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March 3, 2005

VIA FEDERAL EXPRESS

Division of Dockets Management
(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852

**Re: CITIZEN PETITION - Generic Equivalents and Pharmaceutical
Alternatives of Iron Sucrose Injection, USP**

Dear Sir/Madam:

The undersigned, on behalf of Luitpold Pharmaceuticals, Inc., ("Luitpold"), One Luitpold Drive, P.O. Box 9001, Shirley, NY 11967, submits this Petition pursuant to 21 C.F.R. §10.30, to request that the Commissioner of Food and Drugs ("the Commissioner") withhold approval of any Abbreviated New Drug Application ("ANDA") or any 505(b)(2) application for any generic version or other pharmaceutical alternative of VENOFER® (iron sucrose injection, USP) unless and until any such applicant satisfies all of the conditions set forth in this Petition. Furthermore, Luitpold requests that the Food and Drug Administration ("FDA" or "the Agency") establish guidelines for approval of any such product and all other parenteral iron colloidal iron suspensions, in light of the issues raised by the issues discussed in this Petition. Luitpold is the holder of New Drug Application ("NDA") 21-135 for VENOFER® (iron sucrose injection, USP).

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A. ACTIONS REQUESTED

Luitpold requests that the Commissioner take the following specific actions to ensure the even-handed application of the requirements of Section 505 of the Federal Food Drug and Cosmetic Act ("the FFDCA") and the safety and efficacy of any generic version or pharmaceutical alternative of VENOFER® and other parenteral iron colloidal suspensions.

Luitpold requests that the Commissioner not approve as an ANDA any product referencing VENOFER® as the reference listed drug (RLD) unless:

1. The ANDA applicant demonstrates that the processes to manufacture the finished generic product, as well as the Active Pharmaceutical Ingredient ("API") iron sucrose, are identical to the manufacturing processes used to manufacture VENOFER® and its API.
2. The ANDA applicant demonstrates, through competent scientific evidence, that the physico-chemical properties and characteristics of the generic product and its API, specifically its colloidal structure are identical to VENOFER® and its API, and evidence that the finished generic product satisfies all of the requirements for iron sucrose injection, USP.

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3. The ANDA applicant submits adequate *in vivo* bioequivalence data satisfying all current requirements for demonstration of bioequivalence for an ANDA (and that the Agency not grant any bioequivalence waiver to any such ANDA applicant).
4. The ANDA applicant develops a validated *in vitro* release method for determination of bioequivalence of each batch of any generic equivalent of VENOFER®.

Luitpold requests that the Commissioner not approve through the 505(b)(2) process any product referencing VENOFER® as the RLD unless:

1. The 505(b)(2) applicant conducts full scale preclinical and clinical safety and efficacy studies to demonstrate “substantial evidence” that its product is safe and effective.
2. The 505(b)(2) applicant conducts a clinical study of its product in at least 1000 prospectively studied patients as, at a minimum, a post-marketing commitment, and preferably as a condition of approval.
3. The 505(b)(2) applicant be required to include a bolded safety warning and/or a test dose in the labeling for its product until it has conducted such adequate safety testing.

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4. The 505(b)(2) applicant develops a validated *in vitro* release method for determination of bioequivalence of each batch of any pharmaceutical alternative of VENOFER®.

Luitpold requests that the Commissioner establish guidelines relating to these conditions for applications referencing VENOFER® or any other parenteral iron colloidal suspension as the RLD and that, until such guidelines are established, no ANDA or 505(b)(2) application listing VENOFER® or other parenteral iron colloidal suspensions as the RLD be approved.

B. STATEMENT OF GROUNDS

1. Introduction

The FDCA requires that any person filing an ANDA for a generic equivalent of a RLD containing a single active ingredient demonstrates that the active ingredient of the new drug is the same as that of the approved RLD. Section 505(j)(2)(A)(i)(I). As discussed in detail below, a manufacturer of iron sucrose injection, USP, will not be able to produce the same API found in VENOFER® or the same final product as VENOFER® unless it does so by the identical manufacturing processes used by Luitpold and its API supplier. If the identical processes are not employed, and pharmaceutical equivalence cannot be demonstrated through competent scientific evidence, the Commissioner must require that the sponsor of the product demonstrate that the effectiveness and safety of their product is equivalent to that of VENOFER® by performing

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adequate preclinical and clinical safety and effectiveness studies such as were required for the approval of VENOFER® as any non-identical product may not be as safe and/or effective as VENOFER®, as experience has shown. Last, to ensure bioequivalence of each batch, any such application must be required to develop an *in vitro* release test.

2. Background

Currently, three parenteral iron colloidal suspension preparations with different active ingredients are listed in Approved Drug Products with Therapeutic Equivalence Evaluations. These preparations are iron dextran injection, USP; sodium ferric gluconate complex in sucrose injection; and iron sucrose injection, USP. The active moiety of all three of these compounds is elemental iron, supplied as a polynuclear ferric oxy-hydroxide core encased in a hydrophilic carbohydrate shell. In solution, their overall sizes range from 5 to 40 nm. They are not true solutions but colloidal suspensions, requiring special considerations in establishing their safety and therapeutic and bioequivalence requirements for ANDA's, and safety and efficacy requirements for 505(b)(2) applications.

Of these three parenteral iron preparations, only iron dextran injection, USP, is a drug marketed prior to 1962 in the United States. While sodium ferric gluconate and iron sucrose injection were marketed in Europe prior to 1962, they were not approved in the U.S. until 1999 and 2000 respectively. As a pre-1962 drug, iron dextran injection, USP, was reviewed in the

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Drug Efficacy Study Implementation or DESI Review. Attached as Exhibit 1 is the “Drug Efficacy Study Implementation Regarding Certain Iron Preparations for Parenteral Use,” as published in the Federal Register, on Wednesday, June 26, 1968 at 33 Fed. Reg. 9352. In this DESI notice, the FDA concurred with the findings of the National Academy of Sciences – National Research Council, Drug Efficacy Study Group, that the pre-1962 NDA drugs Astrafer, an iron dextran injection, and Imferon, an iron dextran injection, were “shown to be effective and suitable for the treatment of iron deficiency anemia when established conditions exist corroborating iron deficiency anemia not amenable to oral therapy.” Id.

The DESI notice further states: “The active components of preparations of these kinds are complexes of iron and modified carbohydrates. Because of the potential for toxicity associated with the use of these drugs and **the fact that their integrity is dependent to a large degree upon manufacturing procedures**, such preparations continue to be regarded as new drugs (21 U.S.C. 321(p)).” Id. (Emphasis Added). Thus, due to the serious concern that toxicities associated with these compounds, including anaphylaxis and death, which are related to the composition, stability and particle size of the complex, and the fact that they are directly influenced by the manufacturing process, iron dextran injection’s package insert labeling contains a black box warning for the potential of fatal anaphylactic type reactions. Thus, as early as 1968, FDA appreciated the fact that the manufacturing process is especially critical in the manufacture of parenteral iron colloidal suspension preparations, as the safety and effectiveness

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of such preparations is highly dependent on how the API and the finished product are manufactured.

In the 1970's Astrafer was withdrawn from the market and, in 1991, Fisons withdrew Imferon due to cGMP issues. In 1992, INFeD® was approved and designated as the RLD for iron dextran injection, USP. On August 30, 1991, Luitpold had submitted an ANDA for DEXFERRUM® (iron dextran injection, USP) referencing Imferon as the RLD. After withdrawal of Imferon from the market, INFeD was substituted as the RLD.

In its ANDA submission for DEXFERRUM®, Luitpold requested a waiver of *in vivo* bioequivalence studies, providing the Agency with data characterizing colloidal iron core's particle sizes, composition and molecular weights of DEXFERRUM®, Imferon and INFeD®. A summary of this data is provided in Exhibit 2, Lawrence R: "Development and Comparison of Iron Dextran Products." PDA J. Pharm. Sci. Technol., 52: 190-197, 1998.

Luitpold's request for a waiver of *in vivo* bioequivalence studies was denied due solely to a difference in the molecular weight of DEXFERRUM® and INFeD®. As a result, Luitpold was required to conduct bioequivalence and other studies. As the results of bioequivalence testing of the DEXFERRUM® in comparison to INFeD® did not meet the bioequivalence requirements for an ANDA, the product was required to be approved as a 505(b)(2) application. Exhibit 3 contains the review by FDA's Division of Bioequivalence of the pharmacokinetics and iron

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utilization studies performed for DEXFERRUM®'s approval as 505b(2) application. In its reasons for denial of the waiver request, the FDA emphasized the molecular weight data reported by Luitpold and that:

“as with parenteral suspensions, parenteral colloids are considered by the Division of Bioequivalence to be a problem and waivers of *in vivo* bioequivalence studies are not granted. Accordingly, in the 13th edition of Approved Drug Product with Therapeutic Equivalence Evaluations the INFeD therapeutic rating was changed from AP to BP. The therapeutic equivalence rating for DEXFERRUM® is also BP.”

See page F-14.

Because of the possibility of anaphylactic reactions associated with the iron dextran products, a need for parenteral iron products which did not induce such a reaction existed. As a result, R&D Laboratories, Inc., obtained approval of FERRLECIT® (sodium ferric gluconate complex in sucrose injection) in 1999. (The NDA and product were subsequently purchased by Watson Pharma, Inc.). In 2000, Luitpold obtained approval of VENOFER® (iron sucrose injection, USP). (Please note the USP monograph was adopted subsequent to FDA approval.).

Both FERRLECIT® and VENOFER® were approved through full NDA's which included complete preclinical and clinical safety and efficacy information. Despite the fact each had been marketed for 40 years or more (outside of the United States) at the time of approval by FDA (including at higher dosages and for broader indications), the labeling for both products initially contained a bolded safety warning as to hypersensitivity reactions until they submitted

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postmarketing prospective safety studies in a minimum of 1000 patients. Furthermore the labeling of FERRLECIT® required a test dose .In addition, Luitpold was required to develop an *in vitro* release test to establish bioequivalence of each batch. See item 5, page 2, November 6, 2000, FDA approval letter, Exhibit 4 hereto.

At present there are no generic equivalents or other pharmaceutical alternatives [505(b)(2) applications] approved referencing either FERRLECIT® or VENOFER® as an RLD. Watson Pharma, Inc., has submitted two Citizen Petitions - 2004P0070 CP1 and CP2 - requesting that the Commissioner not approve generic equivalents of FERRLECIT® unless certain conditions are satisfied. As VENOFER® is, like FERRLECIT®, a highly complexed colloidal macromolecule with an iron core in aqueous suspension, Luitpold incorporates the arguments made therein, including its responses to all comments, by Watson Pharma, Inc., by reference.

3. The Agency Should Not Approve as an ANDA any Application Referencing VENOFER® as the RLD Unless the ANDA Applicant Demonstrates that the Manufacturing Processes for the Generic Product and its API are Identical to that of Luitpold and its API Supplier

The process to manufacture the iron sucrose API is highly complex and is critical to a safe and effective product. The manufacture of the API for VENOFER® is a multi-step polymerization process involving many individual ingredients which must be conducted in a specific order, at specific rates, in specific amounts and under specific conditions for the reaction

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to proceed correctly. This is not the case with more conventional pharmaceutical substances. Iron sucrose, like sodium ferric gluconate, is a highly complex colloidal macromolecule.

Luitpold has sponsored research to evaluate the structure of these particles. Kudasheva D S, et. al: "Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations" Journal of Inorganic Biochemistry 98: 1757-1769, 2004. See Exhibit 5. In this research, the colloidal particles of VENOFER® and FERRLECIT® were analyzed using atomic force microscopy (AFM). The results found VENOFER® is composed of spherical particles with a diameter of 6 nm with an iron core ranging from 1 to 5 nm in diameter surrounded by a sucrose shell ranging from 1 to 2 nm in thickness, and that FERRLECIT® is composed of spherical particles with a diameter of 5 nm with an iron core ranging from 1 to 3 nm in diameter surrounded by a gluconate shell of about 1.5 nm in thickness and weakly associated sucrose molecules. VENOFER® and FERRLECIT® were also analyzed by absorption spectroscopy, X-ray diffraction, transmission electron microscopy, and elemental analysis.

The properties related to the safety and efficacy of these complexes are dependent on the nature of the iron hydroxide core as well as on the carbohydrate shell and how the two are complexed. See Geisser P, Baer M and Schaub E, "Structure/histotoxicity relationship of parenteral iron preparations." Arzneim.-Forsch./Drug Res.42(II), 12: 1439-1452, 1992. See

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Exhibit 6. For example, the stability of the complex is strongly dependent on the type of carbohydrate used. The release of iron from the complex is strongly dependent on the modification of the interior of the iron hydroxide core.

The manufacturing process of the API is, therefore, critical to creation of these macromolecules and, hence, their stability and iron release rates in finished dosage forms. As emphasized by FDA as early as 1968, as discussed above, the manufacturing process for parenteral iron products is critical for the integrity of the product. While there are specifications, such as in the USP for iron sucrose injection, USP, for pH, molecular weight and turbidity for the finished product, a finished product, merely meeting those specifications may not result in a product whose safety and efficacy, as well as quality, is the same as VENOFER®, nor will it guarantee equivalence of the API. To the contrary, because the manufacturing process for the API is highly complex, employs specialized equipment and is a highly controlled processes, the manufacturing process is absolutely critical to the final structure of the VENOFER® macromolecule. Any variation in any part of the process could result in a macromolecule with, for example, a different complexing of the sucrose carbohydrate to the iron core, which could effect its release rate. A change in its release rate could dramatically affect its safety and/or effectiveness. A product might meet compendial specifications in such a case, but the effect on release rate could totally change the safety and efficacy of the final product when used in humans. Thus, unless an ANDA applicant can demonstrate that the manufacturing processes for

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its API and finished product are identical to that used to manufacture the API in VENOFER® and the finished product VENOFER®, there can be no guarantee that the resulting colloidal macromolecule is the same and that the products are, therefore, of equivalent safety and/or efficacy.

It should be noted that neither the manufacturing process for VENOFER® nor its API has ever been patented or made publicly available. In addition, because the structure of the macromolecule by nature has no clearly defined stoichiometry, its structure has only been partially determined. (See below). Therefore, absent any competent scientific proof of pharmaceutical equivalence developed by a generic applicant, the only way to ensure that a generic of VENOFER® is therapeutically equivalent to VENOFER® is by a demonstration that the manufacturing processes for the API and the finished dosage are identical. If that cannot be shown, there is no way (except by submission of complete preclinical and clinical studies) a generic applicant can show that its product is a pharmaceutical equivalent and, hence, therapeutic equivalent of VENOFER®.

The Agency has previously confirmed that a difference in production of a parenteral iron product could change the safety and/or efficacy of the drug. As FDA noted in its review of Luitpold's Amendment in support of Pharmaceutical Equivalence and Waiver Request for DEXFERRUM® (ANDA # 40-024, November 17, 1992; "aside from molecular weight

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differences (see discussion below) there may be other physico-chemical differences resulting from probable different methods of production...which might matter in terms of efficacy.” See Reference 9, CP1, Docket 2004P.0070. FDA has confirmed that a difference in the manufacturing process of a parenteral iron colloidal suspension product could have a deleterious effect on the final product and its safety and/or effectiveness.

Thus, unless an ANDA applicant can demonstrate that the manufacturing processes for its generic version of VENOFER® and its API is identical to that of VENOFER® and its API, it should not be approved as an ANDA.

4. The Agency Should Not Approve as an ANDA any Application Referencing VENOFER® as the RLD unless the ANDA Applicant Demonstrates, through Competent Scientific Evidence, That the Generic Product and its API is Identical in its Physico-Chemical Properties and Characteristics to VENOFER® and its API

Even if an ANDA applicant could demonstrate that the manufacturing processes in its ANDA for the API and finished dosage forms are identical to that used to manufacture VENOFER® and its API, the Agency should not approve as an ANDA any generic of VENOFER® unless the ANDA applicant can demonstrate through competent scientific evidence that its product, and the API, is identical in its physico-chemical properties and characteristics to VENOFER® and its API. Absent such evidence, the product cannot be considered a pharmaceutical equivalent approvable through an ANDA. While any such product must also

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meet all requirements of the USP monograph, that alone would not suffice to demonstrate pharmaceutical equivalence unless the colloidal structure and stability of the complex can also be demonstrated through competent scientific evidence to be identical.

As noted above, VENOFER® is composed of highly complexed colloidal macromolecules. Unlike conventional pharmaceutical substances, their structure - which is critical to their safety and efficacy - cannot be entirely determined because they exist as nanoparticles or cores with no clearly defined stoichiometry. See Exhibit 5 above, and Funk F, et. al: "Physical and Chemical Characterization of Therapeutic Iron Containing Materials: A Study of Several Superparamagnetic Drug Formulations with the β -FeOOH or Ferrihydrite Structure". Hyperfine Interactions 136: 73-95, 2001. (Exhibit 7).

As indicated, due to the paramagnetic nature of the iron hydroxide cores, it is not possible to conduct standard tests used to characterize the physical structure of these parenteral iron complexes. Since VENOFER® is a colloidal suspension of polynuclear iron (III) hydroxide sucrose complexes, an exact structure of it and its API can only be partially inferred through chemical analysis. Therefore, based on current known methods, it will be impossible for an ANDA applicant to demonstrate any sort of chemical comparability with VENOFER®, and hence that it is a pharmaceutical equivalent, without using the extensive test procedures developed for VENOFER®. Even performing this exhaustive barrage of tests may not guarantee

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that a generic version would be structurally comparable to VENOFER® because one can only partially infer the structure from such results.

Recently efforts have been undertaken to evaluate the physico-chemical properties of several iron compounds. These showed distinct differences. For example, an analysis of purported generic versions of both the iron sucrose API and finished dosage forms have been performed. As the attached Certificates of Analysis (Exhibit 8) clearly show, none of the purported generic products or API's purporting to be iron sucrose match entirely the specifications for VENOFER®. There are significant discrepancies in terms of physico-chemical behavior. Moreover, certain changes to the manufacturing process may alter the physico-chemical characteristics of the drug and negatively impact on the safety profile of a generic iron sucrose product.

As examples, please note the following. An iron saccharate product (iron sucrose is also know as iron saccharate) not identical to VENOFER® called FESIN® is marketed in Japan. This "iron sucrose" is not identical in physico-chemical structure to VENOFER®. It has caused osteomalacia. See Sato K, et. al: "Saccharate Ferric Oxide (SFO) - Induced Osteomalacia: In Vitro Inhibition by SFO of Bone Formation and 1, 25-Dihydroxy - Vitamin D Production in Renal Tubules." Bone 21(1): 57-64, 1997. (Exhibit 9) and Sato K and Shiraki M: "Saccharated Ferric Oxide - Induced Osteomalacia in Japan: Iron-Induced Osteopathy due to Nephropathy."

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Endo. J. 45(4): 431-439, 1998 (Exhibit 10). Furthermore, another purported generic iron sucrose was introduced in Germany called FERRUM VITIS®. Anaphylactic reactions with this product were reported. It was withdrawn from the market. Report by WHO Collaborating Centre Drug Monitoring. (Exhibit 11).

Even different versions of a product which has been marketed for as long as iron dextran injection, USP, all of which met compendial standards, have been shown substantial differences when analyzed. See Exhibit 2 above. This analysis showed marked differences in the physical and chemical properties of the products - such as stability, molecular weight and size, amount of complex variability from nanoparticle to nanoparticle, and reaction to storage stress.

Similarly, the original iron polymaltose complex (IPC) oral grade is another substance produced by the API supplier for VENOFER®. As with VENOFER®, this substance is also highly dependent on its in-house production process. Generic versions of IPC have been marketed. This has allowed scientific comparisons to be made between the different complexes available. In a 2004 publication by Geisser, P. Iron Therapy, Oxidative Stress and Immunology, 2004, edited by Chandra, RK. Nutrition and Immunology in the 21st Century, TSAR Health India. (Exhibit 12) a comparative table clearly illustrates some very major differences between products of different suppliers and also between different batches from a same supplier.

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It should also be noted that in another recent article by Mehta, BC. J. Assoc. Physicians India JAPI, 51:419-421, 2003, (Exhibit 13) from India, the author complained about the “Ineffectiveness of Iron Polymaltose Treatment of Iron Deficiency Anemia.” Such reports involving raw materials supplies from Italy and India, evidence differences in efficacy obtained from arguably the same complexes. The analogy to iron sucrose is obvious.

There is further evidence that it is critical that an ANDA applicant be able to demonstrate that the physico-chemical properties of its product and its API are identical to that of VENOFR® and its API. As has been emphasized in the literature the difference in iron kinetics can be explained by “the different stability of the iron complexes associated with variable binding of iron to other plasma proteins and disparities in iron uptake of the reticulo-endothelial system”. Sunder-Plassmann G and Hörl W H: “Safety of Intravenous Injection of Iron Saccharate in Haemodialysis Patients.” Nephrol. Dial. Transplant 11: 1797-1802, 1996. (Exhibit 14). (This article involved the product FERRIVENIN marketed by Laesovando, of Austria.) The identity of physico-chemical properties - such as colloidal structure and stability of the complex - are critical to iron kinetics and, hence, safety and effectiveness. Unless physico-chemical identity can be shown, and unless the generic applicant develops competent scientific evidence not currently available to completely identify and characterize the colloidal

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macromolecule¹, the Agency should not approve any ANDA referencing VENOFER® as the RLD, as a generic applicant must demonstrate that it is a pharmaceutical equivalent to obtain approval as an ANDA. In the absence of such evidence, the FDA should not approve any such product as an ANDA.

5. The Agency Should Not Approve any ANDA Application Referencing VENOFER® as the RLD unless the ANDA Applicant Demonstrates Therapeutic Equivalence through Satisfactory Bioequivalence Testing

As discussed above, when Luitpold submitted its ANDA for DEXFERRUM®, it requested a waiver of bioequivalence. Because of a difference in molecular weight, and because of the colloidal solution nature of this parenteral drug product, the Agency did not grant the waiver and required Luitpold to conduct bioequivalence studies. The Agency should not approve any ANDA referencing VENOFER® as the RLD unless the generic applicant, if it can first meet the requirements that it demonstrate that the macromolecule is manufactured identically to VENOFER® and is also a pharmaceutical equivalent of VENOFER®, also demonstrates that the generic product is bioequivalent to VENOFER® through appropriate

¹ Should a generic applicant submit a method or method which purports, for example, to show pharmaceutical equivalence, it is important that such method be validated by a comparison of results for the generic product with VENOFER®. For example, the reported molecular weight of parenteral iron products can depend on the method used to determine it. Thus, if a generic applicant can develop a method to demonstrate pharmaceutical equivalence (which appears doubtful based on current scientific knowledge) it must demonstrate comparability to the RLD used in actual comparative testing and not just to reported information about the product, which may be based on other analytical methods that produce different results.

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studies. Absent such a showing, there can be no guarantee that the generic product will be therapeutically equivalent to VENOFER®, and any such ANDA should not be approved. Because of the nature of these products, the Agency should establish guidelines requiring bioequivalence for parenteral iron colloidal suspension products and not grant any bioequivalence waivers.

As noted in Section 1.7 of the preface to Approved Drug Products with Therapeutic Equivalence Determinations:

Active ingredients and dosage forms with potential bioequivalence problems

FDA's bioequivalence regulations (21 CFR 320 .33) contain criteria and procedures for determining whether a specific active ingredient in a specific dosage form has a potential for causing a bioequivalence problem. It is FDA's policy to consider an ingredient meeting these criteria as having a potential bioequivalence problem even in the absence of positive data demonstrating inequivalence. Pharmaceutically equivalent products containing these ingredients in oral dosage forms are coded **BP** until adequate *in vivo* equivalence data are submitted. Injectable suspensions containing an active ingredient suspended in an aqueous or oleaginous vehicle have also been coded **BP**. Injectable suspensions are subject to bioequivalence problems because differences in particle size, polymorphic structure of the suspended active ingredient, or the suspension formulation can significantly affect the rate of release and absorption. FDA does not consider pharmaceutical equivalents of these products bioequivalent without adequate evidence of bioequivalence, such products would be coded AB.

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VENOFER® is an injectable colloidal suspension and, hence, bioequivalence testing must be conducted as a condition of approval of any ANDA.

Furthermore, as stated by the Agency in its review of Luitpold's DEXFERRUM® ANDA; "[a]nother problem is that iron dextran is not a true solution...As with parenteral suspensions, parenteral colloidal solutions are considered by the Division of Bioequivalence to be a problem and waivers of *in vivo* bioequivalence studies are not granted on them." See page F-14, Review of Pharmacokinetics and Iron Utilization Studies, November 28, 1995, ANDA 40-024, Iron Dextran Injection, USP (Exhibit 3).

VENOFER®, like DEXFERRUM®, is a colloidal suspension of iron carbohydrate particles in aqueous solution. As such, it clearly is a product for which a bioequivalence waiver would not be appropriate. Even if a generic applicant could meet the burdens described above to demonstrate pharmaceutical equivalence, therapeutic equivalence should not be presumed as it is for many injectable products. The Agency should require that any generic applicant demonstrate bioequivalence as a condition of approval of any generic referencing VENOFER® as the RLD.

6. The Agency Should Not Approve as an ANDA any Generic Referencing VENOFER® as the RLD unless the ANDA Applicant Submits a Validated *In Vitro* Release Test Confirming the Bioequivalence of Each Batch of Product

As a condition to approval of VENOFER®, the Agency required Luitpold to "develop an *in vitro* release test for VENOFER®", the purpose of which was to demonstrate batch to batch

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bioequivalence. See November 6, 2000, FDA Approval Letter, NDA 21-135, page 2, Exhibit 4. Luitpold developed such a test, which was approved as Supplement 003 to NDA 21 -135 on July 26, 2002. Any ANDA applicant should be required as a condition of ANDA approval to develop its own validated *in vitro* release test to demonstrate batch to batch bioequivalence of the product.

Given the Agency's requirement that Luitpold develop and utilize such a test, in order to assure the safety and efficacy of the product, any generic referencing VENOFER® as the RLD should be subject to the same requirement. As a matter of law, the Agency must assure that all drug products be manufactured and tested in a manner that ensures their identity, strength, quality, and purity. See Sections 501, 505(d)(3) and 505(j)(4)(A) of the FFDCFA. It is likewise fundamental that FDA must apply its standards in an even-handed manner to similarly situated persons and products. See 5 USC § 706(2)(A); *Bracco Diagnostics, Inc. v. Shalala*, 963 F. Supp. 20, 27-28 (D.D.C 1997) ("If an agency treats similarly situated parties differently, its action is arbitrary and capricious in violation of the [Administrative Procedure Act]." (quotation removed)). In requiring Luitpold to adopt *in vitro* release testing to VENOFER® FDA set a rigorous standard of quality that must now be applied to all other iron sucrose products. To do otherwise - particularly for generic products that purport to be the same as VENOFER® - would be arbitrary, capricious, and contrary to law.

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Thus, as a matter of law, any generic of VENOFER® (or any pharmaceutical alternative product submitted for approval through a 505(b)(2) application) should not be approved without the requirement to develop and validate an *in vitro* release test for demonstration of batch to batch bioequivalence.

7. The Agency Should Not Approve as a 505(b)(2) Application any Product Referencing VENOFER® as the RLD unless the 505(b)(2) Applicant Conducts Full Scale Preclinical and Clinical Safety and Effectiveness Studies

Because of the nature of parenteral iron colloidal suspensions like VENOFER®, any product which cannot be shown to be both a pharmaceutical and therapeutic equivalent of VENOFER® should be subject to the requirement to conduct full scale preclinical and clinical studies, even if submitted as a 505(b)(2) application for a difference in, for example, molecular weight or other physico-chemical difference in its composition or the composition of its API. As indicated above, because of the colloidal nature of the macromolecule found in parenteral iron products like VENOFER®, any difference - even a minor one or of a type that might otherwise be acceptable through submission of a 505(b)(2) application - should require that the applicant conduct both preclinical and clinical studies to demonstrate the safety and effectiveness of the product.

The need for such testing is illustrated by a retrospective study analyzing the data from administration of intravenous iron dextran, see Fletes R, Lazarus JM, Gage J, Chertow GM,

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“Suspected Iron Dextran-Related Adverse Drug Events in Hemodialysis Patients.” Am J Kidney Dis. 2001 37(4): 742-749, 2001. (Exhibit 15). Although the products were shown to be comparable with respect to their effectiveness based on pharmacokinetic and iron utilization, it appeared possible that differences in the molecular weight of the products had an effect on their respective safety profiles which differed in up to 8 times higher rates of side-effects of one product versus the other. This demonstrates how even a minor difference in the macromolecules of otherwise similar products significantly may affect their safety.

This is further evidenced where only minor changes are made *in the same product*. As noted by Watson in its February 12, 2004, Citizen Petition - 2004P0070, CP1 - at page 5:

In the mid 1990s, a marked increase in the number of adverse events reports was noted in data coming from Italy and Germany for Ferlixit® (the European brand name for FERRLECIT®). In the first half of 1995, a total of two adverse events were reported in Italy and four in Germany. In the second half of the same year, the adverse event incidence rose to 60 in Italy and 38 in Germany. After an exhaustive investigation of the manufacturing process, it was determined that the source of one of the ingredients of the product had been changed. Although both ingredients from both sources met the rigorous European Pharmacopoeia standards, substitution one for the other resulted in a dramatic change in the safety profile of the final product.

In another case, a preservative-free version of FERRLECIT® was manufactured for use in a clinical study. The product was made in exactly the same manner as the commercial product except that preservative was eliminated. The preservative-free clinical trial material was manufactured using production equipment and

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product batch records according to the process used for the commercial production of the preserved FERRLECIT®. When used in the clinical study an unusually high number of patients discontinued from the study due to adverse events. Although the events cannot be definitely attributed to the change in FERRLECIT® formulation, it is reasonable to suspect that it was a contribution factor.

See, also, Notice to Physicians dated November 16, 1995 on FERRLECIT®, Exhibit 16. (The original in German and a certified translation are attached).

Any minor change in a parenteral iron product - even in the same product - can have a significant effect on its safety and/or effectiveness. In the cases discussed in the second paragraph above, although both ingredients from both sources met the same rigorous European Pharmacopoeia standards, substitution of one for the other resulted in a dramatic change in the safety profile of the final product. See, also, pages 15-18, hereinabove.

Thus, unless it has fulfilled all of the above requirements, any applicant submitting a 505(b)(2) application should be required to conduct preclinical and clinical testing in order to satisfy the requirements of Section 505 that an applicant demonstrate, by substantial evidence, the safety and effectiveness of the product as a condition of approval.

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8. The Agency Should Not Approve as a 505(b)(2) Application any Product Referencing VENOFER® as the RLD unless the 505(b)(2) Applicant Conducts a Prospective Safety Study in at Least 1000 Patients

As a condition of approval of any 505(b)(2) application referencing VENOFER® as the RLD, the Agency should require that the 505(b)(2) applicant conduct a prospective safety study in at least 1000 patients. As set forth in the November 6, 2000, FDA Approval Letter for VENOFER®, Exhibit 4, Luitpold was required to conduct “a study to provide additional safety data (sic) (e.g., incidence of allergic or anaphylactic reactions, cross-reactivity with other parenteral iron preparations.)” This was required despite the fact that VENOFER® had been marketed since 1950 and there was, as a result, a wealth of published information, as well as marketing experience, supporting its safety. Any product submitted as a 505(b)(2) application, due to the nature of this product as discussed above, where even a minor change can greatly effect its safety, should be subject to this same requirement.

At a minimum, such a requirement should be a post-marketing commitment - but given the fact that such a product would at the time of approval essentially be “new” (unlike VENOFER® at its time of FDA approval), Luitpold believes this requirement should be satisfied prior to any 505(b)(2) NDA approval and that FDA should establish guidelines requiring such a study as a precondition of any 505(b)(2) NDA approval.

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9. The Agency Should Not Approve as a 505(b)(2) Application any Product Referencing VENOFER® as the RLD Unless the Labeling of the Product Contains a Bolded Warning and the Requirement for a Test Dose Until it has Conducted Adequate Safety Testing

Should the Agency permit the required safety study to be conducted as a post-marketing commitment, the Agency should require the 505(b)(2) applicant to have both a bolded safety warning in the labeling for its product, as well as required test dose, until such time as such additional safety data is submitted to FDA and found acceptable. The bolded warning for VENOFER® was:

WARNINGS

HYPERSENSITIVITY REACTIONS:

POTENTIALLY FATAL HYPERSENSITIVITY REACTIONS CHARACTERIZED BY ANAPHYLACTIC SHOCK, LOSS OF CONSCIOUSNESS, COLLAPSE, HYPOTENSION, DYSPNEA, OR CONVULSION HAVE BEEN REPORTED RARELY IN PATIENTS RECEIVING VENOFER® (SEE ADVERSE REACTIONS). FATAL IMMEDIATE HYPERSENSITIVITY REACTIONS HAVE BEEN REPORTED IN PATIENTS RECEIVING THERAPY WITH MANY IRON CARBOHYDRATE COMPLEXES. FACILITIES FOR CARDIOPULMONARY RESUSCITATION MUST BE AVAILABLE DURING DOSING. SERIOUS ANAPHYLACTOID REACTIONS REQUIRE APPROPRIATE RESUSCITATION MEASURES. ALTHOUGH FATAL HYPERSENSITIVITY REACTIONS HAVE NOT BEEN OBSERVED IN VENOFER® CLINICAL STUDIES, INSUFFICIENT NUMBERS OF PATIENTS MAY HAVE BEEN ENROLLED TO OBSERVE THIS EVENT. PHYSICIAN VIGILANCE WHEN ADMINISTERING ANY

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**INTRAVENOUS IRON PRODUCT IS ADVISED (SEE
PRECAUTIONS AND ADVERSE REACTIONS).**

Until a 505(b)(2) applicant has met the same requirements for demonstrating safety as VENOFR® , its labeling should be required to bear such a bolded warning, given the serious safety issues potentially associated with parenteral iron products.

Related thereto, it should go without stating that any 505(b)(2) applicant should be able to demonstrate the absence of dextran antibodies caused by use of the product. Since parenteral iron preparations are composed of iron hydroxide cores with carbohydrate shells, exemption from the black box warning required for iron dextran products due to the anaphylaxis associated therewith should only be permitted and approved if the 505(b)(2) applicant submits data showing the absence of dextran in the product and no serious anaphylactic reactions in the clinical trials that should be conducted per sections 8 and 9 above, including in dextran-sensitive patients. Otherwise, such a product should contain a black box warning similar to that for DEXFERRUM® and INFED®, and the requirement for a test dose required for iron dextran products as well as was required for FERRLECIT® until it submitted adequate safety data.

10. Conclusion

For the reasons discussed above, the Agency should not approve an ANDA or 505(b)(2) application referencing VENOFR® as the RLD unless adequate substantial evidence is

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submitted to assure the safety and effectiveness requirements of Section 505 of the FDCA are satisfied.

Because of the unique safety and efficacy considerations for these products, the Agency should establish guidelines for approval of parenteral iron sucrose suspensions, including any referencing VENOFR® as the RLD, and other parenteral iron colloidal suspensions, such as, for example, FERRLECIT®, prior to approving any generic or 505(b)(2) application for any such product. Such guidelines should include, at a minimum, requirements for:

- (1) demonstrating the identity of the manufacturing processes for the API and the finished product to those for the RLD and its API;
 - (2) the submission of validated methods and data demonstrating complete pharmaceutical equivalence, including identity of the colloidal structure and stability of the complex thereof;
 - (3) a requirement for generic applicants to conduct bioequivalence studies and for 505(b)(2) applicants to submit complete preclinical and clinical data;
 - (4) a requirement for generic and 505(b)(2) applicants to develop and submit an *in vitro* release test for demonstration of batch to batch bioequivalence;
- and

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- (5) a requirement for 505(b)(2) applicants to conduct safety studies in at least 1,000 patients and for their labeling to bear a bolded and/or boxed warning and/or a test dose, appropriate to the amount and type of safety and effectiveness information submitted in the application for the product.

Until the Agency establishes such guidelines for parenteral iron colloidal suspensions, it should not approve any generic or pharmaceutical alternative of such product.

In similar cases involving complex non-traditional molecules, the Agency has required such evidence and established such guidelines. See Docket 00D-0835, Draft Guidance for Industry on Conjugated Estrogens, USP: LC-MS Method for Both Qualitative Chemical Characterization and Documentation of Qualitative Pharmaceutical Equivalence; Availability, 65 Fed. Reg. 12556 (March 9, 2000). (See Exhibit 17.) For the reasons discussed herein, the Agency should require the same for generic equivalents and pharmaceutical alternatives of iron sucrose injection, USP (and other parenteral iron colloidal suspensions).

C. Environmental Impact

Petitioner claims a categorical exclusion from the requirement of environmental assessment or environmental impact statement pursuant to 21 C.F.R. §25.31.

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D. Economic Impact

Pursuant to 21 C.F.R. §10.30(b), economic impact information is to be submitted only when requested by the Commissioner following review of this Citizen Petition.

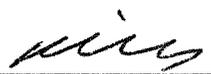
E. Certification

The undersigned certifies that, to the best of their knowledge and belief, this Citizen Petition includes all representative data and information known to the Petitioner, which are unfavorable to the Petition.

Respectfully submitted,

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