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February 15, 2013

SENT VIA FEDERAL EXPRESS

Division of Dockets Management
Food and Drug Administration (HFA-305)
Department of Health and Social Services
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Citizen Petition regarding Proposed Formulation of Voriconazole for Injection 200 mg/vial

Dear Sir or Madam:

I enclose an original and three copies of a citizen petition submitted by Merchant & Gould PC on behalf of a client. The submission is contained in two boxes. Also enclosed is a disc containing an electronic copy of the petition and supporting materials. The petition in the electronic copy contains hyperlinks to the publicly-available source material that is not included among the appendices herein. Please contact me if you have any questions.

Sincerely,

MERCHANT & GOULD P.C.

Edward J. Pardon

2013-1219

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2013 FEB 19 A 9:52

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CITIZEN PETITION

Dear Sir or Madam:

Merchant & Gould P.C., on behalf of a client, submits this petition pursuant to 21 C.F.R. §§ 10.20, 10.30 and 314.99(b) to request the Commissioner of Food and Drugs to take the actions listed below related to the petitioner's proposed formulation for the drug product Voriconazole for Injection 200 mg/vial. The petitioner seeks approval to submit an abbreviated new drug application (ANDA) for its proposed voriconazole product relying on Vfend® I.V. (voriconazole) for Injection 200 mg/vial as the Reference Listed Drug (RLD) (NDA No. 021267, marketed by Pfizer). As outlined below, the petitioner requests the Commissioner to refrain from enforcing the full requirements of 314.94(a)(9)(iii) and 314.127(a)(8)(ii)(B).

I. Action Requested

The objective of this petition is to request the Food and Drug Administration (FDA or "Agency") to consider the petitioner's proposed formulation of Voriconazole for Injection 200 mg/vial as appropriate for an ANDA submission under section 505(j) of The Federal Food Drug and Cosmetics Act (FDCA), even though the proposed formulation contains an inactive ingredient that differs from the RLD by means other than a different preservative, buffer, or antioxidant.

The petitioner submits that its proposed substitution is safe, that the active ingredient of the proposed drug product is the same as the RLD, and that the proposed drug product can be expected to have the same therapeutic effect as the RLD when administered to patients for

each condition of use in the RLD's labeling for which the petitioner will seek approval. Accordingly, the petitioner submits that its proposed product is appropriate for an ANDA submission.

The petitioner therefore respectfully requests that FDA refrain from enforcing its so-called "exception excipient" regulations to permit a "non-exception excipient" change from the RLD.

Specifically, the petitioner requests the FDA to waive the following:

- 21 CFR § 314.94(a)(9)(iii) [relating to **Content and format of an abbreviated application** and *Chemistry, manufacturing and controls.*]

> *Inactive ingredient changes permitted in drug products intended for parenteral use:* 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 under paragraph (a)(3) of this section. 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.

- 21 CFR § 314.127(a)(8)(ii)(B) [relating to **Refusal to approval an abbreviated new drug application.**]

> FDA will refuse to approve an abbreviated application for a new drug under section 505(j) of the act for any of the following reasons: . . . FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be unsafe and will refuse to approve the abbreviated new drug application 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.

The petitioner submits that in this instance, compliance with the "non-exception" inactive ingredient requirement of §§ 314.94 (a)(9)(iii) and 314.127(a)(8)(iii) is unnecessary and that information in the petitioner's submission otherwise justifies a waiver of these provisions. See § 314.90(a)(1), (3).

II. Statement of Grounds

A. Factual Background

Information concerning the RLD and the petitioner's proposed product is outlined below. Briefly, the RLD contains sulfobutyl ether β-cyclodextrin sodium as a solubilizing agent,

whereas the petitioner's proposed product contains hydroxypropyl β-cyclodextrin as a solubilizing agent.

1. Vfend I.V. (voriconazole) for Injection 200 mg/vial and its composition

The RLD as noted in *Approved Drug Products with Therapeutic Equivalence Determinations* is Vfend I.V. (voriconazole) for Injection, 200 mg/vial, which is approved under NDA No. 021267.[1] Vfend is a parenteral drug product intended for intravenous (IV) administration. Vfend I.V. 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). When reconstituted with 19 mL of Water for Injection, the resulting solution contains 10 mg/mL of voriconazole and 160 mg/mL of SBEβCD and must be further diluted prior to administration as an intravenous infusion.[2]

The active ingredient in Vfend I.V. for Injection 200 mg/vial is voriconazole, a broad spectrum triazole antifungal agent. Vfend is 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 apiospermim and Fusarium spp.,* including *Fusarium solani,* in patients intolerant of, or refractory to other therapy.

Voriconazole is a synthetic compound and is designated chemically as (2R,3S)-2-(2,4-difluorophenyl)-3-(5-fluoro-4-pyrimidinyl)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol, with an empirical formula of $C_{16}H_{14}F_3N_5O$ and a molecular weight of 349.3. The structure of voriconazole is shown in Figure 1.

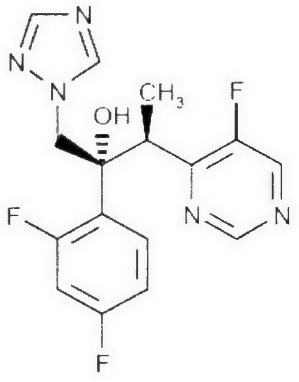

Figure 1. Structure of voriconazole.

[1] Accessed via http://www.accessdata.fda.gov/scripts/cder/ob/docs/tempai.cfm (February 11, 2013).

[2] Vfend product label approved as of November 16, 2011, at 4-5 and 36. Obtained from Drugs@FDA and available at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021266s035,021267s040,021630s026lbl.pdf (accessed February 11, 2013).

Voriconazole is a white to off-white powder in solid state. It is a single diastereomer with two reported pK_a values of 4.98 and 12.0. Voriconazole is a weak base. It is not hygroscopic, it is very slightly soluble in water[3] and has high permeability.[4]

Voriconazole degrades in water; it is susceptible to oxidative degradation and decomposes in acidic and basic media. Photodegradation occurs under severe light stress conditions, and voriconazole degrades greatly under elevated temperature.[5] The compound is semi-polar, which means that it is generally not solubilized by conventional means such as oils, surfactants or water miscible co-solvents.

Because voriconazole is poorly soluble in water, the Vfend label indicates that SBEβCD was used in the RLD formulation as a "vehicle."[6] A Scientific Discussion document published by the European Medicines Agency (EMA) related to Pfizer's Vfend application for Marketing Authorization (MA) in the European market states that by forming inclusion complexes with derivatised cyclodextrins (*i.e.,* SBEβCD), voriconazole could be solubilized to an extent that had not been possible with conventional pharmaceutical approaches. SBEβCD was used at a minimum concentration to achieve a balance between maintaining the targeted voriconazole solubility of 10 mg/ml at 4°C, required to underwrite refrigerated storage after reconstitution, ease of reconstitution and resultant solution viscosity.[7]

Accordingly, it can be concluded that the SBEβCD in the RLD has a solubilizing function in the reconstituted drug product and enables the drug product to be in the form of a true solution when being prepared for administration to a patient.

SBEβCD is a derivative of β-cyclodextrin and is a chiral molecule composed of seven α-D-glucopyranose units. It is synthesized from β-cyclodextrin and 1,4-butane sultone, and the stereochemistry is maintained during derivatization of the starting material.[8] The structure of SBEβCD is shown in Figure 2.

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[3] USP36-NF31 Reference Tables: Description and Solubility: *Voriconazole.*

[4] European Medicines Agency, Vfend: EPAR - Scientific discussion, accessed February 7, 2013 at: http://www.emea.europa.eu/docs/en_GB/document_library/EPAR_-_Scientific_Discussion/human/000387/WC500049753.pdf , provided as **Appendix 1,** at 2.

[5] *See* Appendix 1 at 2.

[6] *See* Vfend product label at 6-7, 9, 20, and 24.

[7] *See* Appendix 1 at 3-4.

[8] *See id.* at 3.

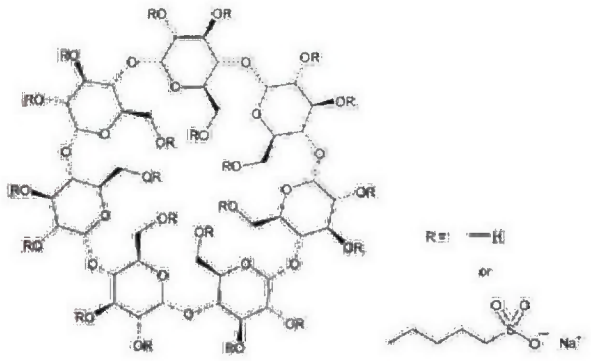

Figure 2. Structure of SBEβCD (adopted from *Betadex Sulfobutyl Ether Sodium Official Monograph, Second supplement to USP 35 – NF 30*).

2. Petitioner's proposed drug product composition

As required by 21 CFR § 314.94 (a)(5) and (6), the petitioner's Voriconazole for Injection 200 mg/vial contains the same active ingredient (voriconazole) in the same quantity (200 mg/vial) as the RLD, and is identical to the RLD in terms of route of administration, dosage form, and strength. In addition, the conditions of use would be the same.

However, the petitioner's drug product differs from the RLD in terms of the inactive ingredient contained in the proposed formulation. More specifically, the substituted β-cyclodextrin functioning as the vehicle in the formulation of the RLD (SBEβCD) has been replaced in the petitioner's drug product formulation by another type of substituted β-cyclodextrin: hydroxypropyl ß-cyclodextrin (HPβCD).

The HPβCD in the petitioner's proposed formulation is a partially-substituted poly(hydroxypropyl) ether of β-cyclodextrin. HPβCD is a derivative of β-cyclodextrin composed of seven α-D-glucopyranose units. The number of hydroxypropyl groups per anhydroglucose unit expressed as molar substitution (MS) ranges from 0.40 to 1.50. The structure of HPβCD is shown in Figure 3.

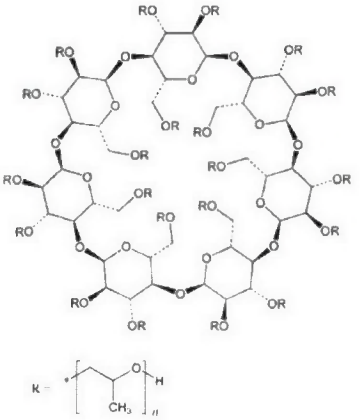

Figure 3. Structure of HPβCD (adopted from *Hydroxypropylbetadex Official Monograph, Second supplement to USP 35 – NF 30*).

A comparison of the qualitative and quantitative composition of the petitioner's proposed formula of Voriconazole for Injection 200 mg/vial and the RLD formulation is given in Table 1. The petitioner intends to propose in its label the same instructions for reconstitution of the product as the instructions given in the RLD label, providing for a solution containing 10 mg/mL of voriconazole and 160 mg/mL of the substituted β-cyclodextrin vehicle. The quantity of substituted β-cyclodextrin in the petitioner's proposed drug product is therefore the same as the quantity of substituted β-cyclodextrin contained in the RLD: 3,200 mg/vial.[9]

Table 1. Qualitative and quantitative composition of petitioner's proposed formula of Voriconazole for Injection 200 mg/vial and RLD Vfend before and after reconstitution.

INGREDIENTS		FUNCTION	QUANTITY	
Petitioner's formula	RLD		mg/vial	mg/mL*
Voriconazole	Voriconazole	Active Ingredient	200	10
Hydroxypropyl ß-cyclodextrin (HPβCD)	Sulfobutyl ether ß-cyclodextrin (SBEβCD)	Vehicle	3,200	160

* following reconstitution with 19 mL of WFI.

B. Legal Basis for Request

1. Legal background

Section 505(j) of the FDCA permits an applicant to submit an ANDA if the proposed product meets certain requirements typically including, among other things, that the proposed active ingredient, conditions of use, route of administration, dosage form, and strength are the same as the listed drug. *See generally* 21 U.S.C. § 355(j).

Title 21 CFR § 314.92(a) identifies those products for which an ANDA is suitable. These include drug products that are (1) the "same as" the listed drug, or (2) declared suitable through the citizen or suitability petition procedures outlined in §§ 10.30 and 314.93. *See* 21 CFR § 314.92(a). The term "same as" means:

> identical in active ingredient(s), dosage form, strength, route of administration, and conditions of use, except that conditions of use for which approval cannot be granted because of exclusivity or an existing patent may not be omitted. If a listed drug has been voluntarily withdrawn from or not offered for sale by its manufacturer, a person who wishes to submit an abbreviated new drug application for the drug shall comply with 314.122.

21 CFR § 314.942(a)(1).

The petitioner's proposed product is identical to the RLD with respect to the characteristics specified in § 314.92 (a) and is therefore the "same as" the RLD. Accordingly,

[9] *See* Vfend product label at 1, 7, 20, and 36.

the petitioner's proposed product is appropriate for an ANDA submission. *See also* 35 U.S.C. § 355(j)(2).

The petitioner's proposed product does not contain the identical inactive ingredients as the RLD because, as noted, the RLD contains SBEβCD whereas the petitioner's proposed product contains HPβCD. However, section 505(j) of the FDCA does not require that the inactive ingredients of the proposed generic product be the same as those used in the listed drug product. To that end, section 505(j)(4)(H) of the FDCA states that that the Secretary "shall approve" an ANDA unless, among other things, the Secretary finds:

> 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 drug 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[.]

21 U.S.C. § 355(j)(4)(H).

With regard to parenteral products, the FDA has established a default position that generally, parenteral drug products must contain the same inactive excipients as the RLD. Specifically, 21 CFR § 314.94 (a)(9)(iii) states:

> *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 under paragraph (a)(3) of this section. 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.

21 CFR § 314.94(a)(9)(iii) (emphasis added).

Furthermore, 21 CFR § 314.127(a) addresses situations in which the FDA will refuse to approve an ANDA. More specifically, 21CFR § 314.127(a)(8)(ii)(B) states:

> FDA will consider an inactive ingredient in, or the composition of, a drug product intended for parenteral use to be *unsafe* and will refuse to approve the abbreviated new drug application 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.

21 CFR § 314.127(a)(8)(iii) (emphasis added). These regulations serve to demonstrate that the primary basis for refusing to approve ANDAs for parenteral drug products with inactive ingredients that differ from the RLD is to address **safety concerns**.

However, FDA's regulations also permit the Agency to waive its default position that is embodied in the foregoing regulations. Specifically, pursuant to 21 CFR § 314.99(b):

> An applicant may ask FDA to waive under this section any requirement that applies to the applicant under §§ 314.92 through 314.99. The applicant shall comply with the requirements for a waiver under § 314.90.

21 CFR § 314.99(b).[10]

Pursuant to 21 CFR § 314.90, the waiver request must contain one of the following:

> (1) An explanation why the applicant's compliance with the requirement is unnecessary or cannot be achieved;
>
> (2) A description of an alternative submission that satisfies the purpose of the requirement; or
>
> (3) Other information justifying a waiver.

21 CFR § 314.90(a).

Correspondingly, the FDA may grant the waiver if it finds that:

> (1) The applicant's compliance with the requirement is unnecessary for the agency to evaluate the application or compliance cannot be achieved;
>
> (2) The applicant's alternative submission satisfies the requirement; or
>
> (3) The applicant's submission otherwise justifies a waiver.

21CFR § 314.90 (b).

2. Waiver request

In this instance, where the solubilizing agent used in the RLD (SBEβCD) will be replaced with another solubilizing agent (HPβCD) from the same group of compounds (substituted β-cyclodextrins), the petitioner submits that compliance with the "non-exception" inactive ingredient requirement of §§ 314.94 (a)(9)(iii) and 314.127(a)(8)(iii) is unnecessary, and that information in the petitioner's submission will otherwise justify a waiver of these provisions. *See* § 314.90(a)(1), (3). The scientific basis for this is outlined in Section II.C below.[11]

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[10] The FDA may also waive § 314.127(a)(8)(iii). *See* FDA Sandostatin Ruling in Docket Nos. 2001P-0574/CP1 and 2005P-0061/CP1 (Mar. 25, 2005), discussed *infra* and provided as **Appendix 2,** at 8 n.14.

[11] To the extent FDA deems this petition to be a suitability petition pursuant to 21 CFR § 314.93 rather than solely a citizen petition under 21 CFR § 10.30, the petitioner requests waiver of the requirements of 314.93(a) identifying the appropriate bases for suitability petitions. The Agency has considered the appropriateness of submitting an ANDA in response to citizen petitions under § 10.30 before. *See, e.g.*, Rakoczy Molino Mazzochi Siwik LLP Petition in Docket FDA-2006-P-0195 (later renumbered as FDA-2006-P-0331) (May 9, 2006), provided as **Appendix 3.** Regardless of how this petition is characterized, the petitioner's proposed product would meet the "sameness" requirement for an ANDA under § 505(j)(2) and 21 CFR § 314.92(a), and reviewing or granting this petition is not inconsistent with the requirements of § 505(j)(2).

3. Legal and technical precedent

The petitioner's request for a waiver of the "inactive ingredient" regulations at 21 CFR §§ 314.94 (a)(9)(iii) and 314.127 (a)(8)(ii)(B) has precedential support because the FDA has previously granted waivers from these regulations to allow the submissions of ANDAs for parenteral products differing in inactive ingredients from the RLD. For example, FDA granted petitions submitted by Ben Venue and Sun Pharmaceuticals Industries seeking to market a discontinued formulation of Novartis' Sandostatin® product (see FDA Sandostatin Ruling provided as **Appendix 2**). Likewise, the FDA also granted petitions submitted by Sandoz Inc., Rakoczy Molino Mazzochi Siwik LLP (hereinafter referred as Rakoczy) and Orchid Healthcare seeking to market a discontinued formulation of Wyeth's Zosyn® product. Furthermore, in this latter case the specific safety concerns with respect to the stability of the discontinued formulation of the RLD, and thus of the generic products relying on the same, were raised by Wyeth. In granting the Rakoczy petition, the FDA noted that "in appropriate circumstances, it may waive the requirement in the regulation that the inactive ingredients in a parenteral drug product approved under an ANDA be the same as those in the reference listed drug (except for preservatives, buffers, and antioxidants)."[12]

The petitioner recognizes that the above-referenced decisions were based on petitions in which the petitioners sought approval to submit ANDAs based on discontinued formulations of previously-approved RLDs pursuant to 21CFR §§ 314.122 and 314.16. Nonetheless, the agency's decision in those petitions demonstrates that the agency can consider an ANDA drug product to be safe even though it contains a different inactive ingredient (other than preservatives, buffers, or antioxidants) from the current RLD. The petitioner believes that, even though the inactive ingredient in its proposed formulation of Voriconazole for Injection 200 mg/vial was not part of a previously-approved voriconazole formulation, there is sufficient data to prove the safety of its proposed formulation and its eligibility for ANDA submission relying on Vfend I.V. as the RLD.

Furthermore, the petitioner believes that its proposed formulation is as effective as the RLD, and would meet requirements for ANDA approval pursuant to FDA's grant of this petition for ANDA submission. And as noted by the FDA in granting the Rakoczy petition, "FDA may not waive a statutory requirement for approval of an ANDA. Thus, differences between the ANDA and RLD formulations that are shown to be unsafe based on available information will preclude ANDA approval (section 505(j)(4)(H) of the Act)."[13] Accordingly, other issues not addressed in this petition can still be addressed by the Agency during the ANDA review process.

Moreover, publicly-available information in the Vfend I.V. NDA shows that in Pfizer's early development program (starting in 1991) its intravenous voriconazole was formulated with HPβCD (the same type of substituted β-cyclodextrin proposed in the petitioner's formulation). SBEβCD as a solubilizing excipient began to be used in Pfizer's intravenous formulation in clinical trials beginning in 1994, and the FDA apparently permitted Pfizer to change the inactive ingredient in its formulation from HPβCD to SBEβCD without requiring bioequivalence studies between those two formulations. Still, voriconazole pharmacokinetic

[12] FDA to Rakoczy and others – Petition Approval in FDA-2006-P-0331, provided as **Appendix 4**, at 11.

[13] *See id.*

parameters for both voriconazole formulations were evaluated and the evaluation performed by Pfizer concluded that the pharmacokinetic results at steady-state obtained for voriconazole when a SBEβCD formulation was administered in repetitive intravenous administration tests "*were similar to the results of previous repetitive intravenous administration tests*" obtained when voriconazole-HPβCD formulation was administered (emphasis added).[14] This implies that the data available within the Vfend NDA submission support the petitioner's claim that efficacy of the drug will not be affected by changing the solubilizing agents. (For further details, please see section C.2.b. below.)

Based on the foregoing as well as the scientific rationale discussed below, the petitioner believes that sufficient safety and efficacy data is available to enable FDA to waive the requested regulations and accept for review an ANDA for voriconazole for injection 200 mg/vial with HPβCD as an inactive ingredient.

C. Discussion

The petitioner is aware that its proposed change in the type of substituted β-cyclodextrin may raise questions regarding the safety and efficacy of its proposed formulation. The petitioner recognizes that these issues concern potential differences in the toxicity, pharmacokinetics, metabolism, and the antifungal activity of the active ingredient due to potentially different kinetics of voriconazole release from different β-cyclodextrin: active ingredient complexes. The petitioner proposes to address these issues as follows.

With respect to safety, the petitioner believes that there are sufficient data demonstrating that the proposed formulation is as safe as the RLD formulation. In particular: (a) the mechanism of active ingredient: β-cyclodextrin complex formation generation and dissociation enables evaluation of the safety of the petitioner's proposed formulation by evaluating the safety of HPβCD itself; (b) the pharmacokinetic and (c) toxicity profiles of HPβCD and SBEβCD are similar; (d) HPβCD has been used in previously-approved products; (e) HPβCD was used in Pfizer's original voriconazole studies with no indication it was considered unsafe; and (f) the petitioner's HPβCD formulation does not contain the mutagenic alkylating agent 1,4 butane sultone that is present in the RLD.

With respect to efficacy, there is sufficient data demonstrating that the petitioner's proposed product will be as efficacious as the RLD formulation. This is because: (a) the proposed change in substituted β-cyclodextrin in the drug product will not influence the pharmacokinetics and pharmacodynamics of the voriconazole active ingredient; (b) the biotransformation of voriconazole is not affected by the type of substituted ß-cyclodextrin; and (c) the antifungal activity of voriconazole is not affected by the type of substituted ß-cyclodextrin.

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[14] Vfend (Voriconazole for Injection 200 mg/vial) CTD document, Section 2.7.6, Summary of Individual Tests, Pfizer Inc., at 420; *see also id.* at 211-12 and 418-19. The document was obtained from http://www.pfizer.co.jp/pfizer/development/clinical_development/new_medicine_info/documents/apply_document/appli_doc_h17_04_vfend_rinsho4.pdf (accessed February 8, 2013). An English translation and portions of the original Japanese document are provided as **Appendix 5.**

1. Petitioner's proposed substitution can be considered safe

a. The mechanism of active ingredient: β-cyclodextrin complex generation and dissociation enables evaluation of the safety of the petitioner's proposed formula by evaluating the safety of HPβCD itself

As noted earlier, the substituted β-cyclodextrin in either the petitioner's proposed product or the RLD functions as a "vehicle."

Substituted β-cyclodextrins are used to increase the water solubility of poorly water soluble compounds. The mechanism of solubilization is based on the ability of substituted β-cyclodextrins to form non-covalent dynamic inclusion complexes in a solution, in which the guest and host molecules are in dynamic equilibrium with the complex.[15] In general, the central cyclodextrin cavity provides a lipophilic microenvironment into which suitably-sized active ingredient molecules may enter and be included. Because no covalent bonds are formed or broken during the active ingredient: β-cyclodextrin complex formation and in aqueous solutions, the complexes are readily dissociated under suitable conditions.[16]

Also as noted earlier, the EMA reported that in the RLD, voriconazole was solubilized by forming inclusion complexes with SBEβCD, which is consistent with the foregoing. The same can be expected for the HPβCD proposed for petitioner's voriconazole product.

The formation of suitable drug: cyclodextrin complexes can be readily achieved by various well known techniques.[17] As a general matter, **the drug compound is rapidly released from these complexes after parenteral administration and cyclodextrins do not appear to substantially alter the intrinsic pharmacokinetics of the drug.**

The major driving force for drug release from a weak inclusion complex is simple dilution. The volume of distribution (V_d) for both SBEβCD and HPβCD is said to be that of extracellular water – about 20% of total body weight, or 14 L for a 70 kg patient. A 5mL injection of a drug: cyclodextrin solution would result in a 1:2,800 dilution. For most drugs, this would be sufficient to completely dissociate the drug from the cyclodextrin. Concern only arises when the K value (binding constant numerical value) for the drug: cyclodextrin complex exceeds 1×10^5 M^{-1} and even this strong binding has been shown to have only a limited effect.[18] The petitioner has experimentally determined binding constants (named in literature as stability constants as well) for its proposed product and the RLD formulation. A

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[15] M. E. Brewster and T. Loftsson, Cyclodextrins as pharmaceutical solubilizers, *Adv. Drug Del. Rev.* 59 (2007) 645-666, provided as **Appendix 6,** at 645, 650.

[16] *See* V. J. Stella *et al.*, Mechanisms of drug release from cyclodextrin complexes, *Adv. Drug Del. Rev.* 36 (1999) 3-16, provided as **Appendix 7,** at 4; V. J. Stella and Q. He, Cyclodextrins, *Toxicol. Pathol.* 36 (2008) 30-42, provided as **Appendix 8,** at 33-35; J. Szejtli, Past, present, and future of cyclodextrin research, *Pure Appl. Chem.* 76 (2004) 1825-45, provided as **Appendix 9,** at 1829-33); R. A. Rajewski and V. J. Stella, Pharmaceutical applications of cyclodextrins. 2. *In vivo* drug delivery, *J. Pharm. Sci.* 85 (1996) 1142-1169, provided as **Appendix 10,** at 1142-44.

[17] *See* E. M. M. Del Valle, Cyclodextrins and their uses: a review, *Process Biochem.* 39 (2004) 1033–1046, provided as **Appendix 11,** at 1040-41.

[18] *See* Appendix 8 at 34.

detailed description of the study and results is provided as **Appendix 12,** "Influence of β-cyclodextrin type (hydroxypropyl β-cyclodextrin and sulfobutyl ether β-cyclodextrin) on voriconazole pharmacokinetic properties: *In vitro* studies." Obtained values for both products are well below 1×10^5 M^{-1} and are actually equal to 319 M^{-1} and 491 M^{-1} respectively.[19] These results indicate that in the human organism the dissociation of both complexes will occur in a similar way, i.e. release of voriconazole from both complexes would be instantaneous.

Furthermore, the literature indicates that cyclodextrins of high pharmaceutical relevance, such as HPβCD and SBEβCD, are likely to show similar kinetic behavior.[20] The explanation for this lies in the similarity of the complexation process and its dynamics for both cyclodextrins. In solution, this is a dynamic process whereby the drug continuously associates and dissociates from the host cyclodextrin and the complex itself is actually composed of a family of species. The association and dissociation reactions occur at very rapid rates for both strong and weak complexes, with the average lifetime of the molecules in the cyclodextrin cavity being in the range of micro- to milliseconds or shorter. **Because these processes occur at such rapid rates which are much faster than many physiological processes, the kinetics of release of a drug molecule from the cyclodextrin cavity following the IV administration should not be a critical parameter and therefore should not impair the drug's pharmacokinetics.**[21] Moreover, following the dissociation of the complex in highly dilute and dynamic systems like the body, the drug has difficulty finding another cyclodextrin with which to reform a complex, and is left free in solution.[22]

The foregoing is further supported by the literature covering studies performed on drugs solubilized either by complexation with different cyclodextrins (with the intent to evaluate the potential influence of the type of cyclodextrin used) or by different means (e.g. the use of cyclodextrin complexation vs. the use of cosolvents).[23] It is also generally accepted that cyclodextrins are eliminated rapidly from the body following dissociation after IV administration and appear in urine unchanged.[24]

In order to further evaluate the above, petitioner performed a series of *in vitro* experiments designed to test the influence of the type of substituted ß-cyclodextrin (HPßCD v. SBEßCD) used on the dissociation of voriconazole from voriconazole: β-cyclodextrin complexes in an aqueous media and in a lipophilic environment. In the latter, the petitioner also evaluated the potential influence of the substituted β-cyclodextrins on voriconazole's permeability through lipophilic membranes and its affinity to bind to proteins. To do so, the petitioner used samples of its proposed drug product and the RLD.

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[19] *See* Appendix 12 at 3-6.

[20] *See* Appendix 6 at 647-650; Appendix 8 at 34-36; Appendix 10 at 1145-47.

[21] *See* Appendix 7 at 5; Appendix 8 at 32-34; Appendix 10 at 1145-47.

[22] *See* Appendix 11 at 1037.

[23] *See* Appendix 8 at 34.

[24] *See id.*

A detailed description of the studies performed and their results is provided in the previously-noted Appendix 12. In summary, the results show that the kinetics of voriconazole release from both tested formulations is similar in both aqueous and lipophilic environments. Further, the results suggest that the permeation of voriconazole released from a complex through lipophilic membranes *in vivo* investigated using immobilized artificial membrane (IAM) chromatography would be unaffected by the type of β-cyclodextrin used. Additionally, studies of voriconazole binding to human serum albumin (HSA) by the fast gradient HSA-HPLC method also show that the release of voriconazole from its β-cyclodextrin complex and its binding to HSA is similar for both types of β-cyclodextrins, thus demonstrating that the distribution of voriconazole *in vivo* (and its efficacy as well) should not be affected by the petitioner's proposed change.

Finally, rat and dog studies performed by Pfizer demonstrated that IV formulations of voriconazole utilizing either HPβCD or SBEβCD did not affect the pharmacodynamics of voriconazole.[25]

Based on the foregoing general knowledge, scientific publications, and studies conducted by the petitioner as well as Pfizer, the petitioner submits it can be concluded that:

- substituted β-cyclodextrins in both the RLD and the petitioner's proposed formulation serve as vehicles or carriers of the drug by keeping the voriconazole in solution and delivering them to the surface of the biological membranes and

- following the IV administration of a drug product containing a voriconazole: substituted β-cyclodextrin complex, a rapid dissociation of the complex will occur and the pharmacokinetics of the drug and cyclodextrin carrier should continue independently of each other such that the pharmacokinetics of the drug should not affect the type of substituted β-cyclodextrin used, nor should the pharmacokinetics of the substituted β-cyclodextrin be affected by the drug.

Accordingly, the petitioner believes it is not unreasonable to assume that following IV administration of its proposed product, a rapid dissociation of complex *in vivo* will occur and **the safety of the proposed petitioner's formula compared to the RLD should be evaluated based on the safety of the proposed inactive ingredients themselves when administered intravenously.** Therefore, the safety of the petitioner's proposed formula compared to the RLD should be evaluated based on the safety of the proposed active ingredient (which is the same as in the RLD) and the inactive ingredient itself.

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[25] Vfend (Voriconazole for Injection 200 mg/vial) CTD document, Section 2.4, Comprehensive Evaluation for Non-Clinical Use, Pfizer, at 19. The document was obtained from http://www.pfizer.co.jp/pfizer/development/clinical_development/new_medicine_info/documents/apply_document/appli_doc_h17_04_vfend_hirinshohyoka.pdf (accessed February 7, 2013). An English translation of pages 19 – 29 of the original Japanese document is provided as **Appendix 13.**

b. The pharmacokinetic profiles of HPβCD and SBEβCD are similar

The pharmacokinetics of HPβCD and SBEβCD are well-described in animals and humans.[26] The pharmacokinetic profiles of these compounds are characterized by comparable volumes of distribution, renal clearance, and elimination half-life.

Following IV administration, both HPβCD and SBEβCD disappear rapidly from systemic circulation and are excreted unchanged in the urine, with minimal or no metabolism.[27] Over 90% of parenterally administered cyclodextrins are eliminated from the body unchanged in the urine via glomerular filtration within approximately 6 hours, and over 99.9% are eliminated within 24 hours. Following IV administration, HPβCD has a small volume of distribution in humans (V_D =0.2 l/kg) and a short half-life ($t_{1/2}$~1.9 h). SBEβCD has a similar volume of distribution and half-life in humans following IV administration. (V_D=0.2 l/kg and $t_{1/2}$~1.6 h). Both are excreted via glomerular filtration with no sign of tubular reabsorption.[28] The half-life, clearance, and volume of distribution are independent of dose and urine levels.

Because elimination of cyclodextrins so strongly depends on renal clearance, renal insufficiency could cause cyclodextrin accumulation and an increased elimination half-life with impaired kidney function with either SBEβCD or HPβCD.[29] A detailed report on the pharmacokinetic parameters of HPβCD in renal-impaired patients along with accompanying information in the petitioner's proposed product labeling that addresses the proposed change in inactive ingredient is enclosed as **Appendix 19.**[30]

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[26] *See* Appendix 8 at 34-36; Appendix 10 at 1145-50; FDA Antiviral Drugs Advisory Committee Briefing Document for Voriconazole (Oral and Intravenous Formulations) 4-Oct-2001 (hereafter "Voriconazole Adv. Com. Document"), available at http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_01_pfizer.pdf (accessed February 11, 2013), at 40, 47, 138, 192, 209 and 217 (cited portions of this document are provided as **Appendix 13A**); T. Irie and K. Uekama, Pharmaceutical applications of cyclodextrins. III. Toxicological issues and safety evaluation, *J. Pharm. Sci.* 86 (1997) 147-162, provided as **Appendix 14,** at 150-51; S. J. Roffey *et al.,* The Disposition of Voriconazole in Mouse, Rat, Rabbit, Guinea Pig, Dog and Human, *Drug Metab. Dispos.* 31 (2003) 731-741, provided as **Appendix 15;** Itraconazole (Sporanox, Janssen) 1999 Pharmacology Review, FDA CDER NDA No. 20966 (hereafter "Sporanox Pharmacology Review"), obtained through Drugs@FDA and available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/99/020996_sporanox_toc.cfm (accessed February 11, 2013).

[27] *See* Appendix 8 at 35.

[28] *See* S. V. Kurkov and T. Loftsson, Cyclodextrins. *Int. J Pharm.* 2012 Jul 5 [Epub ahead of print], provided as **Appendix 16,** at 7-9; *see also* Appendix 8 at 34-5; Appendix 10 at 1165; T. Loftsson and M.E. Brewster, Pharmaceutical applications of cyclodextrins: basic science and product development. *J. Pharm. Pharmacol.* 62 (2010) 1607-1621, provided as **Appendix 17,** at 1610-12; M.A. Von Mach *et al.,* Accumulation of the solvent vehicle sulphobutylether beta cyclodextrin sodium in critically ill patients treated with intravenous voriconazole under renal replacement therapy, *BMC Clin. Pharm.* 6 (2006) 6-11, provided as **Appendix 18,** at 4-6.

[29] *See* Vfend product label at 1, 6, 9 and 24; Appendix 6 at 648; Sporanox 1999 Pharmacology Review (Janssen NDA No. 20966); Appendix 17 at 1611-12l; Appendix 18 at 4-6.

[30] Report: "Pharmacokinetic profile of hydroxypropyl beta-cyclodextrin (HPβCD) following administration of petitioner's Voriconazole for Injection 200 mg/vial" (February. 7, 2013).

Finally, literature data suggests that the pharmacokinetic parameters associated with cyclodextrins are not altered when cyclodextrins are complexed with the host molecule.[31]

c. Publicly available toxicity data shows that HPβCD is safe and the toxicity profiles of HPβCD and SBEβCD are comparable

Both HPβCD and SBEβCD have already been approved by FDA for use in drug products intended for intravenous administration. Details of the toxicology results showing that both compounds have similar safety and toxicity profiles are available in the literature and on file in the applications for voriconazole (SBEβCD in Vfend I.V.) and itraconazole (HPβCD in Sporanox® IV).[32]

Furthermore, during Pfizer's development of the RLD, toxicity studies conducted using both HPβCD-voriconazole and SBEβCD-voriconazole formulations are summarized in the Vfend submission.[33] Among other studies, the toxicity of a voriconazole product formulated with either HPβCD or SBEβCD was evaluated in 1-month intravenous toxicity studies in Sprague Dawley rats treated with 2, 5, 10 and mg/kg of voriconazole intravenously. (See Study Nos. 91076 (HPβCD) and 93096 (SBEβCD) at 30-32 of Vfend Chemistry Review).[34] Although the dose of cyclodextrin for each group of treated animals (2, 5, or 10 mg/kg) was not specifically noted in the publicly-available material, it is not unreasonable to assume that it was 160 mg/kg because that dose was provided in the vehicle control group for each study. As noted, the NOAEL[35] determined in both studies was 2 mg/kg, which was deemed equivalent to a human dose of 0.32 mg/kg/day for 28 days. This demonstrates that both formulations exhibited similar toxicity. These results imply that HPβCD and SBEβCD formulations have similar toxicity profiles.

The safety of HPβCD has also been investigated in several types of animals and in humans, and the results are briefly summarized in Table 2 below. The results indicate that HPβCD has very low toxicity when administered via the parenteral route even at high doses, and the effects of HPβCD on the kidney are reversible and similar to those observed for osmotic agents that are currently being used for parenteral formulations.[36]

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[31] *See* Appendix 8 at 32-35; Appendix 10 at 1145-50; Appendix 14 at 150-51; Appendix 18 at 4-6.

[32] *See* Appendix 14 at 152-55; Sporanox Pharmacology Review; Voriconazole (Vfend, Pfizer) Chemistry Review, FDA CDER NDA Nos. 21266 and 21267, obtained through Drugs@FDA and available at http://www.accessdata.fda.gov/drugsatfda_docs/nda/2002/21-266_21-267_Vfend.cfm (hereafter "Vfend Chemistry Review"), at 27-39 (intravenous studies); S. Gould and R.C. Scott, 2-Hydroxypropyl-β-cyclodextrin (HP-β-CD): a toxicology review. *Food Chem. Toxicol.* 43 (2005) 1451-1459, provided as **Appendix 20;** D. R. Luke *et al.,* Review of the basic and clinical pharmacology of sulfobutylether-β-cyclodextrin (SβECD), *J. Pharm. Sci.* 99 (2010) 3291-3301, provided as **Appendix 21.**

[33] *See* Vfend Chemistry Review at 27-39.

[34] Study No. 93096 also included a 1 month reversibility phase for the 10mg/kg dose with a supplemental group of rats.

[35] No observable adverse effect level.

[36] *See* Appendix 14 at 154-155.

Table 2. Results of toxicity evaluation of HPβCD (adapted from Irie and Uekama, Appendix 14 at 155, Table 4).

Species	Route of Administration	Dose	Remarks
Mouse	Intraperitoneal (acute)	10 g/kg	No mortality
	Intracerebral (acute)	1 μL of 40% (w/v) solution	No necrosis at the injection site
Rat	Intravenous (acute)	2 g/kg	No toxicity
	Intravenous (subacute)	5 g/kg daily for 7 days	No toxicity
	Intravenous (subchronic)	200 mg/kg every second day for 90 days	No toxicity
	Intravenous (subchronic)	50, 100, or 400 mg/kg daily for 90 days	No toxicity at 50 mg/kg, minimal effects at higher doses
	Intravenous (teratogenicity and embryotoxicity)	50–400 mg/kg from day 6 to day 18 of pregnancy	No toxicity
	Intramuscular (acute)	5–40% (w/v) solutions	No or minimal toxicity
Rabbit	Intravenous (teratogenicity and embryotoxicity)	50–400 mg/kg from day 6 to day 18 of pregnancy	No toxicity
	Intravenous (subchronic)	1 g/kg twice a week for 80 days or 2 g/kg daily for 20 days	Reversible vacuolation of renal tubular cells
	Intramuscular (acute)	1 mL of 1–10% (w/v) solutions	No or minimal toxicity
Dog	Intravenous (subchronic)	50, 100, or 400 mg/kg daily for 90 days	No toxicity at 50 and 100 mg/kg, minimal effects at 400 mg/kg
	Intravenous (subchronic)	700–1000 mg/kg daily for 90 days	Reversible vacuolation of renal tubular cells
Monkey	Intravenous (subacute)	200 mg/kg every second day for 91 days	No toxicity
	Intravenous (acute)	10 g/kg	No mortality
Human	Intravenous (acute)	infusion of 5% (w/v) solution at a rate of 470 mg/kg/day, total dose of 30 g over 4 days	No adverse effects
	Intravenous (acute)	infusion at a rate of 100 mg/min, total doses of 0.5–3 g	No adverse effects

Furthermore, in an intravenous dosing study single doses up to 3 g were found to have no measurable effect on kidney function and were well-tolerated by all volunteers. Following a 1 week intravenous study at a single dose level of 1 g, no adverse effects were reported. Administration of HPβCD at a dose of 470 mg/kg/day by IV infusion in a patient with severe hypervitaminosis A did not produce evidence of renal or liver damage, although this dose occasionally caused agitation and pulmonary edema in rabbits and dogs, respectively.[37]

Published toxicity studies imply that the kidney is the primary organ affected by the use of hydrophilic modified β-cyclodextrins (such as HPβCD and SBEβCD), due to their renal route of elimination. According to the literature, the findings are similar and reversible for both HPβCD and SBEβCD.[38] Thus, renal findings coupled with the renal-dependent clearance of both cyclodextrins represent the primary safety concern. Based on above data, however, this concern is no greater for one cyclodextrin than the other.

In summary, **the established toxicity profile of HPβCD is comparable to the toxicity profile of SBEβCD.**

[37] *See* Appendix 8 at 39.

[38] *See* Brewster and Loftsson, Appendix 6 at 648; Stella and He, Appendix 8 at 37; Appendix 14 at 154-155; Appendix 20 at 1457-58; Appendix 21 at 3294, 3297-99; Vfend Chemistry Review at 27-39.

d. HPβCD has been previously approved in an itraconazole parenteral drug product for IV administration where the daily intake level exceeded that of the proposed product

The Agency's Inactive Ingredient Database provides information on inactive ingredients in approved drug products. FDA has noted that:

> once an inactive ingredient has appeared in an approved drug product for a particular route of administration, the inactive ingredient is not considered new and may require a less extensive review the next time it is included in a new drug product. For example, if a particular inactive ingredient has been approved in a certain dosage form at certain potency, a sponsor could consider it safe for use in a similar manner for a similar type of product.[39]

Here, HPβCD already appears on FDA's Inactive Ingredient Database with a listed potency of 0.4 % for IV infusion.[40] It was previously approved in 1999 as an excipient in Sporanox (itraconazole) Injection 10 mg/mL for use at maximum levels that exceed those in the petitioner's proposed product. Sporanox is an antifungal like voriconazole and was approved in the same dosage form as the petitioner's proposed product. Furthermore, in 2009 the Agency also approved Vibativ (telavancin for injection), another drug for intravenous use that also contains HPβCD as an excipient. These approvals demonstrate that HPβCD can be considered safe for use products such as the petitioner's.

Sporanox IV was approved in 1999 and marketed in the United States until 2009.[41] Sporanox contained itraconazole, an antifungal agent, which was solubilized by HPβCD in a molecular inclusion complex. The function of HPβCD in Sporanox was thus similar to its function in petitioner's proposed product. According to the most recently available Sporanox labeling, each mL of drug product contained 10 mg of itraconazole and 400mg HPβCD. The recommended dose was 200 mg itraconazole twice daily for initial 4 doses, followed by 200 mg once daily for up to 14 days.[42] Therefore, it can be calculated that each intravenous dose of Sporanox contained 8 g HPβCD and that the maximum daily intake of HPβCD through administration of the Sporanox was 16 g.

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[39] Inactive Ingredient Search for Approved Drug Products: Frequently Asked Questions, at http://www.fda.gov/Drugs/InformationOnDrugs/ucm080123.htm (accessed February 12, 2013).

[40] Located under search for "cyclodextrin" in FDA Inactive Ingredient database, available at: http://www.accessdata.fda.gov/scripts/cder/iig/index.cfm (accessed February 12, 2013).

[41] From FDA website "Drugs to be Discontinued" at http://www.fda.gov/drugs/drugsafety/drugshortages/ucm050794.htm. Also located at http://www.fda.gov/downloads/Drugs/DrugSafety/DrugShortages/ucm089427.pdf (accessed February 12, 2013).

[42] Sporanox product label for NDA No. 020966, approved April 23, 2009, at 2, 25-27. Obtained from Drugs@FDA and accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020966s022lbl.pdf (February 12, 2013).

Regarding the Telavancin Hydrochloride (Vibativ) formulation, there are two strengths available on the market equivalent to either 250 mg or 750 mg of telavancin as the free base. These contain 2500 mg of HPβCD for the 250 mg telavancin dose and 7500 mg of HPβCD for the 750 mg telavancin dose. According to the available labeling, the recommended dosing regime is 10 mg/kg of active substance administered to the patient over a 60 minute period once in 24 hours.[43] Therefore, it can be calculated that the maximum daily intake of HPβCD administered to a 70 kg patient in the form of Vibativ is 7 g.

The petitioner proposes to include HPβCD at the same quantity and concentration in its product as the quantity and concentration of SBEβCD in the RLD. According to the dosage and administration information in the RLD label,[44] each mL of the drug product at the maximum loading dose of 6 mg/kg of body weight contains 160mg of SBEβCD. Since the recommended maximum loading dose for a 70 kg patient is 420 mg of voriconazole q12h for the first 24 hours, it can be easily calculated that the maximum daily intake of SBEβCD for a 70 kg patient would be 13.440 g. Because the quantity of HPβCD in the petitioner's proposed product will be the same as the quantity of SBEβCD in the RLD, the maximum quantity of HPβCD that would be administered daily to the patient in the form of petitioner's drug product would be 13.440 g as well. This quantity is below the maximum daily intake of HPβCD administrated to patients in the previously-approved Sporanox product.

The RLD label indicates that the minimum duration of IV voriconazole therapy varies from 7 – 14 days, depending upon the indication.[45] By performing a calculation similar to that performed above, it can be seen that a 70 kg patient in the "maintenance dosing period" (*i.e.,* following the initial 24-hour loading period) would receive a maximum daily intake of 8.96 g of HPβCD. The maximum intake of HPβCD with Sporanox during the maintenance period was 8 g and although there is a slightly higher intake associated with the petitioner's product, the values are similar and well below the maximum daily intake of 16 g associated with Sporanox.

The foregoing provides substantial evidence that the HPβCD in the petitioner's proposed product can be generally considered safe and suitable for use in IV formulations as defined by FDA.

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[43] Vibativ product Label for NDA No. 022110, approved September 11, 2009, at 1, 3, and 14. Obtained from Drugs@FDA, and accessed at: http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/022110s000lbl.pdf (February 12, 2013).

[44] Vfend product label at 3-6 and 20.

[45] *See id.* at 3-6.

e. HPβCD was previously used in Pfizer's early voriconazole development program, and there is no indication that it was considered unsafe

The publicly-available information from the Vfend I.V. NDA shows that **Pfizer's IV voriconazole drug product was primarily formulated with HPCβD during its early development.** According to the Voriconazole Advisory Committee Briefing Document,[46] SBEβCD was introduced later as a solubilizing excipient in clinical trials beginning in 1994.[47] The briefing document shows that **clinical studies conducted by Pfizer with the HPβCD formulation included the following:**

- Intravenous single dose studies: *Single Dose Escalation IV study to 4 mg/kg* (a single blind, placebo controlled study, United Kingdom, completed in November 1992, Study No. 207) (Appendix 13A at 173); and *Single Dose Escalation IV study to 8 mg/kg* (a single blind, placebo controlled toleration, safety and pharmacokinetics study, United Kingdom, completed in March 1993, Study No. 213) (Appendix 13A at 173);

- Intravenous multiple dose study: *Multiple Dose IV Study at 3 mg/kg q12h* (a single blind, placebo controlled toleration, safety and pharmacokinetics study, United Kingdom, completed in March 1993, Study No. 214) (Appendix 13A at 173);

- *A radiolabeled Oral and IV Study* (an open, parallel group study to investigate absorption, metabolism and excretion of ^{14}[C]-voriconazole, The Netherlands, completed in February 1994, Study No. 220) (Appendix 13A at 175);

- Supportive phase 1 studies: *Single dose Capsule and IV Study* (a pilot, open, parallel group, pharmacokinetics, safety and toleration study with voriconazole, Italy, completed in October 1993, Study No. 216) (Appendix 13A at 182); *Single Dose Escalation IV Study to 0.9 mg/kg* (a single blind, placebo controlled dose escalation study in healthy male volunteers, United Kingdom, completed in June 1992, Study No. 206) (Appendix 13A at 183); and *Multiple Dose IV Study at 0.9 mg/kg q8h* (a single blind, placebo controlled, single dose study followed by a ten day multiple dose study with voriconazole, United Kingdom, completed in January 1993, Study No. 209) (Appendix 13A at 183).

A total of 84 healthy subjects were enrolled and treated with HPβCD-voriconazole in the first three listed safety, tolerability, and pharmacokinetic studies above (Study Nos. 207, 213, and 214). **Pfizer's NDA submission contains both nonclinical and clinical pharmacokinetic data for IV voriconazole formulated with both HPβCD and SBEβCD which, after reconstitution, contained the same concentration (160 mg/mL) as the**

[46] As previously noted, "FDA Antiviral Drugs Advisory Committee Briefing Document for Voriconazole (Oral and Intravenous Formulations) 4-Oct-2001" or "Voriconazole Adv. Comm. Briefing Document," obtained from http://www.fda.gov/ohrms/dockets/ac/01/briefing/3792b2_01_pfizer.pdf and provided as Appendix 13A.

[47] *See id.* at 13.

HPβCD in the petitioner's proposed product.[48] In both its U.S. submission and its Japanese submission, the studies conducted with HPβCD appeared to be used in the evaluation of the safety of voriconazole formulated with SBEβCD. **No significant safety issues resulting from the use of either vehicle or distinguishing one from the other were noted.**[49]

Moreover, in Pfizer's application for Vfend marketing authorization in Japan, the results of Phase I clinical trials conducted with the HPβCD-voriconazole formulation (studies identified as Nos. 150-209, 150-214 and 150-220, which correspond to the studies identified as Nos. 209, 214 and 220 respectively in the Vfend U.S. submission)[50] were presented as supporting studies for evaluation of voriconazole finished drug product safety, along with the data obtained in studies conducted with the SBEβCD-voriconazole formulation. Although the dosing regimen for voriconazole in the HPβCD formulation was not exactly the same as the dosing regimen applied for the SBEβCD formulation, the same studies were not repeated with the SBEβCD formulation, implying that the results obtained for the HPβCD formulation were considered applicable for evaluation of the SBEβCD formulation. (*See* note 47, *supra.*) Because **no safety issues specifically related to the HPβCD-voriconazole formulation were recorded,** it can be concluded that **both formulations would exhibit similar toxicological profile in the human organism when applied in the same manner in the same dose.**

In addition, the acceptance of a human radiolabeled ADME study conducted with HPβCD-voriconazole indicates acceptance of the fact that the metabolism and excretion of voriconazole are not affected by the specific formulation.[51] This further suggests that FDA saw no safety concerns arising from pharmacokinetic, metabolism, excretion or bioequivalence issues between HPβCD and SBEβCD.

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[48] *See* Vfend Chemistry Review at 27-39 (discussing preclinical intravenous studies) and August 29, 1995 Pharmacologist's Review at 1 (noting that "[m]ost phase II efficacy studies to date have been performed using an oral capsule and an intravenous infusion in the excipient hydroxypropyl-β-cyclodextrin (HPβCD)."

[49] *See* Appendix 13A at 47, 173, 175, 182 and 183; Vfend Chemistry Review at 27-39; Vfend Clinical Pharmacology and Biopharmaceutics Review; Vfend (Voriconazole for Injection 200 mg/vial) CTD document, Section 2.7.4.1.1 Descriptions of Overall Safety Evaluation Plan and Safety Test, Pfizer Inc., at 30, 250, 252, 259, 260, 279, 306 and 387. The original document in Japanese was accessed at http://www.pfizer.co.jp/pfizer/development/clinical_development/new_medicine_info/documents/apply_document/appli_doc_h17_04_vfend_rinsho1.pdf . An English translation and portions of the original Japanese document is provided as
Appendix 22.

[50] *See* Appendix 5 at 208-10 (Study No. 150-209), 211-13 (Study No. 150-214), and 61-64 (Study No. 220); Appendix 13A at 183 (Study No. 209), 173 (Study No. 214), and 175 (Study No. 220). The reports from the Japanese submission (Appendix 5) for Study Nos. 150-209 and 150-214 state that HPβCD was used, and the same formulation used in 150-214 was used in 150-220 (prescription No. S00059CB, Lot No. 3043-007).

[51] The study is described in the Pfizer Japanese submissions as Study No. 150-220 and in the U.S. submission as Study No. 220. *See* Appendix 5 at 61-64; Appendix 22 at 30, 248, 250, 252, 279, 306 and 387; Appendix 13A (Voriconazole Adv. Comm. Document) at 13-15 and 175. The same data is described in a publication by employees of Pfizer Global Research and Development. *See* Appendix 15 at 732-33 and 738 (describing the same procedure and data identified in the Adv. Comm. Document). No other ADME studies were presented to the Advisory Committee.

Furthermore, according to the publicly-available information, Pfizer did not conduct a study comparing the pharmacokinetics of voriconazole administered with a HPβCD formulation versus the pharmacokinetics of voriconazole administered with a SBEβCD formulation.[52] This also suggests that data obtained with the HPβCD formulation were considered adequate for Pfizer to continue Phase 3 clinical studies with an SBEβCD formulation, and that the pharmacokinetics and the safety of voriconazole drug product formulated with HPβCD versus SBEβCD are comparable.

f. The petitioner's HPβCD formulation does not contain the mutagenic alkylating agent 1,4-butane sultone that is present in the RLD

The petitioner's proposed product has an improved toxicity profile over the RLD in at least one respect: unlike the RLD, the petitioner's proposed formulation does not contain the mutagenic alkylating agent 1,4-butane sultone.

SBEβCD sodium used in the RLD is synthesized in one step from beta-cyclodextrin and 1,4-butane sultone.[53] The later compound (1,4-butane sultone) has been shown to be an alkylating mutagenic agent that exhibits evidence of carcinogenicity in rodents.[54] This impurity could be present in SBEβCD, and ultimately the RLD product, as a process-related impurity. In addition, during storage of the RLD the level of 1,4-butane sultone may increase. That is because another impurity potentially present in SBEβCD, 4-hydroxybutane-1-sulfonic acid, can cyclise during storage, also leading to the formation of 1,4-butane sultone.[55]

The petitioner has performed an analysis of the RLD for the presence and quantity of the 1,4-butane sultone impurity and has detected its presence in quantities of up to 0.18 ppm which, when calculated in terms of maximum daily intake, is equivalent to an intake of 2.57 µg/day. This exceeds the general threshold of toxicological concern of 1.5 µg/day established by regulatory agencies. For details on this analysis, please see **Appendix 25.**[56]

The EMA has also raised concern regarding this 1,4-butane sultone impurity in Vfend. As a result, Pfizer has committed to attempt to find an alternative route of synthesis for SBEβCD. Meanwhile, the limit for 1,4-butane sultone was requested to be reduced to less than 1 ppm and should an alternative route of synthesis not be possible, alternative

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[52] *See generally id.*

[53] Appendix 1 at page 3.

[54] MAK Collection for Occupational Health and Safety, Wiley On-Line Library, 1,4-Butane sultone [MAK Value Documentation, 1992], Published Online: 31 JAN 2012, accessed at: http://onlinelibrary.wiley.com/doi/10.1002/3527600418.mb163383isme0004/full , provided as **Appendix 23,** at 46-48.

[55] Australian Public Assessment Report for Ziprasidone mesilate, Proprietary Product Name: Zeldox IM, Submission No: PM-2008-1737-1, Sponsor: Pfizer Australia Pty Ltd., December 2009, provided as **Appendix 24,** at 6.

[56] Report: Determination of Genotoxic Impurity 1, 4-Butane Sultone in Reference Listed Drug Vfend (Voriconazole for Injection 200 mg/vial) and in Petitioner's Voriconazole for Injection 200 mg/vial (February 7, 2013).

formulations will be considered after discussion with Committee for Proprietary Medicinal Products (CPMP).[57]

Because the petitioner's proposed formulation is an alternative to SBEβCD that does not contain potentially carcinogenic impurities, it should be considered favorable from the perspective of the patient safety.

2. The petitioner's proposed drug product is expected to have the same therapeutic effect as the RLD drug when administered to patients

a. The change of substituted βCD in proposed drug product will not influence the pharmacokinetics and pharmacodynamics of the voriconazole active ingredient

As noted earlier, the literature data suggest that following IV administration of drug product a rapid dissociation of the cyclodextrin: drug complex occurs, primarily due to dilution effects, and as a result, the type of substituted ß-cyclodextrin used for complexation should not influence the pharmacokinetics of the drug. This is supported by the petitioner's *in vitro* experimental studies on the kinetics of voriconazole release from its proposed product and that of the RLD, summarized in Appendix 12.

In addition to dilution effects, mechanisms such as competitive displacement (by endogenous and exogenous molecules), plasma and tissue protein binding, and preferential drug uptake by tissues may also play a role in the release of drugs from their cyclodextrin complexes.

The role of competitive displacement raised some issues with the FDA after studies with sugammadex first surfaced. Sugammadex, a modified γ-cyclodextrin, is designed to specifically bind to rocuronium, a neuromuscular blocker, and reverse its blockade. The binding constant of rocuronium to sugammadex is said to be about 10^7 M^{-1}, a value far outside of the normal values of binding of nearly all known drugs to any CD, except for another unusual case - a series of anti-malarials binding to SBEβCD. As noted earlier, when binding constants are greater than 1×10^5 M^{-1}, it is more probable that interactions of drug with cyclodextrin may persist, even on dilution. Therefore, a question arose - could the cyclodextrin used to effectively deliver a specific agent on systemic administration bind to a second co-administered drug and alter its pharmacodynamics and pharmacokinetics? This has not been observed in any known cases, and one could reasonably argue that this is a nonissue except in the very rare case of a drug having an extraordinary interaction with any of the known approvable cyclodextrins. Even here, the effect should be fleeting, because the cyclodextrins are rapidly renally excreted.[58]

In the case of voriconazole-substituted β-cyclodextrin complexes (HPβCD and SBEβCD), experimentally determined values of binding constants are well below 1×10^5 M^{-1}, and are equal to 319 M^{-1} and 491 M^{-1} respectively (Appendix 12 at 6.). This implies that the type of

[57] Appendix 1 at 3.

[58] Appendix 8 at 32-34.

substituted β-cyclodextrin will not have an impact on the drug's pharmacokinetics *in vivo*, since voriconazole would be instantly released from both complexes.

In addition to competitive displacement, binding of drugs to plasma proteins (in particular serum albumin) can contribute to the release of the drug from cyclodextrin complexes as well. *In vitro* experiments performed in order to investigate the competitive binding of eight drugs between human serum albumin and HPβCD in isotonic phosphate buffer saline solution (pH 7.4) showed that the parenteral dose of HPβCD would have to be as high as 70 g to have a detectable effect on the protein binding of drugs that are both strongly protein bound and have high affinity to HPβCD (i.e., have high stability constant value). Weakly protein bound drugs and drugs with low affinity towards HPβCD are shown to be insensitive to the cyclodextrin presence.[59] Furthermore, in the case of diflunisal, which exhibits strong protein binding (>99%) with an HPβCD-complex stability constant equal to 5564±36 M^{-1}, additivity in the binding behavior of the two binders present in solution (HPβCD/Bovine Serum Albumin and HPβCD/Human Serum Albumin) is shown, which implies that there is no significant interaction between the two binding molecules in solution.[60] Voriconazole exhibits relatively low affinity for serum protein binding (58% of the drug is found bound to plasma proteins),[61] so taking into consideration this fact together with the finding that the parenteral dose of HPβCD has to be very high to impact protein binding of the drugs, it can be assumed that co-administration of HPβCD with voriconazole instead of SBEβCD would have a negligible effect on voriconazole plasma protein binding and, therefore, the pharmacokinetic properties of the drug would remain unchanged.

Another potential factor to consider involving drug release from cyclodextrin complexes is preferential drug uptake by tissues. This mechanism most likely applies only to drugs whose physicochemical properties allow them to rapidly diffuse through biological membranes or for which the membrane possesses a specific transporter/receptor.[62] **Cyclodextrin complexation of drugs does not affect their intrinsic ability to permeate lipophilic biomembranes.**[63]

Based on the foregoing, as previously noted due to a fast dissociation complex *in vivo*, the pharmacokinetics of the drug and "carrier" cyclodextrin should continue independently one of each other. Therefore, the pharmacokinetics of the active ingredient drug should not be affected by the type of substituted β-cyclodextrin used in products intended for parenteral administration.

The above conclusion is supported by the published data describing studies performed on drugs solubilized either by complexation with different cyclodextrins (with the intent to

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[59] S.V. Kurkov *et al.*, Parenteral delivery of HPβCD: effects on drug-HSA binding. *AAPS Pharm. Sci. Tech.* 11 (2010) 1152-1158, provided as **Appendix 26,** at 1152, 1155-57.

[60] E.E. Sideris *et al.*, Effect of cyclodextrins on protein binding of drugs: the diflunisal/hydroxypropyl-beta-cyclodextrin model case. *Pharm. Res.* 11 (1994) 90-95, provided as **Appendix 27,** at 92-94.

[61] Voriconazole Adv. Comm. Document, Appendix 13A, at 13; Appendix 15 at 734.

[62] See Appendix 7 at 11-12.

[63] T. Loftsson *et al.*, Cyclodextrins and drug permeability through semi-permeable cellophane membranes, *Int. J. Pharm.* 232 (2002) 35–43, provided as **Appendix 28,** at 35-36.

evaluate the potential influence of cyclodextrin used as complexing agent on the pharmacokinetics of the complexed drug) or solubilized by different means (e.g., solubilized by complexation with cyclodextrin versus formulations using cosolvents). For example, Piel *et al.* studied the IV pharmacokinetic properties of miconazole from a commercial surfactant solution and two cyclodextrin formulations that used HPβCD or SBEβCD. The binding constants of miconazole for both cyclodextrins were shown to be well below 1×10^5 M^{-1} (112.2 M^{-1} for HPβCD and 172.5 M^{-1} for SBEβCD). No significant differences were seen in the pharmacokinetic parameters among the three formulations.[64] Likewise, a study by McIntosh *et al.* demonstrated that pharmacokinetic parameters for the active ingredient etomidate following intravenous injection were similar for the commercial "Amidate" formulation and an alternative SBEβCD formulation.[65] Similarly, in a study by Stella *et al.* it was shown that the pharmacokinetic parameters of methylprednisolone administered as SBE4-βCD solution and co-solvent mixture were not significantly different.[66] In general, with very few exceptions (as Sugammadex and antimalarial drugs mentioned in the text above), the available literature indicates that cyclodextrins do not alter the pharmacokinetic properties of drugs after IV administration.[67]

For HPβCD or SBEβCD, the only route of elimination is renal excretion via glomerular filtration. Because of their fairly high clearance and small volumes of distribution, their half-lives are quite short. This means that immediately after IV administration, HPβCD or SBEβCD appear in the proximal tubules of the kidney. As water is reabsorbed, the cyclodextrins are concentrated. Therefore, for a short period of time, drugs that undergo glomerular filtration, that are passively well reabsorbed, and that also have a significant binding to HPβCD or SBEβCD may be retained in the urine at these early time points. Many of these drugs are excreted only to a small extent in the urine, but this can be increased by the presence of the cyclodextrins. For example, when given IV with HPβCD, the renal excretion of unchanged carbamazepine is increased (Brewster *et al.*) when compared to dosing with the carbamazepine tablet and tended to be faster than that after suspension or solution administration. However, this is insufficient to alter its plasma PK properties, as the renal excretion only increased from about 0.5% to about 2.3%.[68]

In summary, the results of the above studies demonstrate that the change in substituted β-cyclodextrin in the petitioner's proposed product will not affect the pharmacokinetics and

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[64] G. Piel *et al.*, Comparison of the IV pharmacokinetics in sheep of miconazole-cyclodextrin solutions and a micellar solution, *Int. J. Pharm.* 180(1) (1999) 41-45, provided as **Appendix 29,** at 43-45.

[65] M. P. McIntosh *et al.*, *In vitro* and *in vivo* evaluation of a sulfobutyl ether β-cyclodextrin enabled etomidate formulation, *J Pharm. Sci.* 93 (2004) 2585-2594, provided as **Appendix 30,** at pages 2589-92.

[66] V. Stella *et al.*, The effect of SBE4-β-CD on I.V. methylprednisolone pharmacokinetics in rats: comparison to a co-solvent solution and two water-soluble prodrugs, *Int. J Phar.* 120 (1995), 189-195, provided as **Appendix 31,** at 193.

[67] *See* Appendix 8 at 32-34.

[68] M.E. Brewster *et al.*, Intravenous and oral pharmacokinetic evaluation of a 2-hydroxypropyl-β-cyclodextrin-based formulation of carbamazepine in the dog: comparison with commercially available tablets and suspensions, *Pharm. Sci.* 86 (1997) 335-339, provided as **Appendix 32,** at 337 & 338 Fig. 2.

pharmacodynamics of voriconazole versus the RLD. The foregoing is also supported by the results of studies provided by Pfizer in support of its US Vfend I.V. NDA submission (discussed in Section C.1.c) and in Pfizer's Japanese Vfend I.V. submission, which is discussed below.

As stated previously in section C.1.e, results of Phase I clinical trials conducted with HPβCD-voriconazole formulation are presented in the Japanese Vfend submission. In the CTD Section 2.7.6, *Summary of Individual Tests,* a detailed description of all conducted studies is provided, together with values of determined pharmacokinetic parameters.[69] Although there is no direct *head-to-head* study between HPβCD-voriconazole and SBEβCD-voriconazole formulations where both products are administered using the same dosage regime and PK parameters are determined at the same time points, there is sufficient data implying that the pharmacokinetics of voriconazole were not affected by the type of substituted β-cyclodextrin present in the formulation. The lack of a *head-to-head* comparison also implies that there were no concerns arising from potential pharmacokinetic, metabolism, excretion or bioequivalence differences between the HPβCD and SBEβCD formulations and the data obtained with the HPβCD formulation were considered relevant and adequate to evaluate voriconazole pharmacokinetics. A summary of supporting clinical trials is given in the text that follows.

As stated previously, SBEβCD was introduced as a solubilizing excipient in clinical trials beginning in 1994, so the first voriconazole single- and multiple-dosing studies were performed with HPβCD as a vehicle. Single blind, placebo comparison, single dosing (3mg/kg) and repeated dosing (3mg/kg 2 times a day for 10 days) trials where HPβCD was used as a solubilizing agent were conducted in order to examine the pharmacokinetics, safety and tolerability when voriconazole was administered intravenously to healthy adult males (Study No. 150-214, Appendix 5 at 211-13). Results are shown in Table 3 below.

Table 3. Average values of Voriconazole pharmacokinetic parameters determined in plasma in Study No. 150-214.[70]

Pharmacokinetics Parameters [a)]	**Day 1**	**Day 5**	**Day 8**	**Day 12**
C_{max} (ng/mL)	2135	3097	3420	3621
T_{max} (h)	0.83	1.03	1.00	1.00
$AUC_{\tau U}$(ng·h/mL)	5215	13210	16381	16535
AUC (ng·h/mL)	6023	NA	NA	23571
AUC_t (ng·h/mL)	5858	NA	NA	22723
CL (mL/min/kg)	8.3	NA	NA	3.0
V_{ss} (L/kg)	2.2	NA	NA	1.5
k_{el} (/h)	0.124	NA	NA	0.107
$t_{1/2}$ (h)	5.6	NA	NA	6.5[b]

NA = No calculation performed.

a) Geometric average values are shown for C_{max}, AUC_τ, AUC, AUC_t and CL, arithmetic average values for T_{max}, V_{ss}, k_{el}, and harmonic average values for $t_{1/2}$.

b) In one case, $t_{1/2}$ was 21.7 hours due to an outlier, subject 30006. (*See* Appendix 5 at 212-13.)

[69] *See* Appendix 5 at 61-64, 208-213, 416-17, and 420.

[70] *Id.* at 212.

This study showed that Voriconazole accumulates in plasma when it is repeatedly administered. Voriconazole concentration in plasma reached a steady state on Day 3 through Day 6 of the repeated administration.

In an open-label, parallel-group study, the absorption, metabolism and excretion of ^{14}C-Voriconazole (administered intravenously) was examined (Study No. 150-220, Appendix 5 at 61-64). The formulation contained HPβCD,[71] and voriconazole was given at an IV dose of 3 mg/kg BID for 10 days with IV ^{14}C-Voriconazole administered on Day 6, when the pharmacokinetics of voriconazole were measured. In this study voriconazole was not administered at a loading dose of 6 mg/kg. However, by Day 6 pharmacokinetic parameters were near steady state and the obtained values can be compared with the values obtained in Study No. 150-214, described above. Results are shown in Table 4 below.

Table 4. Pharmacokinetics of ^{14}C-Voriconazole (HPβCD formulation) on Day 6 after IV Administration of 3mg/kg Voriconazole BID during 10 Days in Study No. 150-220.[72]

Pharmacokinetic Parameters [a)]	
C_{max} (ng/mL)	3330
T_{max} (h)	1.00
AUC_{0-12} (ng·h/mL)	18694
AUC_t (ng·h/mL)	-
AUC (ng·h/mL)	-
k_{el} (/h)	0.1169

a) Geometric averages are shown for C_{max}, AUC_τ and AUC, and arithmetic averages for T_{max} and k_{el}.

As can be seen from Tables 3 and 4, Study Nos. 150-214 and 150-220 showed comparable C_{max}, T_{max} and k_{el} values. Although the AUC_{0-12} (value of 18694 ng·h/mL) in Study No. 150-220 is slightly higher than the value obtained in Study No. 150-214 (AUC_τ=16381 ng·h/mL on Day 8), this value is likely within the range of pharmacokinetic variability observed for voriconazole. (The coefficients of variation, CV, of the average steady state plasma voriconazole concentration predicted from the Phase 1 population pharmacokinetic model during administration of 200 mg orally or 3 mg/kg intravenously q 12 h were 94% and 100%, respectively).[73]

Later, in a single blind, random, tertiary cross-over, IV dose escalation study conducted in healthy adult males with a formulation containing SBEβCD (Study No. 150-226, Appendix 5 at 414-16), it was shown that the voriconazole AUC measured in plasma did not increase proportionally to the administered dose of the drug when the dose was increased from 3 mg/kg to 6 mg/kg, suggesting that voriconazole has non-linear pharmacokinetics. The same study concluded that voriconazole metabolism becomes saturated since the body clearance declined when an increased amount of voriconazole was administered. These conclusions are

[71] *See* note 50, *supra*.

[72] Appendix 5 at 63.

[73] Voriconazole Adv. Comm. Document, Appendix 13A, at 19.

in line with the phenomena previously observed in study No. 150-214 conducted with HPβCD as vehicle, in which it was also shown that voriconazole exhibits nonlinear pharmacokinetics and during repeated administration steady-state clearance and the distribution volume of Voriconazole seemingly decreased but voriconazole accumulated in plasma.[74]

Another study using a SBEβCD-voriconazole formulation, Study No. 150-227 (Appendix 5 at 417-20), showed results consistent with those of Study No. 150-214. Study No. 150-227 was a single blind, placebo controlled, multiple dose, intravenous study with a loading dose of 6 mg/kg twice per day on the first day and maintenance doses of 3 mg/kg twice per day for the next 9 days (one time on the last day). Results are shown in Table 5 below.

Table 5. Voriconazole pharmacokinetic parameters determined in plasma from Study No. 150-227.[75]

Pharmacokinetic Parameters [a)]	**Day 1**	**Day 3**	**Day 6**	**Day 10**
C_{inf} (ng/mL)	4675	2891	3141	2983
C_{max} (ng/mL)	4695	3031	3150	3063
T_{max} (h)	0.94	0.94	1.06	1.06
C_{min} (ng/mL)	--	456	389	420
AUC_τ (ng·h/mL)	13217	13584	12928	13245
AUC_τ ratio [b)]	--	2.4	2.2	2.2
C_{max} ratio [b)]	--	1.4	1.5	1.4
k_{el} (/h)	--	--	--	0.1038
$t_{1/2}$ (h)	--	--	--	6.7
CL_p (mL/min/kg)	--	--	--	4.2
V_{ss} (L/kg)	--	--	--	1.6
Average protein bonding ratio (%)	61 ± 3.4[c)]	--	--	58 ± 2.9
Note: The cells with "--" have no data available in the source; they have not been measured for that day.				

C_{inf}: concentration in plasma, CL_p: Systematic plasma clearance, CL_r: Renal clearance

a) C_{inf}, C_{max}, C_{min}, and AUC_τ are geometric averages, T_{max}, AUC_τ ratio, C_{max} ratio, k_{el}, CL_p, CL_r and V_{ss} are arithmetic averages, $t_{1/2}$ is a harmonic average.

b) Ratio compared to day 1 (Standardized by administration dose)

c) Data after single administration

One of the conclusions from Study No. 150-227 was that the concentration of voriconazole in the plasma reached a steady state by Day 3, which is in line with the findings of a previous repetitive intravenous administration study conducted with HPβCD-voriconazole formulation, Study No. 150-214.

Furthermore, Study No. 150-227 was a parallel-group, double-blind, randomized, placebo-controlled study with healthy adult males given IV voriconazole formulated with SBEβCD with a loading dose of 6 mg/kg two times a day on the first day and maintenance doses of 3, 4 or 5 mg/kg two times a day for the subsequent six days. (Appendix 5 at 56-60.) On Day 7 of the study with a maintenance dose of 3 mg/kg dose, C_{max}, AUC_τ and T_{max} were 3006 ng/mL, 13919 ng·h/mL and 1.07 h, respectively. These findings are comparable to the results

[74] *Compare* Appendix 5 at 416 *with id.* at 212.

[75] Appendix 5 at 419.

obtained with the SBEβCD formulation in Study No. 150-227 and with the HPβCD formulation in Study No. 150-214.[76]

In summary, given that the high inter-individual variability in the pharmacokinetics of voriconazole,[77] the results from the above-mentioned studies (Nos. 150-227 and 150-230 conducted with the SBEβCD-voriconazole formulation and Nos. 150-214 and 150-220 conducted with the HPβCD-voriconazole formulation) show that the pharmacokinetic parameters of voriconazole appear to be comparable when administered as a SBEβCD-voriconazole formulation or as a HPβCD-voriconazole formulation.

b. The biotransformation of voriconazole is not affected by the type of substituted ß-cyclodextrin

The petitioner has also considered whether its proposed HPβCD formulation will have an influence on voriconazole metabolism compared to the RLD, and how voriconazole affects the biotransformation of HPβCD versus that of SBEβCD in the RLD.

It is general knowledge that cyclodextrins are not metabolized and the only route of elimination for HPβCD or SBEβCD is renal excretion via glomerular filtration. On the other hand, voriconazole is eliminated entirely by metabolism via the cytochrome P450 system, with a minimal portion of the drug eliminated unchanged in the urine. Since there are no literature data reporting that cytochrome P450 enzymes are involved in HPβCD or SBEβCD metabolism (particularly the enzymes involved in metabolism of voriconazole) and both of these β-cyclodextrins are eliminated rapidly from the body and appear in the urine unchanged, it is unlikely that either of them, or the proposed change from SBEβCD to HPβCD, will affect voriconazole biotransformation. This conclusion is supported by the already-referenced ADME study conducted by Pfizer using voriconazole formulation containing HPβCD, which was accepted as the only ADME study in the Pfizer NDA submission for voriconazole.[78]

Available data also demonstrate that the metabolism and excretion of substituted β-cyclodextrins are not affected by voriconazole itself, and therefore it can be assumed that the biotransformation of all complex subunits (active substance and substituted β-cyclodextrins) will be independent of each other.

A summary of available literature data is given in the attached **Appendix 33**, which is an expert report entitled "Evaluation of influence of sulfobutyl ether beta-cyclodextrin (SBEβCD) or hydroxypropyl beta-cyclodextrin (HPβCD) on voriconazole biotransformation in human organism."

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[76] *Compare* Appendix 5 at 58 (Study No. 150-230) *with id.* at 419 (Study No. 150-227) and 212 (Study No. 150-214).

[77] Appendix 13A at 19.

[78] *See* note 51, *supra.*

c. The antifungal activity of voriconazole is not affected by the type of substituted ß-cyclodextrin

In vitro studies evaluating the microbiological potency of voriconazole formulated with HPβCD versus SBEβCD were performed in order to evaluate the effect of either vehicle on the antifungal activity of voriconazole. Determination of Minimal Inhibitory Concentrations (MICs), which indicates the antifungal activity of voriconazole, was performed on three *Candida* strains identified in the RLD labeling as quality control microorganisms - *Candida albicans* ATCC 90028, *Candida krusei* ATCC 22019 and *Candida parapsilosis* ATCC 6258.[79] There were no statistically significant differences in the MICs of either formulation against each of three tested strains. Thus, the results indicate that the antifungal activity of the drug product is not affected by the petitioner's proposed formulation change.

For further details, please see the report provided as **Appendix 34**.

III. Conclusion

For the reasons set forth above, the petitioner believes that there are sufficient grounds demonstrating the safety and efficacy of its proposed formulation and its eligibility for ANDA submission relying on Vfend I.V. as the RLD.

IV. Environmental Impact

A claim for categorical exclusion of the requirement for submission of an environmental assessment is made pursuant to 21 CFR 25.31.

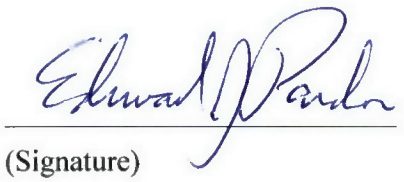
V. Economic Impact

Pursuant to 21 CFR 10.30(b) economic impact information is to be submitted only when requested by the Commissioner. This information will promptly be submitted, if so requested.

VI. Certifications

The undersigned certifies, that to the best of its knowledge and belief, this petition includes all information and views on which the petitioner relies, including representative data and information known to the petitioner that are unfavorable to the petition.

[79] Vfend product label at 31.



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