 10). You include information related to, among other things, the mechanism of action of the active ingredient, pharmacokinetic profiles and toxicity of the inactive ingredients, previously approved products, and therapeutic effect.

As explained above, drug products for parenteral use must contain the same inactive ingredients as the RLD, except that an inactive ingredient may differ if it is a preservative, buffer, or antioxidant, provided that the applicant demonstrates the safety and efficacy of the proposed product (see section I.C above; §§ 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B)). The regulations governing inactive ingredients in parenteral drug products were issued to address particular safety concerns posed by those products. In addressing comments on proposed § 314.127 regarding changes in inactive ingredients, the Agency noted in the preamble of the final rule that under the statute, the inquiry is whether these inactive ingredients are "safe under the conditions prescribed, recommended, or suggested in the labeling" and that the regulation "reflects this concern, which is particularly acute for parenteral drug products" (57 FR 17950 at 17970, April 28, 1992).

In light of the heightened safety concerns for parenteral products, as reflected in the regulations, FDA places more stringent limitations on the variations permitted in inactive ingredients for those products. You note that FDA has waived the inactive ingredient regulations for parenteral products in instances where ANDA applicants sought approval of formulations based on discontinued formulations of previously-approved RLDs (Petition 9). For proposed ANDAs that contain differences in non-exception excipients, FDA generally has granted waivers of the inactive ingredient sameness requirement in situations where (1) the proposed product duplicates a discontinued formulation of the drug that FDA has previously approved as safe and effective and (2) FDA determines the drug was not discontinued for reasons of safety or effectiveness. In such cases, FDA's previous approval of the discontinued formulation reflects the Agency's finding that the product (including formulation containing certain inactive ingredients) was safe and effective. This finding, together with FDA's determination that the product was not discontinued for reasons of safety or effectiveness, confirms that it is still appropriate to rely on the Agency's findings of safety and effectiveness and that the statutory standard for safety of inactive ingredients can be met without the need for extensive evaluation of additional data to make the necessary safety determination.

You recognize that the proposed formulation contains a non-exception excipient and does not duplicate a previously-approved RLD (Petition 9). You state that you are aware that the proposed formulation may raise questions regarding the safety and effectiveness of the proposed product. You recognize that the issues concern potential differences in the toxicity, pharmacokinetics, metabolism, and antifungal activity of the active ingredient due to potentially different kinetics of active ingredient release from different β-

cyclodextrin.

We conclude that the proposed formulation does not meet the requirements of the inactive ingredient regulations for parenteral products proposed in an ANDA. Your proposed product contains a non-exception excipient that raises certain issues described above and the 505(b)(2) pathway would be the appropriate pathway for evaluating them. FDA does not intend to grant a waiver of the inactive ingredient regulations for parenteral products under the circumstances outlined in your petition. This decision is consistent with the purpose of the inactive ingredient regulations which were intended to prevent the use of unfamiliar inactive ingredients, or inactive ingredients of a type more likely to raise safety concerns for parenteral drugs, that cannot be adequately and/or expeditiously addressed in the ANDA context.

In addition, because the petitioner's proposed formulation of voriconazole for injection contains a non-exception excipient that differs from that used in the RLD's formulation and does not duplicate a previously approved formulation, FDA does not intend to accept the proposed formulation of voriconazole for filing as an ANDA. Parenteral drug products that are not approvable in an ANDA under section 505(j) of the FD&C Act because they differ from the listed drug in inactive ingredients other than differences in exception excipients may instead be the subject of an application submitted under section 505(b)(2) of the FD&C Act. An applicant that seeks approval for a 505(b)(2) application that differs from an RLD in this manner must establish the safety and efficacy of any differences from the listed drug it references.

III. CONCLUSION

For the foregoing reasons, the Petition is denied.

Sincerely,

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