FOLEY HOAG LLP

1717 K Street, N.W.
Washington, DC 20006-5350

202.223.1200 main
202.785.6687 fax

THIS COPY CONTAINS CONFIDENTIAL AND PROPRIETARY BUSINESS INFORMATION EXEMPT FROM PUBLIC DISCLOSURE THAT HAS BEEN REDACTED FOR PUBLIC COMMENT

Areta Kupchyk
202-261-7324 direct
akupchyk@foleyhoag.com

October 25, 2019

Via Hand Delivery

Division of Dockets Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

CITIZEN PETITION

The undersigned, on behalf of Vifor Fresenius Medical Care Renal Pharma France ("Vifor Fresenius"), the holder of the new drug application ("NDA") for VELPHORO® (sucroferric oxyhydroxide), submits this citizen petition under 21 U.S.C. § 355, 21 C.F.R. § 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs take the actions requested herein.

Specifically, based on the claims and defenses being asserted in connection with U.S. Patent No. 9,561,251 in *Vifor Fresenius Medical Care Renal Pharma Ltd. et al. v. Lupin Atlantis Holdings SA et al.*, No. 18-390-LPS

(D. Del.), Vifor Fresenius believes that at least one abbreviated new drug application ("ANDA") referencing VELPHORO® has been submitted seeking approval of a proposed generic drug that does not include the same mixture of starches as found in VELPHORO®'s sucroferric oxyhydroxide active ingredient.

Changes to the starches in the complex sucroferric oxyhydroxide mixture raise questions regarding whether such a proposed generic product contains the same active ingredient as VELPHORO®, as required by Section 505(j)(2)(A)(ii) of the Food, Drug, and Cosmetic Act ("FDCA"). Accordingly, Vifor Fresenius requests that FDA set standards for identity for determining whether proposed generic drugs that do not have the same starches as in VELPHORO®'s sucroferric oxyhydroxide contain the "same" active ingredient as the reference listed drug ("RLD"). In particular, Vifor Fresenius requests that FDA set standards for identity that are sufficient to confirm that any proposed drugs that alter the starches used have equivalent physicochemical properties, iron release characteristics, phosphate adsorption characteristics, and toxicity profiles as the active ingredient in VELPHORO®.

ACTIONS REQUESTED

Vifor Fresenius requests that the Commissioner:

1) Determine that standards for identity are needed for proposed generic versions of VELPHORO® that change the starches used in the sucroferric oxyhydroxide active ingredient.
2) Set standards for identity that require a sponsor of an ANDA for a generic version of VELPHORO® with such changes to show active ingredient sameness by submitting:
    1. Evidence of physicochemical equivalence;
    2. Evidence of equivalence from *in vitro* assays;

3. Evidence of equivalence from limited *in vivo* and genotoxicity studies.

STATEMENT OF GROUNDS

I. Background

A. VELPHORO® (sucroferric oxyhydroxide)

VELPHORO® is a phosphate binder, administered orally as a chewable tablet. It has been approved by FDA for the control of serum phosphorus levels in patients with chronic kidney disease ("CKD") on dialysis.[1] The active ingredient in VELPHORO® is sucroferric oxyhydroxide, a mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches.[2] The specific form of polynuclear iron(III)-oxyhydroxide in VELPHORO® is characterized by its method of manufacture, including the starches and other carbohydrates used, and its physicochemical properties.

Patients with CKD have diminished filtration and excretion of phosphates via the kidneys. Serum phosphorus concentration is primarily determined by the ability of the kidneys to excrete dietary phosphate in order to maintain physiological balance. In advanced stages of CKD, patients suffer from hyperphosphatemia, an excess of phosphate in the bloodstream.

As a result, patients can suffer from elevated phosphate levels, which create well known health risks.[3] Such elevated phosphate levels may lead to metastatic calcification, a condition where calcium and phosphate precipitate in

---

[1] Ex. 1, VELPHORO® Label at 1.

[2] *Id*. at § 11.

[3] Ex. 2, Cozzolino et al., *Preclinical Pharmacokinetics, Pharmacodynamics and Safety of Sucroferric Oxhydroxide*, Current Drug Metabolism. 2014; 15(10):953-65; Ex. 3, Hruska et al., *Hyperphosphatemia of chronic kidney disease*, Kidney Intl. 2008; 74:148-57.

arteries, soft tissues, and other organs, which can affect existing atherosclerotic plaques and aortic valves.[4] Elevated serum phosphate and calcium-phosphate products are also associated with an increased risk of mortality in dialysis patients.[5] For these reasons, adequate control of phosphate levels in CKD patients is critically important.

VELPHORO®, a phosphate binder, is administered orally to patients in order to limit and control phosphate adsorption, thereby controlling the phosphate levels of CKD patients. After ingestion of VELPHORO®, phosphate binding takes place in the aqueous environment of the gastrointestinal tract through interactions between the sucroferric oxyhydroxide and the phosphate in the diet.[6] The bound phosphate is then eliminated with feces.[7]

One of the advantages of VELPHORO® is that its iron-containing particles are insoluble and therefore not absorbed or metabolized.[8] As a result, the iron is generally excreted in the feces with bound phosphate rather than being absorbed or metabolized, and only minimal amounts of iron will be absorbed into the bloodstream.[9]

---

[4] Ex. 4, Ritz et al., *Some Cardiac Abnormalities in Renal Failure, in* 27 Advances in Nephrology 85-103 (Jean-Pierre Grunfeld, et al. eds., 1997); Ex. 5, Raine, *Acquired Aortic Stenosis in Dialysis Patients*, Nephron. 1994; 68:159-68; Ex. 3, Hruska et al., *supra* note 3.

[5]Ex. 6, Block et al., *Mineral Metabolism, Mortality, and Morbidity in Maintenance Hemodialysis*, J. Am. Soc. Nephrol. 2004; 15:2208-18.

[6] Ex. 1, VELPHORO® Label at § 12.1.

[7] *Id*.

[8] *Id*. at § 12.3.

[9] NDA 205109 at 2.3.S.1.2; *see also* Ex. 2, Cozzolino et al., *supra* note 3; Ex. 7, Wilhelm et al., *The iron-based phosphate binder PA21 has potent phosphate binding capacity and minimal iron release across a physiological pH range in vitro*, Clin. Nephrol. 2014; 81(4):251-58.

However, the possibility that iron could be absorbed or metabolized is a potential risk for iron-carbohydrate products. If the iron were to be absorbed, it could lead to changes in iron indices, storage, and accumulation, and to iron overload. Excessive iron absorption poses well-recognized safety issues. For example, patients with iron overload conditions exhibit constantly elevated reactive non transferrin bond iron (or "NTBI") levels.[10]

B. History of VELPHORO® and Changes to its Composition During the NDA Approval Process

During clinical trials for VELPHORO® two drug substances were used: The drug substance designated as PA21 was used initially in Phase 1 and Phase 2 clinical trials. PA21 was subsequently replaced with a drug substance designated as PA21-2 for Phase 3 clinical trials and drug-drug interaction studies.

Both PA21 and PA21-2 consist of a mixture of iron(III)-oxyhydroxide, sucrose, and starch. [redacted] PA21-2 differs from PA21 in the type of starch used in the sucroferric oxyhydroxide mixture. [redacted]

[10] Ex. 8, Geisser et al., *The Pharmacokinetics and Pharmacodynamics of Iron Preparations*, Pharmaceutics. 2011; 3:12-33, 20; Ex. 9, Brissot et al., *Non-transferrin bound iron: A key role in iron overload and iron toxicity*, Biochimica et Biophysica Acta. 2012; 1820:403-10.

[11] Ex. 10, Briefing Document for Type C Meeting at 33.

[12] *Id.*

[redacted]

In proposing the change from PA21 to PA21-2 to FDA, Vifor Pharma, then the sponsor of the NDA, conducted analyses to ensure that the efficacy and safety profile of PA21-2 was the same as PA21 despite the change in starch. [redacted]

In addition, Vifor Pharma performed *in vitro* testing of PA21-2 to evaluate its phosphate binding and iron release. *In vitro* phosphate adsorption testing confirmed [redacted].[17] Similarly, iron release testing showed that PA21-2 [redacted][18]

---

[13] *Id.*

[14] *Id.* Treatment adherence results are included in Section 14.2, Dose Titration Study, in the VELPHORO® Prescribing Information. Ex. 1, VELPHORO® Label at § 14.2.

[15] Ex. 10, Briefing Document for Type C Meeting at 45.

[16] *Id*. at 35, 45.

[17] *Id.* at 35-36.

[18] *Id.* at 45.

In addition to these *in vitro* studies, Vifor Pharma conducted a reduced toxicology program to confirm the similarity of PA21 and PA21-2. Specifically, it conducted: 1) a four-week comparative toxicity study in rats; and 2) *in vitro* genetic toxicity studies. The four-week rat study showed similar results for PA21 and PA21-2 with respect to tissue iron levels, confirming that this particular change in starch source did not alter the iron uptake or overload properties of PA21.[19] Similarly, the genetic toxicity studies showed similar findings for PA21-2 as compared to PA21, confirming no genotoxic impurities were present in the starches used.[20]

Based on these studies and data, FDA agreed that i) Vifor Pharma had sufficiently established the physicochemical comparability of PA21 and PA21-2[21]; ii) that the toxicity profile of PA21-2 had been sufficiently established to permit longer-term Phase III studies[22]; and iii) that it was acceptable to use the PA21-2 formulation for the remaining Phase III clinical program to support a later NDA application for PA21-2.[23] Long-term Phase III studies using PA21-2 were thereafter conducted to support an NDA application for PA21-2, which as discussed above [redacted]. Long-term clinical studies of PA21, containing [redacted], have not been conducted.

---

[19] Ex. 10, Briefing Document for Type C Meeting at 61-63.

[20] *Id.* at 61-63.

[21] *See* Ex. 11, February 17, 2009 FDA Preliminary Responses for a Meeting with FDA at ¶ 1.

[22] *Id.* at ¶ 2.

[23] *See id.* at ¶ 4.

The NDA for VELPHORO®, using PA21-2 as the proposed formulation for the sucroferric oxyhydroxide active ingredient, was approved in November 2013.

The currently-approved label for VELPHORO® describes the sucroferric oxyhydroxide drug substance as "a mixture of polynuclear iron(III)-oxyhydroxide, sucrose, and starches."[24] It further states that each tablet of VELPHORO® contains 500 mg iron and "approximately 1.4 g of carbohydrates (750 mg sucrose and 700 mg starches)."[25] In both instances, the label lists the starch component of the active ingredient in the plural: "starches."

C. FDA's Product-Specific Bioequivalence Guidance for Sucroferric Oxyhydroxide

In March of 2015, FDA issued a draft guidance on sucroferric oxyhydroxide setting forth FDA's recommendations for bioequivalence studies to support generic versions of VELPHORO®.[26] This guidance recommended two *in vitro* studies, an *in vitro* equilibrium binding study and an *in vitro* kinetic binding study, for demonstrating bioequivalence to sucroferric oxyhydroxide in chewable, oral tablet form. The guidance does not describe how sponsors of generic versions of VELPHORO® should establish active ingredient sameness.

Vifor Pharma submitted comments on May 8, 2015. These comments set forth Vifor's position that VELPHORO® is a complex drug, largely defined by its specific manufacturing process, and cannot be fully characterized by

---

[24] Ex. 1, VELPHORO® label, at § 11.

[25] *Id.*

[26] Ex. 12, FDA Draft Guidance on Sucroferric Oxyhydroxide (March 2015).

physicochemical analyses.[27] It also recommended studies for assessing bioequivalence.[28]

II. Statutory and Regulatory Background

Section 505(j) of the Food, Drug, and Cosmetic Act ("FDCA") governs the ANDA approval process for generic drugs.[29] While the ANDA applicant is not required to submit clinical studies to establish the safety and effectiveness of the product, the FDCA requires any person filing an ANDA to provide information demonstrating among other things that the "active ingredients of the new drug are the same" as the reference listed drug.[30] In addition to establishing sameness, the FDCA also separately requires that the ANDA sponsor submit "information to show that the new drug is bioequivalent to the listed drug."[31]

The FDCA does not define the type or amount of information that an ANDA applicant should submit to establish the sameness of the active ingredient in the generic drug product and reference listed drug product. Instead, FDA exercises broad discretion in making a finding of sameness of an

---

[27] Ex. 13, Comments in Response to FDA's Draft Guidance for Industry on Bioequivalence Recommendations for Sucroferric Oxyhydroxide, Docket No. FDA-2007-D-0369 (May 8, 2015) at 3-4.

[28] *Id.* at 12-13. Since the two *in vitro* tests recommended by FDA are not biorelevant, Vifor Pharma argued that additional more complex in vitro assays are required to stimulate physiologically relevant conditions. *Id.* at 12. Vifor Pharma's comments urged FDA to revise the March 2015 guidance to include a more extensive set of studies to assess bioequivalence of a generic sucroferric oxyhydroxide. *Id.* at 12-13.

[29] 21 U.S.C. § 355(j).

[30] 21 U.S.C. § 355(j)(2)(A)(ii).

[31] 21 U.S.C. § 355(j)(2)(A)(iv). *See also* 21 C.F.R. § 314.3.

active ingredient.[32] In adopting its implementing regulations, FDA has explained that active ingredients are the same if they meet "the same standards for identity."[33] FDA further explains that these standards generally are those described in the U.S. Pharmacopeia (USP) but "in some cases, FDA may prescribe additional standards that are material to the ingredient's sameness."[34]

In situations where potentially clinically meaningful differences between generics and reference listed drugs are identified, FDA has implemented requirements that ANDA sponsors must meet to show product sameness. For instance, in response to a petition submitted by Aventis Pharmaceutical, Inc. regarding Lovenox® (enoxaparin sodium injection), FDA concluded that five criteria (or standards for identity) together would provide sufficient information to conclude that generic enoxaparin has the same active ingredient as Lovenox®.[35] Likewise, in response to a petition submitted by Teva Pharmaceuticals regarding Copaxone® (glatiramer acetate injection), FDA determined that active ingredient sameness between a generic glatiramer acetate injection and Copaxone® could be accomplished by a review of four criteria: (1) the fundamental reaction scheme; (2) physicochemical properties including composition; (3) structural signatures for polymerization and

---

[32] *See generally Serono Labs. v. Shalala*, 158 F.3d 1313, 1318-20 (D.C. Cir. 1998) (interpreting active ingredient sameness within the meaning of the Act and FDA regulations); Ex. 14, FDA Response to Lovenox Citizen Petition, Dkt. No. FDA-2003-P-0273 (July 23, 2010) ("Lovenox Citizen Petition Response") at 25-26.

[33] *See* 57 Fed. Reg. 17950 at 17959.

[34] *Id.*

[35] Lovenox Citizen Petition Response at 11-23. The five criteria included: (1) equivalence of physicochemical properties; (2) equivalence of heparin source material and mode of depolymerization; (3) equivalence of disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species; (4) equivalence in biological and biochemical assays; and (5) equivalence of *in vivo* pharmacodynamics profile.

depolymerization; and (4) results in a biological assay.[36] These criteria were determined "based on [a] current understanding of the product, its indication, and its mechanism[s] of action" and "taken together, [were] designed to provide overlapping and confirmatory evidence of active ingredient sameness through which FDA can conclude that generic glatiramer acetate injection has the same active ingredient as Copaxone."[37]

When evaluating active ingredient sameness for iron-carbohydrate products, FDA has urged a sameness analysis of the "overall complex" in order to establish sameness in physicochemical properties.[38] To establish such sameness for iron sucrose, FDA recommends that *in vitro* characterizations should include attributes such as the composition of carbohydrate shell and surface properties.[39] FDA has also recommended that "equivalence in the stoichiometric ratios of iron, sucrose, and other relevant components need to be established."[40]

ARGUMENT

Changes to the starches in the complex sucroferric oxyhydroxide mixture raise concerns as to whether a proposed generic product including such changes contains the same active ingredient as VELPHORO®, as required by Section 505(j)(2)(A)(ii) of the FDCA. FDA should require that proposed generic versions of sucroferric oxyhydroxide that do not contain the same starches as

---

[36] Ex. 15, FDA Response to Copaxone Citizen Petition, Dkt. No. FDA-2015-P-1050 (Apr. 16, 2015) at 21.

[37] *Id*. at 21.

[38] Ex. 16, FDA Draft Guidance on Iron Sucrose (Nov. 2013).

[39] *Id*.

[40] *Id*.

VELPHORO®[41] submit data sufficient to meet standards for identity that ensure that those products contain the same active ingredient as VELPHORO®.

Accordingly, Vifor Fresenius requests that FDA set standards for identity for determining whether proposed generic drugs that do not have the same starches as in VELPHORO®'s sucroferric oxyhydroxide contain the "same" active ingredient as VELPHORO®. In particular, Vifor Fresenius requests that FDA set standards for identity that require evaluations similar to those that Vifor Pharma undertook upon changing from PA21 to PA21-2. Sponsors of ANDAs where such changes have been made should be required to submit evidence sufficient to confirm equivalence of the active ingredient in its physicochemical properties, iron release, phosphate adsorption, and toxicity profile to the active ingredient in VELPHORO®.

I. FDA Should Set Standards for Identity for VELPHORO®

A showing that a proposed generic drug has the same active ingredient as the reference listed drug is not optional. The FDCA expressly requires that any person filing an ANDA provide information sufficient to show that the "active

---

[41] This Petition is limited to products that change or omit one or more of the starches of sucroferric oxyhydroxide present in VELPHORO®'s active ingredient. As noted above, Vifor Fresenius previously submitted comments in response to FDA's product specific bioequivalence guidance for sucroferric oxyhydroxide. For reasons described in the previously-submitted comments, Vifor Fresenius believes that, for all proposed generic products the bioequivalence guidance is insufficient. With respect to those reasons, Vifor Fresenius rests on the previously-submitted comments, and does not reiterate or raise them here with respect to this Petition.

However, products in which one or more of the starches of the sucroferric oxyhydroxide active ingredient mixture have been changed or omitted raise unique issues that go beyond bioequivalence. They raise questions as to whether the proposed generics contain the "same" active ingredient at all. Thus, even if FDA disagrees with Vifor Fresenius's previously-submitted comments, it should set more stringent standards for identity for proposed generic products that change or omit one or more of the starches of the sucroferric oxyhydroxide mixture to ensure that such a change does not introduce a clinically significant difference between the active ingredients used in the proposed generic as compared to the approved reference listed drug.

ingredients of the new drug are the same" as the reference listed drug.[42] Active ingredient sameness is a fundamental premise of the logic behind the Hatch-Waxman Amendments; without a showing of sameness (among other things) of the active ingredient used, the "expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed [RLD] product" is unwarranted.[43]

Thus, although FDA has broad discretion in determining whether and when two drugs contain the same active ingredient, FDA must nevertheless determine that a proposed generic drug has met the sameness requirement before it can approve an ANDA. FDA has in the past set standards for identity that relate to potentially "clinically significant" differences, particularly for complex or poorly characterized active ingredients.[44] Thus, consistent with FDA's prior precedent and guidance, FDA should examine whether a proposed generic drug that omits or changes a starch in VELPHORO® active ingredient nevertheless meets "the same standards for identity" as VELPHORO®'s sucroferric oxyhydroxide active ingredient.[45]

Here, there are no standards for identity for sucroferric oxyhydroxide set forth in the U.S. Pharmacopeia (USP). Accordingly, FDA should instead "prescribe additional standards that are material to the ingredient's sameness."[46]

---

[42] 21 U.S.C. § 355(j)(2)(A)(ii).

[43] Ex. 17, FDA Response to Citizen's Petitions, Dkt. No. FDA-2004-P-0494 (Mar. 31, 2011) ("Ferrlecit Citizen Petition Response") at 3-4; Ex. 14, Lovenox Citizen Petition Response at 9.

[44] *See* section III.B.4.

[45] *See* 57 Fed. Reg. 17950 at 17959.

[46] *Id.*

This is necessary where a generic sponsor has changed or omitted a starch in VELPHORO®'s sucroferric oxyhydroxide active ingredient because changes to the carbohydrates in sucroferric oxyhydroxide may affect the pharmacological activity of the sucroferric oxyhydroxide mixture and thus introduce a clinically significant difference. VELPHORO® is a complex drug, largely defined by its specific manufacturing process and complicated interplay of its various components, including the iron, sugar, and starches.[47] Evaluating the sameness of iron-carbohydrate drug products requires assessing the overall chemistry of these complex drugs. In iron-carbohydrate products, both the iron moiety and the carbohydrates play a role in the pharmacological activity of the overall active ingredient. Indeed, studies have shown that "[d]ifferences in core size and carbohydrate chemistry determine pharmacologic and biologic differences" in iron-carbohydrate products.[48] These differences may in turn affect the therapeutic and safety profile of the product. "Iron carbohydrates … are complex macromolecules, and their physicochemical and biological properties are closely dependent on the manufacturing process such that subtle structural modifications may affect" their therapeutic and safety profile.[49] Indeed, the European Medicines Agency has observed that for the parenteral iron-anemia products, "[d]ifferences in tissue distribution and toxicological profiles have been described for nanoparticle iron preparations with different

---

[47] *See*, *e.g.*, Ex. 18, Crommelin et al., *Different Pharmaceutical Products Need Similar Terminology*, The AAPS J. 2014; 16(1):11-14, 11; Ex. 19, Schellekens et al., *How to Regulate Nonbiological Complex Drugs (NBCD) and Their Follow-on Versions: Points to Consider*, The AAPS J. 2014; 16(1):15-21.

[48] Ex. 20, Danielson, *Structure, Chemistry, and Pharmacokinetics of Intravenous Iron Agents*, J. Am. Soc. Nephrol. 2004; 15:S93-98, S93.

[49] Ex. 21, Rottembourg et al., *Do two intravenous iron sucrose preparations have the same efficacy?* Nephrol. Dial. Transplant. 2011; 26:3262-67, 3263.

carbohydrate coat and differences in toxicity have been described for nanoparticle iron preparations with the same carbohydrate coat but differences in the manufacturing process."[50]

The nature and amount of the carbohydrate in the active ingredient are thus important, as they affect both the structure of the iron particle, as well as the therapeutic and safety profile of the overall active ingredient.[51] For this reason, for other iron-carbohydrate products, FDA has recognized the importance of the composition and structure of the carbohydrate component in assessing the physicochemical properties and the sameness of iron-carbohydrate active ingredients.[52] The carbohydrates such as the sugar or starches present in sucroferric oxyhydroxide are therefore part of the active ingredient and important to evaluating active ingredient sameness. Thus, for other iron-carbohydrate products, FDA has recommended that the sameness analysis consider the "overall complex," including both carbohydrate components as well as the iron core.[53] FDA has indicated it will require a showing not only of the same polynuclear iron oxyhydroxide core as the reference drug, but also the same carbohydrates.[54] It has required "[e]quivalence in the stoichiometric ratios of iron, sucrose, and other relevant

---

[50] Ex. 22, *Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications*, European Medicines Agency (Mar. 17, 2011) at 4.

[51] *See* Ex. 23, Desai, *Challenges in Development of Nanoparticle-Based Therapeutics*, The AAPS J. 2012; 14(2):282-95, 291 ("The complex nature of nanoparticle-based medicines with their multiple components, where more than one component can affect pharmacological behavior of the active, contrasts against standard drugs where there is usually a single active agent and the other components mostly serve as inactive formulation aids (excipients).").

[52] *See Amarin Pharms. Ir. Ltd. v. FDA*, 106 F. Supp. 3d 196, 211 (D.D.C. 2015) ("Active ingredient" refers to the "entire molecule[] or mixture[], and not simply the 'active moiety.'").

[53] Ex. 17, Ferrlecit Citizen Petition Response at 11.

[54] *Id.* at 9.

components," and has recommended an analysis of "composition of carbohydrate shell and surface properties."[55] Thus, the Agency rightfully recognizes that the active ingredient in these types of products consists of an iron component and a carbohydrate component which interact in potentially unpredictable ways to achieve the intended pharmacological activity.

FDA has also recognized the importance of characterization of the physicochemical properties of the iron-oxyhydroxide core in assessing the sameness of other iron-carbohydrate products.[56] FDA has indicated that it cannot conclude that two iron-carbohydrate products contain the same active ingredient for purposes of ANDA approval without "evidence of equivalence of the iron core."[57] This includes "iron core characterizations including but not limited to core size determination, iron oxide crystalline structure and iron environment" as well as "particle morphology."[58] Other evidence of differences in structure between the iron cores of two active ingredients—such as differences in Mössbauer spectroscopy data or in molecular weight, among

---

[55] Ex. 16, FDA Draft Guidance on Iron Sucrose (Nov. 2013).

[56] Ex. 17, Ferrlecit Citizen Petition Response at 11-13; Ex. 16, FDA Draft Guidance on Iron Sucrose (Nov. 2013).

[57]Ex. 17, Ferrlecit Citizen Petition Response at 11-13.

[58] Ex. 16, FDA Draft Guidance on Iron Sucrose (Nov. 2013); Ex. 24, FDA Draft Guidance on Sodium Ferric Gluconate Complex (June 2013). The European Medicines Agency ("EMA") has also concluded that variations in particle size result in differences in how nanoparticulate compounds behave. Ex. 22, *Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications*, European Medicines Agency (Mar. 17, 2011) at 3 ("Any variation in mean/median size and distribution and/or the accuracy of methods employed for nano-sizing may result in … different physicochemical properties leading to a different biopharmaceutical profile …."); *see also* Ex. 20, Danielson, *supra* note 48, at S95 (particle size is related to the rate of release of iron from the iron hydroxide); Ex. 23, Desai, *supra* note 51 at 285 (2012) ("Particle size and size distribution is one of the most widely accepted defining characteristic of nanoparticle-based medicines because size can significantly impact the PK, biodistribution, and safety…. [In addition,] [n]anoparticle surface properties are also critical determinants for nanoparticle behaviors and interactions with proteins and cells.").

others—will also show a lack of sameness.[59] In addition, to measure the potential for release of free iron, FDA recognizes that the amount of labile, or weakly bound, iron under physiologically relevant conditions must be assessed.[60]

Importantly, and consistent with FDA's approach discussed above, the type and amount of starch used in sucroferric oxyhydroxide can have significant effects on properties of the overall active ingredient, including its levels of iron release and phosphate adsorption. This is shown by data which Vifor Fresenius is submitting with this petition. [redacted]

[59] Ex. 17, Ferrlecit Petition Response at 11-13; Ex. 20, Danielson, *supra* note 48 at S93-95 (differences in core size and carbohydrate chemistry result in differences in molecular weight, which in turn affect the rate of iron release from the ferric hydroxide core).

[60] Ex. 16, FDA Draft Guidance on Iron Sucrose (Nov. 2013); Ex. 24, FDA Draft Guidance on Sodium Ferric Gluconate Complex (June 2013); *see also* Ex. 25, Van Wyck, *Labile Iron: Manifestations and Clinical Implications*, J. Am. Soc. Nephrol. 2004; 15:S107-11, S107.

[61] [redacted]

[62] *See* Ex. 26, Declaration of Erik Philipp Ph.D.at ¶¶ 2-7.

[63] *Id.* at ¶¶ 8 - 12.

Furthermore, the starch used in sucroferric oxyhydroxide can have significant effects on properties of the approved drug product (chewable tablets) containing the active ingredient, in particular the disintegration time of such high load chewable tablets, which has been shown to be an issue for Fosrenol® (lanthanum carbonate) chewable tablets.[64]

Thus, the amount, type, and even the source of the starch can potentially affect clinically relevant properties of the active ingredient. FDA must therefore set standards for identity necessary to confirm that proposed generic products that omit or change any of the starches in VELPHORO®'s sucroferric oxyhydroxide contain the same active ingredient as the RLD.

II. Recommended Criteria (Standards for Identity) to Determine Equivalence

To ensure equivalence of generic drugs that change or omit a starch from sucroferric oxyhydroxide as compared to VELPHORO®, FDA should require any sponsor of such a product to provide evidence showing that, despite the change in starch, the proposed generic is 1) equivalent to VELPHORO® with respect to physicochemical characteristics including both the iron core and carbohydrate components; 2) equivalent in iron release and phosphate adsorption as shown through *in vitro* assays; and 3) equivalent as shown through confirmatory *in vivo* and genotoxicity studies.

A. Evidence of Physicochemical Equivalence

As discussed above, changes to carbohydrates used in complex iron-carbohydrate mixtures have the potential of altering the characteristics of the

---

[64] Ex. 27, Floege, *Phosphate binders in chronic kidney disease: a systematic review of recent data*, J. Nephrol. 2016; 29:329-40; Ex. 28, Chuang et al., *A peritoneal dialysis patient with an unusual abdominal Film*, Kidney International. 2007; 72:1291-92; Ex. 29, Mozzane, *Ingestion of Lanthanum Carbonate Tablets*, Am. J. Kidney Dis. 2013; 62(4):844-46, 844.

particles in the mixture, including the properties of the iron core. Accordingly, where a proposed generic product changes or omits one of the starches, FDA should require the submission of data to confirm equivalence between the physicochemical properties of the sucroferric oxyhydroxide mixture in the proposed generic product with VELPHORO®'s active ingredient.

As an initial matter, data should be submitted showing that the ratios of iron(III)-oxyhydroxide, sugar, and starch in the proposed generic product is equivalent to the ratios in VELPHORO®. As discussed above, Vifor Pharma submitted information, when it transitioned from PA21 to PA21-2, showing [redacted] even though the starch had changed.[65]

But, in addition, where a generic sponsor has changed or omitted one of the starches in VELPHORO®'s active ingredient, it should also be required to submit detailed information to confirm that change has not altered the properties of the active ingredient. Proposed generic products are unlikely to be able to show they have an essentially identical manufacturing process as VELPHORO®.[66] Therefore, upon changing or omitting a starch, the generic sponsor should be required to submit robust evidence confirming physico-chemical equivalence of both the iron and carbohydrate components of the sucroferric oxyhydroxide mixture.

FDA has required this type of showing from generic sponsors on numerous occasions in situations where a proposed generic might differ from the RLD due to natural variation, manufacturing differences, or products that

---

[65] Ex. 10, Briefing Document for Type C Meeting at 33-36.

[66] Vifor Pharma was able to make this showing upon the transition to PA21-2, as the manufacturing protocol for PA21 and PA21-2 were essentially the same except for the change in starch.

are difficult to fully characterize. For example, in response to a citizen petition regarding the parenteral iron supplement Ferrlecit® (sodium ferric gluconate complex in sucrose injection), FDA wrote that "[d]ata showing equivalence of physicochemical properties between the generic product and Ferrrlecit provide important evidence that the active ingredient in the final generic product is the same as that of the RLD. FDA will only approve a generic sodium ferric gluconate product that references Ferrlecit as the RLD if the physicochemical properties are determined to be equivalent to those of Ferrlecit."[67] The agency continued:

> Sodium ferric gluconate complex in sucrose can be characterized and compared to the RLD, Ferrlecit, by using several characterization techniques. For example, techniques that assess the structure of Ferrlecit through various complementary approaches, such as Mossbauer spectroscopy, X-ray diffraction, polarography (voltammetry), UV/vis spectroscopy, electron spin resonance, and elemental analysis, among other techniques, can be used to provide evidence of equivalence of the iron core. In addition, equivalence of the particles that make up the overall complex for sodium ferric gluconate complex in sucrose can be demonstrated using characterization tools such as size-exclusion chromatography, analytical ultracentrifugation, and dynamic light scattering, among other means. Taken together, these characterization techniques may be used to demonstrate equivalence in terms of physicochemical characteristics of the active ingredient in the generic sodium ferric gluconate product to that contained in Ferrlecit.[68]

In other, similar circumstances FDA has likewise required generic sponsors to provide evidence of physicochemical equivalence to support a

---

[67] Ex. 17, Ferrlecit Citizen Petition Response at 11.

[68] Ex. 17, Ferrlecit Citizen Petition Response at 11.

finding of active ingredient sameness. For example FDA's decision in *Serono Laboratories v. Shalala*, affirmed by the D.C. Circuit, required that the active ingredient of proposed generic versions of Pergonal® (a hormone product) "must have the same primary structure, i.e., the same protein backbone and amino acid sequence as Pergonal. . . . ."[69] In addition, FDA required that variations between the hormone's isoforms – *i.e.* proteins with differing carbohydrate side chains – show the same degree of batch-to-batch variation as the reference product.[70] Thus, for Pergonal, FDA required a showing of both core structural similarity as well as a showing that any less material differences were within the same tolerance as the active ingredient in the RLD.

Similarly, in its response to a citizen petition related to generic forms of Lovenox (enoxaparin sodium injection), FDA required evidence of physicochemical equivalence to establish active ingredient sameness. Enoxaparin is an anticoagulant comprising low molecular weight heparins, which is essentially a mixture of relatively short oligosaccharide chains.[71] In deciding a citizen petition related to the sameness of proposed generic products, FDA required that generic sponsors show equivalence of physicochemical properties to establish sameness by providing data on properties such as molecular weight distribution and overall chemical composition.[72] FDA reasoned that such evidence of equivalence of physicochemical properties provides "information on the broad characteristics of enoxaparin and is thus an

---

[69] *Serono*, 158 F.3d at 1318.

[70] *Id.* at 1318-20.

[71] Ex. 14, Lovenox Citizen Petition Response at 5.

[72] Ex. 14, Lovenox Citizen Petition Response at 11-12.

important element in establishing active ingredient sameness."[73] FDA additionally required evidence comparing the proposed generic product and the RLD with respect to source material and mode of depolymerization,[74] as well as evidence that both the proposed generic and the RLD shared similarities in the disaccharide building blocks used and how they were distributed and organized to form the oligosaccharide chains.[75] In other words, FDA once again required meaningful evidence of physicochemical sameness above and beyond bioequivalence assays.

FDA followed this type of approach again in a citizen petition response related to Copaxone, a mixture of peptide copolymers.[76] There, among other things, FDA required generic sponsors to show that the active ingredient in their proposed product had equivalence in physicochemical properties to the active ingredient in the RLD. FDA wrote that evidence of equivalent physicochemical properties such as molecular weight distribution, composition, and spectroscopic fingerprints were "critical" to evaluating active ingredient sameness. As the agency explained, such evidence provides "broad, but critical, characterizations that are able to confirm active ingredient sameness at a greater level of quantitative detail," which provided a more meaningful guarantee of equivalency than could be provided by similarities in the underlying reaction scheme alone.[77]

---

[73] *Id.* at 12-13.

[74] *Id.* at 13-15.

[75] *Id.* at 19-21.

[76] Ex. 15, Copaxone Citizen Petition Response at 10.

[77] *Id.* at 23-24.

Thus, in situations where there may be differences between the active ingredient in a proposed generic and the RLD – due to natural differences, differences in manufacturing, or the existence of complex, heterogenous mixtures – FDA precedent has repeatedly required submission of evidence to confirm equivalence in key physicochemical properties before making the finding of active ingredient sameness required by the FDCA. Those concerns apply with just as much force here. Where an ANDA sponsor has changed or omitted a starch used in VELPHORO®'s sucroferric oxyhydroxide, FDA should require data to confirm that such a change does not result in a product with different physicochemical properties. This should include characterization of both the iron core and carbohydrate components of the sucroferric oxyhydroxide mixture as well as the mixture as a whole. Indeed, FDA's response to the Ferrlecit citizen petition sets out many assays that a generic sponsor could conduct, such as iron core characterization through Mossbauer spectroscopy, and other techniques. FDA's response to that petition also suggests assays for characterization of the entire mixture through size-exclusion chromatography and other tools.[78] It should require the same type of showing here.

B. Evidence of Equivalency Through *In Vitro* Assays

In addition, FDA should require iron release and phosphate adsorption studies from generic sponsors who change or omit one of the starches in VELPHORO®'s active ingredient. These assays will provide important confirmation that any change to the active ingredient has not affected the efficacy or safety of the sucroferric oxyhydroxide. Specifically, FDA should

[78] Ex. 17, Ferrlecit Citizen Petition Response at 11.

require that sponsors conduct *in vitro* iron release testing and phosphate adsorption testing.

Consistent with this recommendation, as discussed above, when Vifor Pharma made the change from PA21 to PA21-2, it submitted *in vitro* data testing their iron release and phosphate adsorption properties to confirm that the change in starch did not result in any detrimental changes of these properties of the active ingredient.[79]

FDA's bioequivalence guidance currently does recommend *in vitro* phosphate binding studies of proposed generic sucroferric oxyhydroxide.[80] However, FDA does not appear to recommend or require iron release studies, which Vifor Pharma submits is a key omission. This issue is of particular concern where a generic sponsor has made changes to their proposed sucroferric oxyhydroxide by changing or omitting a starch. [redacted] Thus, where a generic sponsor has changed the formulation of their proposed sucroferric oxyhydroxide by changing or

---

[79] *See* Ex. 10, Briefing Document for Type C Meeting at 36, 41, 43, 45.

[80] *See* Ex. 12, *supra* note 26. However, Vifor Fresenius believes the assays recommended in the draft guidance are not sufficiently robust for the reasons discussed in Vifor Fresenius's previously submitted comments – *see* Ex. 13, *supra* note 27, at 12-14. That said, Vifor Fresenius believes FDA is correct in requiring phosphate adsorption assays as evidence of bioequivalence and active ingredient sameness.

[81] Ex. 26, Declaration of Erik Philipp Ph.D.at ¶ 8-12.

omitting a starch, confirmatory testing of iron release in relevant physiologic conditions should be conducted to ensure that the product is equivalent to VELPHORO® in its iron release profile. This type of confirmatory *in vitro* testing, in addition to physicochemical characterization, is not unusual. As FDA observed in its response to the Lovenox citizen petition, evidence of physicochemical similarity "provide[s] crucial evidence of equivalent molecular diversity" but evidence showing equivalence in biological and biochemical assays provide "additional important evidence of active ingredient sameness."[82]

Indeed, in its response to a citizen petition raising sameness issues for generic forms of Ferrlecit, FDA required both *in vitro* and *in vivo* assays comparing the iron release characteristics of the generic product and the RLD.[83] FDA wrote that these assays were "needed to demonstrate that the rate and extent of iron absorption of the generic sodium ferric gluconate product do not show a significant difference from the rate and extent of absorption of the RLD."[84] FDA should similarly require confirmatory iron release testing here.

C. Evidence Through Confirmatory *In Vivo* and Genotoxicity Studies

Lastly, FDA should require that sponsors that change or omit a starch in their proposed sucroferric oxyhydroxide conduct confirmatory testing through limited *in vivo* and genotoxicity studies to verify that the toxicity and safety profile of their product has not changed.

---

[82] Ex. 14, Lovenox Citizen Petition Response at 21.

[83] Ex. 17, Ferrlecit Citizen Petition Response at 13-14.

[84] *Id*. at 14.

Once again, this approach is consistent with agency precedent. As discussed above, in both the Lovenox and Ferrlecit citizen petition responses, FDA required some form of confirmatory *in vivo* testing to demonstrate that potential differences in the active ingredient of the generic product did not alter the safety profiles in ways that might not be captured by broad physicochemical similarities. FDA similarly required evidence of equivalence through a biological assay in its Copaxone citizen petition response, writing that such evidence "serves as a confirmatory test of equivalence and provides complementary confirmation of sameness."[85]

Indeed, when Vifor Pharma made the change from PA21 to PA21-2, it provided FDA data from a 4-week rat study to confirm that the iron uptake and safety profile of the product was not affected by the proposed change in the starch used.[86] Vifor Pharma also provided data from two genotoxicity studies to confirm the absence of genotoxic impurities in the starches used.[87] The burden for a generic sponsor to conduct these types of basic *in vivo* and genotoxicity studies is not high, but will provide important confirmatory evidence of active ingredient sameness. FDA should require at least this basic testing from generic sponsors who similarly change or omit one of the starches in VELPHORO®'s sucroferric oxyhydroxide.[88]

---

[85] Ex. 15, Copaxone Citizen Petition Response at 28.

[86] Ex. 10, Briefing Document for Type C Meeting at 61-63.

[87] *Id.*

[88] As mentioned above, the drug product's profile, such as its disintegration time, can also be affected by the type of starch(es) used in the drug substance.

CONCLUSION

For the reasons stated above, Vifor Fresenius requests that the Commissioner grant this citizen petition and set standards for identity, as set forth above, for determining whether a product which does not contain the same starch as VELPHORO® contains the same active ingredient as VELPHORO®.

ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 C.F.R. § 25.31.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

CERTIFICATION

I certify that, to my best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: December 2018. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: Vifor Fresenius Medical Care Renal Pharma France. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,

Areta Kupchyk
Foley Hoag LLP
155 K Street, NW
Washington, DC 20006-5350
202-223-1200
akupchyk@foleyhoag.com

Counsel for Vifor Fresenius
Medical Care Renal Pharma
France

INDEX OF EXHIBITS

18. Crommelin et al., *Different Pharmaceutical Products Need Similar Terminology*, The AAPS J. 2014; 16(1):11-14

19. Schellekens et al., *How to Regulate Nonbiological Complex Drugs (NBCD) and Their Follow-on Versions: Points to Consider*, The AAPS J. 2014; 16(1):15-21

20. Danielson, *Structure, Chemistry, and Pharmacokinetics of Intravenous Iron Agents*, J. Am. Soc. Nephrol. 2004; 15:S93-98

21. Rottembourg et al., *Do two intravenous iron sucrose preparations have the same efficacy?* Nephrol. Dial. Transplant. 2011; 26:3262-67

22. *Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications*, European Medicines Agency (Mar. 17, 2011)

23. Desai, *Challenges in Development of Nanoparticle-Based Therapeutics*, The AAPS J. 2012; 14(2):282-95

24. FDA Draft Guidance on Sodium Ferric Gluconate Complex (June 2013)

25. Van Wyck, *Labile Iron: Manifestations and Clinical Implications*, J. Am. Soc. Nephrol. 2004; 15:S107-11

26. Declaration of Erik Philipp, Ph.D., executed Oct. 24, 2019

27. Floege, *Phosphate binders in chronic kidney disease: a systematic review of recent data*, J. Nephrol. 2016; 29:329-40

28. Chuang et al., *A peritoneal dialysis patient with an unusual abdominal Film*, Kidney International. 2007; 72:1291-92

29. Mozzane, *Ingestion of Lanthanum Carbonate Tablets*, Am. J. Kidney Dis. 2013; 62(4):844-46

FOLEY HOAG LLP

S. Trivedi

1717 K Street, NW
Washington, DC 20036-5342

Division of Documents Management
Department of Health and Human Services
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, MD 20852

HAND DELIVERY

RUSH

CONFIDENTIAL