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1501 K Street, N.W.
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August 8, 2025

Re: Docket No. FDA-2021-P-0893

Dear Mr. Griffin and Ms. Marden:

This letter responds to the citizen petition that you submitted on behalf of Vifor (International) Inc., Switzerland (Vifor) which the Food and Drug Administration (FDA or Agency) received on August 3, 2021 ("Petition" or "the Vifor Petition"), and a subsequent submission providing scientific arguments in support of the Petition titled *White Paper: Scientific Considerations in Identifying the Active Ingredient of Iron carbohydrate Complexes* submitted on November 5, 2021 ("White Paper"). In the Petition, you request that:

1. Pursuant to 21 CFR 10.25(a) and 10.30, that FDA withdraw all portions of the Agency's May 26, 2021, response to Citizen Petition Docket No. FDA-2016-P-1163 ("the 2021 Petition Response") that purport to change the established name and redefine the active ingredients of "iron-containing complex drugs," including Venofer.

2. Pursuant to 21 CFR 10.35(b), that FDA indefinitely stay its decision to change the established name and redefine the active ingredients of iron-containing complex drugs, and that FDA maintain the distinct established names and active ingredients of these products, many of which have been settled for decades, and reverse the actions taken to date to change the names and active ingredients of these products, including but not limited to changes in Drugs@FDA and the Agency's publication *Approved Drug Products with Therapeutic Equivalence Evaluations* ("the Orange Book").

3. Pursuant to 21 CFR 10.25(a) and 10.30, that FDA refrain from taking any further action to implement the changes described in the 2021 Petition Response, including but not limited to any action to change the product label or labeling for Venofer, any action to modify the existing Product Specific Guidance (PSG) for Venofer or iron sucrose, or any action to change the established name of Venofer to ferric oxyhydroxide.

4. Pursuant to 21 CFR 10.25(a) and 10.30, FDA give Vifor advance notice and an opportunity to be heard prior to contacting any naming authority (including the World Health Organization (WHO), the United States Adopted Names (USAN) Council, or the United States Pharmacopeia (USP)) regarding Venofer or iron sucrose.

In the 2021 Petition Response, FDA determined that the active ingredient in certain parenteral iron products — Venofer (NDA 021135, approved on November 6, 2000), Ferrlecit (NDA

020955, approved on February 18, 1999), INFeD (NDA 017441, approved on April 29, 1974), Dexferrum (NDA 040024, approved on February 23, 1996), Proferdex (NDA 017807, approved on March 26, 1981), and Iron Dextran (NDA 010787, approved on April 25, 1957)[1] — is ferric oxyhydroxide (iron (III) oxyhydroxide or FeOOH). In the 2021 Petition Response, the Agency also determined that the active ingredient for Velphoro chewable tablet for oral use (NDA 205109, approved on November 27, 2013) is ferric oxyhydroxide, and updated relevant statements in the Orange Book and in Drugs@FDA to reflect this determination.[2] On May 26, 2021, FDA changed the active ingredient for each of these products in Drugs@FDA and the Orange Book from those shown in the table below to ferric oxyhydroxide:

Drug Product	**Active Ingredient**
Venofer (iron sucrose) injection, for intravenous use	Iron Sucrose
Ferrlecit (sodium ferric gluconate complex in sucrose), injection, for intravenous use	Sodium Ferric Gluconate Complex
INFeD (iron dextran injection), for intravenous or intramuscular use	Iron Dextran
Dexferrum (iron dextran injection)	Iron Dextran
Proferdex (iron dextran injection)	Iron Dextran
Iron Dextran (iron dextran injection)	Iron Dextran
Velphoro (sucroferric oxyhydroxide) chewable tablet for oral use	Sucroferric oxyhydroxide

FDA has carefully considered the information submitted in the Petition and in the White Paper, and in comments submitted to this docket. For the reasons stated below, the Agency is reversing its decision in the 2021 Petition Response that the active ingredient for the identified parenteral iron products is ferric oxyhydroxide. Instead, the Agency concludes that the active ingredient for each of these identified parenteral iron products is the iron carbohydrate complex[3] that the Agency had previously found to be the respective active ingredient for each of the identified parenteral iron products. Therefore, the Agency concludes that the active ingredient is iron sucrose in Venofer, sodium ferric gluconate complex in Ferrlecit, and iron dextran in InFeD, Dexferrum, Proferdex, and Iron Dextran.

The Agency will make conforming revisions to Drugs@FDA and the Orange Book accordingly. Moreover, in light of the Agency's decision, the established names for these identified parenteral

[1] For the purpose of this response to the Petition, the Agency will use the term "certain parenteral iron products" or "identified parenteral iron products" to refer to Venofer, Ferrlecit, InFeD, Dexferrum, Proferdex, and Iron Dextran. Dexferrum, Proferdex, and Iron Dextran have been discontinued from marketing.

[2] FDA will need additional time to evaluate and respond to the requests related to Velphoro in the Vifor Petition. Therefore, this is a partial response to your Petition. FDA intends to respond to your other requests at a later date.

[3] In this response, when referring to the complex of the iron core with carbohydrates generally (or when quoting the Petition), we use the term iron carbohydrate complex. The term iron carbohydrate complex encompasses the terms "polynuclear ferric oxyhydroxide carbohydrate complex," "polynuclear ferric hydroxide carbohydrate complex" and "polynuclear ferric oxide carbohydrate complex." In the context of the identified parenteral iron products, the term "iron core" encompasses the terms "polynuclear ferric oxyhydroxide core," "polynuclear ferric hydroxide core" and "polynuclear ferric oxide core."

iron products will be consistent with the identity of their respective active ingredients. The Agency will also revise relevant PSGs to, among other things, reflect its conclusion that the active ingredient for the identified parenteral iron products affected by these PSGs is the iron carbohydrate complex that previously defined each of their respective active ingredients.[4]

In light of the Agency's decision, your requests 1., 2., and 3. listed above as they apply to the identified parenteral iron products are granted, while request 4. is moot.

This response to the Petition provides only the Agency's reasons for its decisions with respect to the active ingredient for the identified parenteral iron products. The Agency continues to evaluate the issues raised in the Petition with respect to Velphoro and intends to respond to those requests at a later date.

I. BACKGROUND

A. Legal Framework

The Agency's regulations in 21 CFR 314.3 define "active ingredient" as "any component that is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals. The term includes those components that may undergo chemical change in the manufacture of the drug product and be present in the drug product in a modified form intended to furnish the specified activity or effect."

The Agency understands that for a "complex" to be an active ingredient, the complex should be a component that in its entirety is intended to furnish pharmacological activity (or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease, or to affect the structure or any function of the body of man or other animals).[5]

The Agency's understanding is described in further detail in a draft guidance for industry titled *Sameness Evaluations in an ANDA — Active Ingredients*, which provides, among other things, recommendations on the assessment of an active ingredient in complexes, chelates, and clathrates.[6] In this draft guidance, the Agency states that in general, the complex, chelate, or

[4] These PSGs are: Draft Guidance on Ferric Oxyhydroxide (revised Sept. 2021), previously Draft Guidance for Iron Sucrose (recommended Mar. 2012, revised Nov. 2013); Draft Guidance on Ferric Oxyhydroxide (revised Nov. 2022), previously Draft Guidance for Iron Dextran (recommended Oct. 2016); and Draft Guidance on Ferric Oxyhydroxide (revised Nov. 2022), previously Draft Guidance on Sodium Ferric Gluconate Complex (recommended Jun. 2013).

[5] The term "complex" in the context of determining the identity of the active ingredient is not defined in the Federal Food, Drug, and Cosmetic Act (FD&C Act) or the Agency's implementing regulations. However, complexes are discussed by the Agency in the context of the regulatory determination of the active moiety of such complexes. Specifically, 21 CFR 314.3 defines an active moiety as "the molecule or ion, excluding those appended portions of the molecule that cause the drug to be an ester, salt (including a salt with hydrogen or coordination bonds), or other noncovalent derivative (such as a complex, chelate, or clathrate) of the molecule, responsible for the physiological or pharmacological action of the drug substance.

[6] *Sameness Evaluations in an ANDA — Active Ingredients*, Guidance for Industry (Nov. 2022) ("Active Ingredient Sameness Guidance"), available at https://www.fda.gov/media/163018/download. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA

clathrate will be considered part of the active ingredient only if the complex is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease associated with the approved use of the drug product.[7]

B. Background

1. The Agency's Decision in the 2021 Petition Response with Respect to the Identity of the Active Ingredient in the Identified Parenteral Iron Products[8]

In analyzing the identified parenteral iron products, the Agency concluded in the 2021 Petition Response that under an application of the Agency's regulations, neither the carbohydrates nor the specific characteristics of the polynuclear ferric oxyhydroxide presentations of the identified parenteral iron products[9] "furnish pharmacological activity."[10] The Agency concluded instead that ferric oxyhydroxide alone is the component that furnishes the pharmacological activity of the identified parenteral iron products, namely iron delivery, and is thus the active ingredient under the Agency's regulatory definition in 21 CFR 314.3.[11]

In reaching its conclusion that only ferric oxyhydroxide, and not the polynuclear ferric oxyhydroxide array is the active ingredient, the Agency emphasized that severing a coordinate Fe-O bond in the polynuclear ferric oxyhydroxide array, by removing a repeat ferric oxyhydroxide unit, does not destroy the inherent pharmacological activity, i.e., the ability to release iron. This includes the ability of the remaining ferric oxyhydroxide repeat units in the resulting arrays (and thus the arrays themselves) or that of the "severed" ferric oxyhydroxide unit to release iron.[12] The Agency also stated that the size of the polynuclear ferric oxyhydroxide array was not expected to change the inherent pharmacological properties of ferric oxyhydroxide repeat units, thus lending further support to the conclusion that ferric oxyhydroxide alone was the active ingredient.[13]

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guidance web page at https://www.fda.gov/regulatory-information/search-fda-guidance-documents. In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word should in Agency guidance means that something is suggested or recommended, but not required.

[7] Id. at 8.

[8] The Vifor Petition does not challenge the Agency's determination that the active moiety in the identified parenteral iron products is ferric oxyhydroxide (FeOOH). Accordingly, this response does not address this active moiety determination by the Agency.

[9] For convenience and brevity, the Agency in the 2021 Petition Response focused on Venofer to make its arguments regarding the identity of the active ingredient, extending these arguments to the other identified parenteral iron products. To the extent possible, the Agency will do the same in this response to Vifor's Petition. The Agency will clarify if any of the scientific and legal arguments made in this response to Vifor's Petition are specific to any one of the identified parenteral iron products.

[10] 2021 Petition Response at 39-40.

[11] Id. Specifically, the 2021 Petition Response stated that "ferric oxyhydroxide, regardless of its presentation — polymorphic form or the physical size and structure of the "polynuclear array" formed by repeating "repeat units" of ferric oxyhydroxide — furnishes the pharmacological activity.

[12] 2021 Petition Response at 42. In contrast, the Agency said that the severing of a covalent bond (such as a coordinate bond) in non-polynuclear or non-polymeric small molecules generally yields one or more different molecules with different physicochemical characteristics.

[13] Id. See also, 2021 Petition Response at 44.

With respect to the carbohydrates in the identified parenteral iron products, the Agency stated that carbohydrates (sucrose in Venofer and Ferrlecit,[14] and dextran in each of the identified parenteral iron products containing iron dextran) do not furnish pharmacological activity but are merely excipients[15] providing stability. The formulation process with, among other things, the respective carbohydrate yields specific drug products that are colloidal suspensions of particles comprising polynuclear ferric oxyhydroxide that upon parenteral administration furnish a bioavailable and nontoxic form of iron.[16]

In summary, the Agency in the 2021 Petition Response found that the identified parenteral iron products can generally be described as consisting of a ferric oxyhydroxide core stabilized by a carbohydrate (dextran in the iron dextran parenteral products (InFeD, Dexferrum, Proferdex, and Iron Dextran), sucrose in Ferrlecit, and Venofer),[17] or characterized as "a mixture of ferric oxyhydroxide with a carbohydrate (for example, sucrose in the case of Venofer)."[18]

2. Vifor's Petition and White Paper[19]

a. Vifor's Arguments Regarding the Determination in the 2021 Petition Response that Ferric Oxyhydroxide is the Active Ingredient

With regard to the Agency's determination that the active ingredient in the identified parenteral iron products is ferric oxyhydroxide, you assert that the Agency's determination is contrary to its regulations. Specifically, you state that "[t]he regulations provide a specific definition of the term 'active ingredient,'" and that "FDA's determination that the active ingredient of all four of these drugs is mononuclear ferric oxyhydroxide is inconsistent with the regulation and scientifically inaccurate."[20] You assert that the entire iron carbohydrate complex is the "component that is intended to furnish pharmacological activity" and has a "direct effect" in treatment and on the

[14] Ferrlecit is composed of ferric oxyhydroxide hydrate complexed to sucrose with a chelating gluconate function in a molar ratio of two iron molecules to one gluconate.

[15] 2021 Petition Response at 47, citing the USP Guideline for Submitting Requests for Revision to USP–NF, Submission Guideline for Excipients (2016) (USP Excipients Guidelines, 2016) that listed examples of excipient functions which include among others:

- Aid in the processing of the drug delivery system during its manufacture
- Protect, support, or enhance the stability, bioavailability, or acceptability of the product to patients
- Enhance any attribute of the overall safety
- Assist in the effectiveness and/or delivery of the drug
- Assist in maintaining the integrity of the drug product during storage

[16] 2021 Petition Response at 45. The Agency clarified that this did not mean that the FeOOH molecules that make up the FeOOH repeat units in the Venofer polynuclear array lack the pharmacological activity of phosphate binding associated with Velphoro, making the point that both pharmacological activities are inherent characteristics of FeOOH, with one or other dominating based on factors such as reaction conditions, site of action, and formulation characteristics.

[17] 2021 Petition Response at 6, 8.

[18] 2021 Petition Response at 44.

[19] The Vifor Petition presents numerous legal and policy arguments that the Agency does not need to address for the purpose of this response. Therefore, this section will not address all the arguments and assertions made in the Vifor Petition but will only address those that the Agency needs to address for the purpose of this partial response with respect to the identified parenteral iron products.

[20] Petition at 4.

structure and function of the body, and is therefore the active ingredient of such products.[21] Specifically, you assert that parenteral iron carbohydrate complex products require the "entire iron carbohydrate complex" to safely and effectively treat anemia.[22] You provide a historical narrative dating back to as early as 1932 that suggests that the parenteral administration of "naked" ferric oxyhydroxide i.e., ferric oxyhydroxide not complexed to a carbohydrate(s) ("non-complexed")[23] has been conclusively shown to be toxic to the human body. Years of scientific research to overcome these clinical toxicities eventually led to the development of iron carbohydrate complexes in which the carbohydrate is essential to the safe and effective parenteral delivery of iron.[24] You assert that the amount and nature of the carbohydrate determines the efficacy as well as the structure and function of the drug.[25] Your arguments are described in further detail below.

i. History of Delivering Parenteral Iron

You assert that although the link between anemia and low iron levels and the value of iron supplementation was recognized centuries ago, identifying iron as the key therapeutic agent was only the beginning of an extensive search for a means to safely and effectively deliver iron to anemic patients.[26] Specifically, you note that historically parenteral iron treatments were difficult to develop in light of the serious adverse events associated with the rapid dissolution of iron after injection.[27] A 1932 study in which iron ammonium citrate was parenterally administered to patients caused severe and dangerous side effects including hypotension, tachycardia, nausea, and vomiting that led the authors to conclude that "parenteral administration of iron should be avoided."[28] A subsequent 1946 study in which patients parenterally received either non-complexed colloidal ferric hydroxide or ferric oxide, also resulted in serious adverse effects such as facial flushing, swelling and stiffness of the tongue and face, vomiting and hypotension.[29] You assert that the reactions noted by the authors may have been due to rapid iron dissolution or aggregation of non-complexed ferric hydroxide particles after injection,[30] and that these early studies showed that when administered parenterally, non-complexed iron does not appear to efficiently reach the bone marrow and likely rapidly distributes into other tissues (e.g. endothelium) and induces serious adverse reactions.[31] You find that in retrospect, the toxicity of

[21] Petition at 30-31.
[22] Petition at 31.
[23] This response will use the term "non-complexed" in lieu of "naked" when referring to iron that is not complexed with carbohydrates. For purposes of this response, both terms are interchangeable. "Non-complexed iron" includes non-complexed ferric oxyhydroxide, ferric hydroxide, and ferric oxide.
[24] Petition at 6-7, 31.
[25] Id.
[26] Petition at 5.
[27] Petition at 6, White Paper at 3-4.
[28] Petition at 6, White Paper at 3, citing Clark Heath et al., Quantitative Aspects of Iron Deficiency in Hypochromic Anemia, Iron Deficiency (Aug. 1, 1932).
[29] Petition at 6, White Paper at 3, citing Anne Tompkins Goetsch et al., Observations on the Effect of Massive Doses of Iron Given Intravenously to Patients with Hypochromic Anemia, 1 Blood (Mar. 1946). You assert that in retrospect, the toxicity of "naked" iron is not surprising because naked iron typically does not exist unbound in the human body and is instead sequestered, stored and transported within complex proteins like ferritin, or transferrin. White Paper at 4.
[30] Petition at 6.
[31] White Paper at 3-4, citing Knutson, M.D., Non-transferrin-bound iron transporters, 133 Free Radical Biol, & Med. 101-11 (2019).

non-complexed iron is not surprising because non-complexed iron typically does not exist unbound in the human body and is instead sequestered, stored and transported within complex proteins like ferritin or transferrin.[32] You thus assert that practitioners concluded that parenteral ferric oxyhydroxide and associated molecules, standing alone, were neither safe nor effective for treatment of anemia.[33]

ii. The Entire Iron Carbohydrate Complex is the Active Ingredient

You assert that to avoid the adverse events documented after ferric hydroxide administration, research shifted to developing iron-based complexes that would not release iron too quickly, that optimize the release of iron, and that do not result in anaphylactic reactions. You assert that this involved an informed design approach with respect to the characteristics of the "entire molecule" to achieve these objectives such that the safety and efficacy of the drug product relies on the entire iron carbohydrate complex.[34] You note that the iron carbohydrate complex in the identified parenteral iron products was designed to be similar to endogenous serum ferritin, which safely stores iron, such that the iron carbohydrate complex could control the availability and uptake of iron in the body and make the iron bioavailable.[35]

You assert that the entire iron carbohydrate complexes are intended to facilitate clearance from the serum by macrophages and delivery to the liver and spleen to provide iron to the physiological iron storage and transport system.[36] You assert that the physicochemical characteristics of the entire iron carbohydrate complex drive the rate and extent of uptake into the monocyte phagocytic system and the rate and extent of biodegradation, and thus the carbohydrate component is fundamental in controlling the pharmacological activity, i.e., iron delivery after the product is parenterally administered into the patient.[37] Consequently, according to you, the identified parenteral iron products exhibit different pharmacological profiles based on ferritin as a pharmacodynamic parameter.[38] You assert that the degree to which the carbohydrate affects the pharmacological activity, and therefore the safety and effectiveness, of the entire iron complex is illustrated by significant differences in their pharmacokinetic[39] profile (such as differences in elimination half-times ($t_{1/2}$)) and pharmacodynamic profiles,[40] their kinetic profiles[41](labile or robust), their thermodynamic properties[42] (weak or strong), and their recommended dosage, administration, and safety information.[43] For example, in contrast with Venofer and Ferrlecit, the labeling for INFeD uniquely includes a boxed warning due to the particularly notable risk of anaphylactic reactions. In addition, the dosage instructions for Ferrlecit indicate much lower doses due to the risk of severe adverse events; administering

[32] White Paper at 4, citing Torti, F.M. & Torti, S.V., Regulation of Ferritin Genes and Protein, 99 Blood 3505-16 (2002).
[33] Petition at 6.
[34] Id.
[35] Petition at 7, White Paper at 4, 24.
[36] White Paper at 4.
[37] Petition at 7, White Paper at 24.
[38] Petition at 7, White Paper at 4, 24.
[39] White Paper at 19-22.
[40] White Paper at 23-24.
[41] White Paper at 4, 27.
[42] White Paper at 4, 18-19.
[43] Petition at 7, White Paper at 1.

Ferrlecit using the dosing instructions for either INFeD or Venofer would pose a significant health risk to patients.

In summary, you use the above arguments, among others, to conclude that the entire iron carbohydrate complex must be understood as the "component" of the drug "intended to furnish pharmacological activity or other direct effect," thus making it the active ingredient of the identified parenteral iron products.

b. Vifor's Assertions that the Agency's Determination that Ferric Oxyhydroxide is the Active Ingredient will Create Medication Errors in Prescribing and will Undermine Effective Pharmacovigilance

Separately, in the Petition you assert that the Agency's decision that the identified parenteral iron products all share the same active ingredient and established name will "harm the public health by increasing the risk of medication error and undermining effective pharmacovigilance" because these products are not therapeutic equivalents and not substitutable for each other.[44] Specifically, you assert that these products contain different drug substances, are approved for different indications, and have different routes of administration,[45] dosing schedules, vial strengths, maximal doses for single administration, risks, and benefits.[46] You assert that despite these differences FDA's decision to nevertheless declare that they all have the same active ingredient presents an unacceptable risk of confusion that will lead inevitably to medication error in many vulnerable patient populations.[47]

II. DISCUSSION

The Agency has reviewed your arguments in the Petition and White Paper regarding the identity of the active ingredient for the identified parenteral iron products, relevant published literature and other relevant information regarding the identified parenteral iron products. We find that under the Agency's regulation in 21 CFR 314.3 defining "active ingredient" and the Agency's understanding of when a complex is considered to be the active ingredient of a drug product, the active ingredient in the identified parenteral iron products is the iron carbohydrate complex. Therefore, with respect to the identified parenteral iron products, the Agency reverses its decision in the 2021 Petition Response in which it found that the active ingredient was ferric oxyhydroxide and that the carbohydrate component was merely an excipient. The Agency reached its decision in this response based primarily on two interrelated reasons:

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[44] Petition aet 3, 20-21, 26-28.

[45] All the identified parenteral iron products are approved for intravenous administration. InFeD is also approved for intramuscular administration.

[46] Id.

[47] Id. You assert that if all the identified parenteral iron products were described in certain registries as having the same active ingredient, a pharmacist filling a prescription for "ferric oxyhydroxide" to treat a patient suffering from anemia will not know whether the healthcare provider intended for the patient to receive iron dextran, sodium ferric gluconate complex, or iron sucrose. You assert that this is no trivial risk because these products are known to present significant but different safety issues. For instance, the labeling for iron dextran includes a boxed warning regarding the high incidence of severe allergic reactions, but the labeling for sodium ferric gluconate complex or iron sucrose does not.

1. A reassessment of the Agency's understanding of the pharmacological activity of the identified parenteral iron carbohydrate complexes.
2. The ability of the entire iron carbohydrate complex to safely and effectively deliver iron by overcoming toxicities and other adverse side effects associated with the parenteral administration of non-complexed iron.

The Agency's reasons are discussed in greater detail below.

A. Pharmacological Activity of the Identified Parenteral Iron Products is Understood in the Context of the Approved Use for these Products; Stable Complexation Allows for the Safe and Effective Parenteral Delivery of Iron in Patients with Iron Deficiency Anemia

As noted above, in the 2021 Petition Response, the Agency concluded that ferric oxyhydroxide was the component that furnished the pharmacological activity of the identified parenteral iron products, namely iron delivery, and was thus the active ingredient in the identified parenteral iron products. The Agency also found that pharmacological activity was an "inherent" characteristic of the ferric oxyhydroxide alone and that the carbohydrates present in these products were merely excipients only providing "stability" to the identified parenteral iron products.

In general, a complex will be considered part of the active ingredient only if the complex is intended to furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease associated with the approved use of the drug product.[48] An assessment of whether a complex furnishes pharmacological activity is best understood in the context of the approved use of the drug product.[49]

In the case of the identified parenteral iron products, the approved use of the drug product is the treatment of iron deficiency anemia (IDA or anemia)[50] which involves the parenteral administration of the drug for safe and effective iron delivery in patients with anemia. Whether a complex can be considered the active ingredient for the identified parenteral iron products should be analyzed in the context of the approved use of the identified parenteral iron products. This necessarily involves a more fulsome understanding of whether and/or how a purported iron carbohydrate complex plays a role in the pharmacological activity of the drug product from injection to the therapeutic benefit it is intended to provide. Or in other words, this necessarily involves an examination of whether and/or how a purported iron carbohydrate complex impacts iron delivery once injected in a patient with IDA in need of iron supplementation or replacement, and how this compares with non-complexed iron.

[48] Active Ingredient Sameness Guidance. at 8.
[49] *Id.* at 8-9.
[50] All of the identified parenteral iron products are approved for the treatment of anemia, some with additional considerations and requirements. Venofer is indicated for the treatment of IDA in patients with chronic kidney disease (CKD); Ferrlecit is indicated for the treatment of IDA in adult patients and in pediatric patients age 6 years and older with CKD receiving hemodialysis who are receiving supplemental epoetin therapy; InFeD is indicated for the treatment of adult and pediatric patients of age 4 months and older with documented iron deficiency [including anemia] who have intolerance to oral iron or an unsatisfactory response to oral iron.

The mechanism of iron delivery in the body after parenteral administration of iron carbohydrate complexes, although highly complex and not fully known, is generally understood to be as follows: iron is administered parenterally in the form of an iron carbohydrate complex composed of an iron core complexed with carbohydrate molecules.[51] Iron carbohydrate complexes of this type "behave as prodrugs," since the iron has to be released from the iron core.[52] After administration, stable iron carbohydrate complexes are taken up by endocytosis by macrophages of the reticuloendothelial system (RES) (also referred to in literature as the mononuclear phagocyte system (MPS)) and processed to cleave iron from the complex.[53] The resulting iron can be incorporated into ferritin and remain transiently stored within the macrophage or can be transported out of the macrophage and ultimately sequestered by transferrin for transport in the serum to the sites of utilization, e.g., in the bone marrow for hemoglobin synthesis or in the liver for storage in ferritin. The key elements of the mechanism of iron delivery from injection to availability at the sites of utilization are described in the labeling for iron carbohydrate complexes, for example, in the labeling for InFeD which states:[54]

> Circulating iron dextran is removed from the plasma by cells of the reticuloendothelial system, which split the complex into its components of iron and dextran. The iron is immediately bound to the available protein moieties to form hemosiderin or ferritin, the physiological forms of iron, or to a lesser extent to transferrin. This iron which is subject to physiological control replenishes hemoglobin and depleted iron stores.

A key step in this process is the uptake of the *entire* iron carbohydrate complex by macrophages of the MPS. For this to occur, the entire iron carbohydrate complex must be "stably complexed." The Agency in the 2021 Petition Response found that the carbohydrate was an excipient providing a "stability" function which can be understood to mean functions such as thermal stability and product stability across certain higher pH ranges provided by simple carbohydrates such as sugars. This is different from "stable complexation." Upon further review of the published literature and other relevant information regarding the identified parenteral iron products, the Agency understands stability in this context to mean "stable complexation" or in other words, the carbohydrate facilitating the protection of the iron core from hydrolysis, precipitation, and polymerization (polynuclearization) in the plasma prior to uptake of the entire stable iron carbohydrate complex by macrophages.[55]

Stable complexation that allows for the uptake of the entire iron carbohydrate complex by the macrophages helps minimize the formation of non-transferrin-bound iron (NTBI) that can arise from excessive iron release into the bloodstream while enabling effective delivery of parenteral

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[51] Danielson J. Structure, chemistry, and pharmacokinetics of intravenous iron agents. Am. Soc. Nephrol. 2004;15:S93–S98.

[52] Geisser P, Burckhardt S. The pharmacokinetics and pharmacodynamics of iron preparations. Pharmaceutics. 2011 Jan 4;3(1):12-33.

[53] Danielson J. Structure, chemistry, and pharmacokinetics of intravenous iron agents. Am. Soc. Nephrol. 2004;15:S93–S98. Note that the terms RES and MPS are used interchangeably, although the latter term is now the prevalent term in contemporary scientific literature.

[54] INFed NDA 017441, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/017441s179lbl.pdf. See Section 12, Clinical Pharmacology, Subsections 12.1, Mechanism of Action, and 12.3, Pharmacokinetics.

[55] Published literature also reflects this understanding of stability in the context of parenteral iron products. See, for example, Geisser P, Burckhardt S. The pharmacokinetics and pharmacodynamics of iron preparations. Pharmaceutics. 2011 Jan 4;3(1):12-33.

iron to the MPS. Stable complexation by the carbohydrate thus mitigates the historical safety concerns of adverse effects due to excessive iron release, aggregation, and oxidative toxicity associated with the parenteral administration of non-complexed iron which deliver iron, albeit in a manner that is neither safe nor effective.[56,57]

In summary, stable complexation with carbohydrates allows for the safe and effective parenteral delivery of iron to patients with anemia, in sharp contrast to parenteral iron delivery by non-complexed iron which comes with serious attendant risks. The entire stable iron carbohydrate complex in the identified parenteral iron products furnishes the necessary pharmacological activity — iron delivery — for the treatment of patients with anemia.

The Agency's approach to determining if a complex is an active ingredient and if it furnishes pharmacological activity associated with the safe and effective approved use of the product has longstanding precedent. In the context of a therapeutic class of metal complexes the Agency has employed a similar approach to assessing the active ingredient. For example, the Agency determined that the entire gadolinium complex, and not just gadolinium, is the active ingredient in gadolinium-based contrast agents (GBCAs) for use in magnetic resonance imaging (MRI). Although gadolinium by itself could be used as an MRI agent, the high toxicities associated with free gadolinium in plasma would render such products therapeutically unviable in MRI procedures unless complexed with appropriate ligands. Similar to the way iron must be in the form of an iron carbohydrate complex to be viable, a GBCA must be complexed to mitigate toxic effects.

Therefore, in the context of the identified parenteral iron products, the Agency finds that the entire iron carbohydrate complex is the active ingredient because it furnishes pharmacological activity associated with the approved use of the drug. Specifically, the entire iron carbohydrate complex effectuates safe and effective parenteral iron delivery in the treatment of patients with anemia. This lies in sharp contrast with non-complexed iron, which is associated with significant toxicity risks rendering it completely unviable as a parentally administered therapeutic agent to treat patients with anemia.[58]

[56] Felix Funk et al., The New Generation of Intravenous Iron: Chemistry, Pharmacology, and Toxicology of Ferric Carboxymaltose, 60 ARZNEIMITTELFORSCHUNG (June 2010).
[57] Geisser P, Baer M, Schaub E. Structure/histoxicity relationship of parenteral iron preparations. Arzneimittelforschung. 1992;42:1439-52.
[58] The Agency notes, however, that the aforementioned factors and considerations would likely be inapplicable to a drug where the active ingredient is viable with or without a complex (e.g., can furnish pharmacological activity or other direct effect in the diagnosis, cure, mitigation, treatment, or prevention of disease associated with the approved use of the drug product with or without a complex). In such cases, the active ingredient would likely not be the complex.

B. Vifor's Other Arguments in Support of the Iron Carbohydrate Complex as the Active Ingredient in the Identified Parenteral Iron Products.

1. Differences in Certain Pharmacokinetic Parameters and Clinical/Pharmacodynamic Outcomes Between Iron Carbohydrate Complexes

The Agency has reviewed your assertions and arguments in the Petition and White Paper to support a finding that the active ingredient in the identified parenteral iron products is the iron carbohydrate complex. These include, among others, differences in pharmacological effects between the identified parenteral iron products with different carbohydrates; and differences in certain clinical endpoints and pharmacodynamic parameters between these products.

With regard to differences in pharmacological effects, you assert that observed differences between the different iron carbohydrate complexes in: (1) serum clearance kinetics; (2) tissue distribution; (3) pharmacodynamics; and (4) safety profiles "clearly indicate that the specific iron carbohydrate complexes are responsible for furnishing the pharmacological activity . . . of each product's active ingredient."[59] You assert that known pharmacokinetic parameters differ widely amongst even the more similarly configured iron carbohydrate preparations, products with the active ingredients iron sucrose and sodium ferric gluconate complex, and that these differences underscore that even small changes in iron carbohydrate complexes produce clinically relevant changes in the pharmacokinetic profiles that impact subsequent biodistribution and pharmacodynamic activity.[60] You provide information on select pharmacokinetic parameters, for example, the terminal half-life (t1/2)[61] of the colloidal iron carbohydrate complex in plasma which shows that this pharmacokinetic parameter varies from 1.42 hours and 5.2 hours for Ferrlecit and Venofer, respectively, to 20 hours for an iron dextran product.[62] You also assert that "biodistribution profiles in key pharmacologic target tissues differ widely between iron sucrose, sodium ferric gluconate complex and iron dextran."[63]

With respect to differences in certain clinical and pharmacodynamic outcomes between these iron carbohydrate complexes, you assert that clinical study data confirm that iron carbohydrate complexes exhibit different effects of clinical endpoints and pharmacodynamic parameters.[64] For example, you assert that in head-to-head studies of iron carbohydrate complexes with various carbohydrates ligands, significant differences in clinical outcomes such as proteinuria and infusion reactions have been demonstrated.[65] You, therefore, assert that "[c]ollectively, these clinical data confirm the entire complex is necessary to furnish the pharmacologic effect, as

[59] White Paper at 19.
[60] White Paper at 19-20. See Table 4, citing Geisser P, Burckhardt S. The pharmacokinetics and pharmacodynamics of iron preparations. Pharmaceutics. 2011 Jan 4;3(1):12-33.
[61] The pharmacokinetic parameter terminal half-life of a drug is the time it takes for the plasma concentration of the drug to decrease by 50% during the terminal (elimination) phase
[62] White Paper at 19-20. See Table 4, citing Geisser P, Burckhardt S. The pharmacokinetics and pharmacodynamics of iron preparations. Pharmaceutics. 2011 Jan 4;3(1):12-33.
[63] Petition at 20-27.
[64] Petition at 30.
[65] Petition at 30-32 (Table 5 provides a summary of certain clinical studies).

differences would not be observed if all pharmacologic effects were derived from repeat units of mononuclear ferric oxyhydroxide."[66]

For the reasons described in Section II.A. above, we agree that the active ingredient in the identified parenteral iron products is the iron carbohydrate complex. We do not agree, however, that the pharmacokinetic and clinical/pharmacodynamic information you provide "***clearly*** indicate that the specific iron carbohydrate complexes are responsible for furnishing the pharmacological activity . . . of each product's active ingredient," nor can the Agency conclude as you do that the clinical safety and pharmacodynamic information you provide "[c]ollectively, . . . ***confirm*** the entire complex is necessary to furnish the pharmacologic effect."

Instead, the Agency believes that the pharmacokinetic and clinical/pharmacodynamic information you present is consistent with the above conclusion that the active ingredient in the identified parenteral iron products is the iron carbohydrate complex and not ferric oxyhydroxide alone because it is unlikely that differences in certain pharmacokinetic parameters, biodistribution profiles, clinical safety and pharmacodynamic parameters would be observed if the pharmacological activity of the identified iron parenteral products was derived solely from ferric oxyhydroxide.

2. Risk of Medication Errors and Reduced Pharmacovigilance

As noted above, the Agency upon approval of the identified parenteral iron products adopted a naming convention that recognized the entire iron carbohydrate complex as the active ingredient, one that prevailed for decades. The Agency has reviewed your arguments that changing the name of the active ingredient and the established name of the identified parenteral iron products (Venofer, Ferrlecit, and certain iron dextran products) to ferric oxyhydroxide from their respective iron carbohydrate complexes may result in medication errors while also undermining pharmacovigilance. In particular, you note that the identified parenteral iron products have different indications, dosing schedules, vial strengths, maximal doses for single administration, risks, and benefits, and thus, changing the identity of the active ingredient to ferric oxyhydroxide increases the risk of medication error at multiple points in the drug dispensing process.

The Agency believes that reversing the name of the active ingredient and established name for the relevant parenteral iron products from ferric oxyhydroxide to their respective iron carbohydrate complex recognized upon approval obviates these concerns and renders your arguments moot.

III. CONCLUSION

For the reasons discussed in this response, the Agency is reversing its decision in the 2021 Petition Response that the active ingredient in and established name of the identified parenteral iron products discussed in this response is ferric oxyhydroxide, finding instead that the active ingredient and established name for each of the identified parenteral iron products is their respective iron carbohydrate complex. Therefore, the Agency concludes that the active ingredient is iron sucrose in Venofer, sodium ferric gluconate complex in Ferrlecit, and iron

[66] Petition at 30.

dextran in InFeD, Dexferrum, Proferdex, and Iron Dextran. The Agency will make conforming revisions to Drugs@FDA and the Orange Book concomitantly with the issuance of this response, and revise and publish relevant draft PSGs that reflect the Agency's determination that the entire iron carbohydrate complex and not ferric oxyhydroxide is the active ingredient.

Sincerely,

GEORGE F. TIDMARSH -S

Digitally signed by GEORGE F. TIDMARSH -S
Date: 2025.08.08 04:39:43 -04'00'

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