September 24, 2024

By Electronic Submission
Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
3630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2021-P-0893 Supplemental Comment to August 3, 2021, Citizen Petition and Petition for Stay Submitted by Sidley Austin LLP on Behalf of Vifor (International) Inc., Switzerland

To Whom It May Concern:

On behalf of the more than 37,000,000 Americans living with kidney diseases and the nearly 22,000 nephrologists, scientists, and other kidney health care professionals who comprise the American Society of Nephrology (ASN), thank you for the opportunity to provide supplemental comments in support of Vifor's August 3, 2021 citizen petition (Docket No. FDA-2021-P-0893). The Petition requests that the U.S. Food and Drug Administration (FDA) reverse certain actions announced on Wednesday, May 26, 2021. Those FDA actions include, among other things, changes to the established names and active ingredient names of sucroferric oxyhydroxide and three IV iron products—iron sucrose, sodium ferric gluconate, and iron dextran—to "ferric oxyhydroxide." FDA's actions also included steps to implement the change in active ingredient name in Drugs@FDA and the Orange Book.

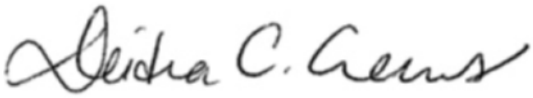
In May 2021, FDA changed the long-standing active ingredient and established names of four iron-carbohydrate drugs to ferric oxyhydroxide without public notice. Each of these products had been previously approved by FDA with a distinct active ingredient and established name. Without notice, FDA made the active ingredient and established name the same for all four products. This action created patient safety concerns and caused confusion among health providers.

As ASN wrote November 17, 2021, ASN's member nephrologists are directly responsible for the care of 550,000 Americans with kidney failure. The majority of these people, and many additional individuals with kidney diseases, experience anemia with iron deficiency as well as hyperphosphatemia. Ongoing management of anemia and hyperphosphatemia is a critical part of treating kidney diseases. ASN is concerned by FDA's determination that all pharmacologic compounds with a ferric oxyhydroxide core have the same "active moiety" or "active ingredient," which is not how these compounds are viewed or used in nephrology.

As a result of Vifor's submission of its citizen petition, FDA's Center for Drug Evaluation and Research (CDER) released a memorandum (attached) on July 1, 2024 announcing that it is re-evaluating its determination regarding the naming of these iron products. We are appreciative that FDA has stated that it is currently accepting the original active ingredient names of these iron products as the agency reviews its decision.

While ASN is grateful that the agency is re-evaluating its earlier determination, we strongly urge FDA to ensure the safety of our patients by permanently reversing the May 2021 decision. We are including our comment letter from November 2021 as we believe the facts stated therein remain constant. Please feel free to contact David White, ASN Regulatory and Quality Office, at dwhite@asn-online.org to discuss this matter further.

Sincerely,



Deidra C. Crews, MD, ScM, FASN

President

November 17, 2021

By Electronic Submission
Division of Dockets Management
Food and Drug Administration
Department of Health and Human Services
5630 Fishers Lane, Rm. 1061
Rockville, MD 20852

Re: Docket No. FDA-2021-P-0893 Comment to August 3, 2021, Citizen Petition and Petition for Stay Submitted by Sidley Austin LLP on Behalf of Vifor (International) Inc., Switzerland

To Whom it May Concern:

The American Society of Nephrology (ASN) respectfully submits these comments to the Citizen Petition on behalf of the more than 37,000,000 Americans living with kidney diseases and the 21,000 nephrologists, scientists, pharmacists, and other kidney health care professionals who are ASN members. The Petition requests that the U.S. Food and Drug Administration (FDA) reverse certain actions announced on Wednesday, May 26, 2021. Those FDA actions include, among other things, changes to the established names and active ingredient names of sucroferric oxyhydroxide and three IV iron products—iron sucrose, sodium ferric gluconate, and iron dextran—to "ferric oxyhydroxide." FDA's actions also included steps to implement the change in active ingredient name in Drugs@FDA and the Orange Book.

ASN's member nephrologists are directly responsible for the care of 550,000 Americans with kidney failure. The majority of these people, and many additional individuals with kidney diseases, experience anemia with iron deficiency as well as hyperphosphatemia. Ongoing management of anemia and hyperphosphatemia is a critical part of treating kidney diseases. ASN is concerned by FDA's determination that all pharmacologic compounds with a ferric oxyhydroxide core have the same "active moiety" or "active ingredient," which is not how these compounds are viewed or used in nephrology.

While the compounds recently combined into the "ferric oxyhydroxide" category have some similarities, critical differences exist in dosing, schedule, route, risks, and even indication.

- IV iron dextran is indicated for the treatment of iron deficiency anemia and has a black box warning due to a rate of anaphylaxis higher than any other IV iron therapy, and therefore requires a test dose.

- IV iron sucrose and sodium ferric gluconate are indicated for the treatment of iron deficiency anemia but must be administered in much lower doses than iron

dextran due to increased rate of free iron release into the blood, which can cause hypotension, nausea, and vomiting.

- Oral sucroferric oxyhydroxide is indicated as a phosphate binder for the treatment of hyperphosphatemia in dialysis patients. Little, if any free iron is released in the GI tract, making it *unsuitable for the treatment of iron deficiency anemia.*

The reasons why the products above have different efficacy and safety characteristics as well as indications (iron replacement versus phosphate binder) is that the sugar or carbohydrate moiety or ratios determine whether the ferric oxyhydroxide remains insoluble (and can be used to bind phosphate) or whether it solubilizes and can release iron (for treatment of iron deficiency). Thus, the sugar or carbohydrate components directly affect the action of the ferric oxyhydroxide, the indication for which the product can be used as well as its efficacy and safety and how it is administered. These components are not simply 'stabilizers.' In addition, the size of the ferric oxyhydroxide particles as well as size of carbohydrate groups affect binding of the iron-carbohydrate complex and iron release, which effect type and rate of adverse events of the IV iron products. These iron-containing products are not therapeutically interchangeable. Unfortunately, by grouping these compounds together under one generic name will lead many practitioners to believe that they are therapeutically interchangeable.

It is critical for clinicians and pharmacists to distinguish among these six available IV iron compounds (dextran, sucrose, gluconate, ferumoxytol, carboxymaltose, and derisomaltose) that have widely different dosing schedules and adverse reactions as well as the one available oral phosphate binding product.

As a result of FDA's actions, databases and software used by professionals to prescribe, order, and dispense iron products will no longer be able to easily distinguish among these products. From ASN's perspective the following issues are of concern for medication errors.

- Various drug coding systems are used today to identify drug products within compendia and databases (e.g., Generic Product Identifier, Rx Norm, Generic Code Number). Changing these unique products to one generic name has the potential to cause a domino effect that will likely affect decision-making at the individual level, population-level, and the ability to accurately conduct post-market safety surveillance and comparative effectiveness and safety research.

- The compendia that physicians, nurses, and clinical pharmacists use is fundamental to providing safe medication use practices. It is unclear how changing these unique generic names to one generic name will alter compendia summaries and subsequently the interface with the multiple healthcare software applications used at dialysis facilities, hospitals, clinics, and infusion centers.

- Prescribers may wrongly assume the products are interchangeable and prescribe the wrong product.

- Since all these products share the same generic ingredient name, prescribers may wrongly assume that the indications, side effects, warnings, and precautions are the same, potentially placing a patient at risk for an avoidable adverse event or using the wrong product for a specific indication (i.e., phosphate binder versus iron replacement).

- The dosing of iron products is unique to the individual product. Prescribers may be confused or unaware of the product differences including dosing, infusion time, or need for dilution if the active ingredient appears to be the same.

- Compendia are also used to develop clinical decision support electronic modules for IV iron administration. These modules will no longer be able to clarify the selection and subsequent dosing and monitoring information for the prescriber leading to confusion and importantly the risk of selecting the wrong drug and wrong dose, *two of the "top 5" medication errors.*

- Algorithms designed for safe medication use practices will also be affected. This concern includes patient allergy screening, identification of drug-drug interactions and therapeutic drug duplications. Algorithms and clinical decision support tools will require reconfiguration (likely manually) and testing before implementation could occur.

- Drug information resources will now put iron sucrose, sodium ferric gluconate and iron dextran in a single drug monograph. This step requires the clinician to navigate the text to accurately determine dosing, administration requirements, (test dose, infusion rate) and adverse effects for each product.

- Big data are also increasingly used to evaluate comparative effectiveness or safety of drug products. If these ferric oxyhydroxide products cannot be distinguished from one another with commonly used drug coding systems used within databases, this could significantly bias research results or make it impossible to evaluate post-market safety and effectiveness of existing and new products.

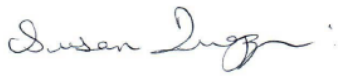
Although IV iron compounds may be roughly equivalent in efficacy (1000mg will generally raise the hemoglobin level of a patient with iron deficiency anemia around 1gm/dL), these compounds can by no means be considered therapeutically equivalent. Of particular concern, the IV iron complex products, iron sucrose, sodium ferric gluconate, and iron dextran, vary greatly in structure, dosing, and risks, particularly anaphylactic shock.

Managing anemia for patients undergoing dialysis has always been a complex issue. FDA's recent determination that all pharmacologic compounds with a ferric

oxyhydroxide core have the same ‘active ingredient’ or ‘active moiety’ will further complicate the management of anemia and phosphate control and put the health and safety of these 550,000 individuals at risk. ASN urges FDA to revisit its decision and take action to protect these individuals.

Thank you for this opportunity to comment on the Citizen Petition. To discuss this letter, ASN’s comments, or the society, please contact David White, ASN Regulatory and Quality Office, at dwhite@asn-online.org or (202) 460-4635.

Sincerely,



Susan E. Quaggin, MD, FASN
President