

0938 '06 JUN -2 P3:37

June 2, 2006

Dockets Management Branch
Food and Drug Administration
Department of Health and Human Services
Room 1061, HFA-305
5630 Fishers Lane
Rockville, MD 20852

**Re: CITIZEN PETITION 2005P-0095 – Generic Equivalents and
Pharmaceutical Alternatives of Iron Sucrose Injection, USP**

The undersigned hereby submits comments to the citizen petition referenced above in accordance with 21 C.F.R. §10.20 and §10.30, and requests that the Commissioner of the Food and Drug Administration (“FDA”) refrain from taking administrative action regarding the approval and/or the effective date of final approval of any and all abbreviated new drug applications (“ANDAs”) for a generic version of iron sucrose injection USP, unless and until the ANDA applicant demonstrates conformity with USP monograph specifications, and obtains *in vitro* release test bioequivalence data and *in vivo* bioequivalence data. The undersigned supports some of the requests delineated in petition 2005P-0095 filed by Luitpold Pharmaceuticals, Inc. (“Luitpold”). However, the undersigned expresses opposition to several other requests made through petition 2005P-0095, specifically with regard to certain proposed requirements related to the manufacturing and clinical investigation of generic versions of iron sucrose, or 505(b)(2) applications for other pharmaceutical alternatives of iron sucrose injection.

As described in greater detail below, this request is necessary and appropriate to ensure there is sufficient data within each application to demonstrate the chemical equivalence and bioequivalence of the generic product to the innovator product.

2005P-0095

C 1

A. ACTION REQUESTED

The undersigned petitioner requests that the FDA Commissioner stay the final approval and/or effective date of any iron sucrose injection ANDAs unless the applicant for a generic version of iron sucrose injection USP takes the following specific actions to ensure the safety and efficacy of the generic version:

- Provide evidence establishing that all specifications of the USP monograph for iron sucrose injection have been met;
- Provide evidence of adequate *in vivo* bioequivalence (“BE”); and
- Provide evidence of adequate *in vitro* release test BE.

These requested actions with regard to USP monograph specifications, *in vitro* release test BE data and *in vivo* BE data pharmacokinetic study will ensure that the generic drug version’s chemical composition, physicochemical properties, integrity, stability, and pharmaceutical properties will match those of VENOFER® (iron sucrose injection USP).

The petitioner further recommends that the Commissioner reject several of the petitioned requirements requested by Luitpold in its Citizen Petition 2005P-0095 of March 3, 2005. Specifically, the undersigned petitioner:

- Opposes the request that the Agency should not approve as an ANDA any application referencing VENOFER® as the reference listed drug unless the ANDA applicant demonstrates that the manufacturing processes for the generic product and its active pharmaceutical ingredient (“API”) are identical to that of Luitpold and its API supplier;
- Opposes the request that the Agency should not approve as an ANDA any application referencing VENOFER® as the reference listed drug unless the ANDA applicant demonstrates that the generic product and its API is identical in its physicochemical properties and characteristics to VENOFER® and its API; and
- Opposes the request that the Agency should not approve as a 505(b)(2) application any product referencing VENOFER® as the reference listed drug unless the applicant conducts full scale preclinical and clinical safety and effectiveness studies.

The rejection of these specific requests in Luitpold’s Citizen Petition 2005P-0095 are appropriate because it will assure that incidental, irrelevant, and technically impossible restrictions are not imposed on the production of generic versions of a colloidal iron formulation which, by definition, is heterogeneous. In particular, FDA should reject Luitpold’s specific request for the following reasons: (1) iron sucrose for injection is a colloidal suspension which cannot be defined as a single chemical entity; (2) minor manufacturing differences commonly occur during the production of marketed drugs

without impacting quality or therapeutic characteristics; and (3) a comparison of approval requirements for VENOFER® iron sucrose injection with DEXFERRUM® iron dextran injection further support the conclusion that requirements for clinical studies of new iron sucrose products should be negotiated with FDA on a case-by-case basis. Below, we provide additional information in support of our request.

B. STATEMENT OF GROUNDS

I. Background On Iron Sucrose Physicochemical Properties

Parenteral iron injection products include iron sucrose injection USP, iron dextran injection USP, sodium ferric gluconate complex in sucrose injection, iron saccharate, iron sorbitol, and chondroitin sulfate iron colloid. These complex formulations have been developed to improve the utility of non-heme iron for treatment of anemia, which if uncomplexed with carbohydrate would hydrolyze and polymerize.¹ Each of these preparations contains ferric iron as the active ingredient. They are spheroidal iron-carbohydrate complexes created such that the interior core of iron-oxyhydroxide is maintained in a stable colloidal suspension by the protective carbohydrate shell, with resultant slow release of bioactive iron.² The core itself is polynuclear (*i.e.*, containing multiple covalently linked iron, OH, and O₂ groups in lattice form), and the carbohydrate coating is similarly polymeric. Based on the different chemistries of these products, they can vary with regard to clearance after injection, iron release *in vitro* and release/utilization *in vivo*, and maximal tolerated dose.

Iron sucrose, and the other parenteral iron agents, is formulated as nanoparticle suspensions in aqueous solution. As these are polymeric materials, the sizes of both the interior iron core and the complete saccharide-bound complexes are quite variable. For example, the iron core diameter in iron sucrose ranges between approximately 1-5 nm (mean 3 nm, \pm 2 nm SD), and the intact particle ranges in diameter from approximately 3-11 nm². Accordingly, the molecular weights of iron sucrose particles vary greatly. Recognizing this unavoidable heterogeneity, the USP Monograph acceptance criteria for iron sucrose injection includes average complex molecular weight which can span nearly a 2-fold range of weight (34,000-60,000 Da). Chemical composition and physical properties of iron sucrose formulations are obviously approximate concepts.

¹ Funk, F., Long, G.J., et al. 2001. 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.

² Danielson, B.G. 2004. Structure, chemistry and pharmacokinetics of intravenous iron agents. *J. Am. Soc. Nephrol.* 15:S93-98.

II. Request That ANDA Applicants Submit Evidence That USP Monograph Specifications Have Been Met

The USP Monograph for iron sucrose injection includes acceptable parameters, and test methods, for iron content (percent of labeled amount), pH, alkalinity, turbidity, weight-average and number-average molecular weight ranges, documented absence of low-molecular weight complexes, specific gravity, osmolarity, and limit of ferrous iron (II). We fully support the view that any generic formulations of iron sucrose injection meet all USP monograph specifications, and that any products failing to meet these criteria not be considered generic versions of VENOFER®. Several foreign-marketed iron sucrose products (Feriv®, Hematin®, Fe-Back®, Fe-Lib®), described as “generic” iron sucrose injection by Luitpold in its April 3, 2006 addendum to its petition 2005P-0095, were shown by data included in the addendum submission to fail several of the USP monograph acceptance criteria for iron sucrose. Those products should not qualify as generic versions of VENOFER®, and consider such data as evidence that the USP monograph criteria are capable of distinguishing between iron sucrose formulations that at a minimum, may satisfy the criteria of being pharmaceutically equivalent.

However, because these named products clearly do not qualify as generic iron sucrose, we object to Luitpold’s use of these examples to support their requested requirements of physicochemical and manufacturing process identity for iron sucrose generics. We maintain that considerations of Feriv®, Hematin®, Fe-Back®, and Fe-Lib® are irrelevant to a discussion of data requirements for a generic formulation of VENOFER®, a drug product which fully complies with USP monograph specifications.

III. Request That ANDA Applicants Submit Adequate *In Vivo* Bioequivalence Data

ANDA applications are required to include an *in vivo* BE study unless exempted by waiver. The regulatory option for waiver of the standard BE study in support of a parenteral drug ANDA (21 C.F.R. § 320.22) requires that the drug product is a solution, and contains active and inactive ingredients in the same concentration as the reference drug product. In clear distinction to the types of products that could theoretically qualify for exemption of the standard BE study, iron sucrose for injection is a colloidal suspension -- not a true solution -- and it has a range of complexed iron sucrose concentrations. Final products are specifically prepared to a given elemental iron concentration (*e.g.*, 20 mg/mL), and the variable complexed sucrose component generates a considerable range in total molecular weight and final complex concentration. Accordingly, waiver of the usual *in vivo* BE study is not appropriate for iron sucrose injection.

FDA’s review of generic iron dextran DEXFERRUM® specifically notes in the denial of BE waiver request that parenteral colloidal solutions are considered problematic, and that waivers of *in vivo* BE studies are not granted for those types of products. FDA emphasizes this point in the preface to the Approved Drug Products with Therapeutic

Equivalence Determination, specifically citing the problems of injectable suspensions due to variable size and polymorphic structure of the drug. In FDA's discussion of criteria and physicochemical evidence to assess actual or potential bioequivalence problems (21 C.F.R. § 320.33), factors associated with problems include active drug ingredients with low aqueous solubility. Particle size and/or surface area are specifically noted as physicochemical evidence indicative of the potential for BE equivalence problems, with structural characteristics of such problematic materials including the presence of polymorphic forms. Iron sucrose is characterized by each of these problematic issues.

Bioavailability is especially critical for the therapeutic properties of parenteral iron preparations because the body's utilization of iron requires direct clearance of the injected therapeutic moiety into the reticuloendothelial system. However, the pharmacokinetics of parenteral iron-carbohydrate agents are known to include clearance rates which are dependent on molecular weight of the complexes,³ such that lower molecular weight complexes are cleared fastest. Reticuloendothelial system clearance also is known to be saturable at high drug doses, which can add an additional layer of uncertainty regarding anticipated bioavailability. Given the complexity of iron sucrose formulations and their pharmacokinetics, it is unreasonable to believe that *in vitro* analytic characterization would necessarily predict *in vivo* pharmacokinetics and substitute for the usual BE study.

IV. Request That ANDA Applicants Submit Adequate *In Vitro* Release Test Bioequivalence (BE) Data

Stability of iron sucrose injection prominently involves maintaining iron within the core of the iron sucrose particle. Free iron is not in a biologically useful form, and therefore should be minimized. Furthermore, if iron is released it cannot be transferred to cells of the reticuloendothelial system as intact complex, and profound toxicity can result. Colloidal formulations of iron buried within carbohydrate particles were purposely developed to minimize the toxicity from free ferric iron. Prior to development of colloidal iron-saccharide complexes, therapeutic replacement of iron as an unprotected ferric compound was limited to approximately 8 mg due to adverse reactions including severe hypotension,⁴; such replacement comprises less than 10% of the safely administered quantity of iron sucrose. However, it is known that differences in colloidal iron products' core size and chemistry can influence iron release rates *in vitro*.⁵ Given this unavoidable variability, *in vitro* release test BE data provide important evidence, both from the chemical and clinical perspectives, that iron sucrose products are equivalent with regard to this important safety parameter.

As a post-market commitment upon approval of VENOFER®, FDA required development of an *in vitro* release test and specifications. Such testing serves as a surrogate for batch-to-batch bioequivalence, and indicates integrity and stability of the

³ Id.

⁴ Id.

⁵ Id.

complex formulations to prevent released iron toxicity *in vivo*. Release testing is practical, and should be considered mandatory for guaranteeing the safe and effective substitutability of a generic iron sucrose preparation.

V. FDA Should Reject Luitpold's Manufacturing Process "Identity" Argument

Luitpold's March 3, 2005 petition includes the request that the Agency should not approve as an ANDA, any application referencing VENOFER® as the reference listed drug 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. FDA should reject that request on the grounds that it is both unnecessary and impossible.

Minor manufacturing changes occur commonly during the lifespan of a marketed drug as source reagents change, manufacturing steps are optimized, new quality tests are instituted, etc. As long as such changes do not demonstrably alter the characteristics of the final product, they are considered relatively incidental, requiring internal notation of the changes, or at most, a supplemental application to FDA identifying the change and documenting the lack of effect on product quality. Manufacturing changes in general, even when major (with the exception of a change of ingredients) rarely if ever relegate a marketed product to the "new drug" category such that clinical testing is required. Therefore, we maintain that a demonstrable difference between two manufacturing processes does not necessarily impact either product efficacy or safety, and that it is unnecessary for the manufacture of generic iron sucrose to exactly match the process used for the innovator product.

We further object to Luitpold's request because it is impossible to satisfy this requirement. The precise details of a drug's manufacture are trade secrets, and a generic manufacturer would have no conceivable way of knowing whether the two processes were identical or differed in some respect.

We further note that some of the statements and arguments in Luitpold's petition relating to the importance of the manufacturing processes are based on concepts which have been taken out of context, are misguided, or otherwise misleading. Specific examples are provided below.

First, the 1968 Federal Register DESI notice statement (cited as Exhibit 1: Federal Register 1968⁶ on Luitpold's petition at p. 6) was correct then and remains correct today in maintaining that manufacturing procedures for parenteral iron formulations can impact product integrity. The general concept that manufacturing procedures can impact the integrity of a product is a well-established fact for all drug products. However, the Federal Register DESI statement is not in reference to generic products that are required to satisfy

⁶ 33 *Fed. Reg.* 9352, 9354 (June 26, 1998) (Drug efficacy study implementation announcement regarding certain iron preparations for parenteral use.).

current USP criteria. Furthermore, since 1968, numerous technological advances have been developed and are available for use in the physicochemical evaluation of iron sucrose (e.g., X-ray diffraction, transmission electron microscopy, atomic force microscopy, high pressure liquid chromatography, Mössbauer spectroscopy, etc.). These technologies have dramatically changed the ability to evaluate an iron sucrose preparation. The Federal Register statements regarding the importance of manufacturing procedures and the resultant conclusion that these products constitute new drugs should not automatically be applied to generic formulations of iron sucrose, as stated in the Luitpold petition.

Second, Luitpold's discussion of demonstrable structure/histotoxicity relationships as support for the critical nature of the manufacturing process (cited as Exhibit 6: Geisser 1992⁷ on petition pp. 10-11) highlights differences in toxicity between iron sucrose and non-sucrose iron preparations (e.g., iron complexed to dextran, maltrin, gluconic acid, chondroitinsulfate, and others), as well as differences between ferric and ferrous iron therapeutic drugs. The findings that vastly different iron formulations can have different organ toxicities are irrelevant to issues regarding generic versions of a particular formulation such as iron sucrose. Furthermore, the structure/histotoxicity data presented in that paper for three lots of iron sucrose support the conclusion that the different iron sucrose preparations tested actually have *similar* histotoxicity, not dissimilar as implied in the petition.

Third, Luitpold argues in its petition that, "[t]he 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." See Petition at p. 11. It relies exclusively on the Geisser article (Exhibit 6 to Luitpold's petition) as support for this contention. The Geisser article, however, does not relate at all to the API manufacturing processes. Rather, it illustrates (not surprisingly) major differences in degradation kinetics between iron sucrose vs. non-sucrose iron formulations. When one considers demonstrable differences between 3 batches of iron sucrose, this variability is actually minimal. The data presented in the Geisser article suggest that it is not the "manufacturing process" at issue with regard to product stability, but rather the major differences in chemical composition between the various iron preparations.

VI. FDA Should Reject Luitpold's Physicochemical Identity Argument

Luitpold's March 2005 petition includes a request that the Agency not approve as an ANDA any application referencing VENOFER® as the reference listed drug unless the ANDA applicant demonstrates that the generic product and its API is identical in its physicochemical properties and characteristics to VENOFER® and its API. We oppose this request because it is both unnecessary and technically impossible.

⁷ Geisser, P., Baer, M., and Schaub, E. 1992. Structure/histotoxicity relationship of parenteral iron preparations. *Arzneim. Forsch./Drug Res.* 42:1439-52.

Luitpold's petition posits a requirement for "identical" characteristics between a generic and VENOFER®, but without further definition other than to claim that meeting of USP monograph requirements would not by itself provide sufficient assurance of pharmaceutical equivalence. Describing two preparations of iron sucrose as "identical" or "non-identical" is a difficult concept given that parenteral iron formulations comprise suspensions of very heterogeneous particles. The acknowledged heterogeneity is clearly illustrated in the USP monograph for iron sucrose injection, in which a preparation of particles within a nearly 2-fold range of molecular weight (34,000 – 60,000 Da) conforms to specifications. Even matching this level of variability can be a challenge. The VENOFER® package insert and two references from the Luitpold petition (Exhibit 2: Lawrence 1998⁸ and Exhibit 5: Kudasheva 2004⁹) document a wide range of molecular weights and several-fold variation in iron sucrose particle diameter, even within a single lot of product. While we agree that a generic product needs to match the innovator with regard to composition and physical characteristics, *i.e.*, the "sameness" requirement for generic drug products, the concept of "identical" is meaningless given the chemical and structural variability of the particles that constitute these products.

We further suggest that concepts included in FDA's draft Guidance for Industry, "ANDAs: Pharmaceutical Solid Polymorphs; Chemistry, Manufacturing, and Controls Information," are pertinent. In this guidance, FDA provides recommendations on assessing sameness when a drug substance exists in polymorphic forms. Acceptance of drug polymorphism for generic products is clearly indicated in the guidance; *e.g.*, "...differences in drug substance polymorphic forms do not render drug substances different active ingredients for the purposes of ANDA approvals," and "...using a drug substance polymorphic form that is different from that of the RLD may not preclude an ANDA applicant from formulating a generic drug product that exhibits bioequivalence and stability." Given that parenteral iron formulations are polymorphic, we suggest that the concepts of this guidance apply to iron sucrose, and that USP monograph parameters along with *in vitro* release test and *in vivo* bioequivalence data should suffice to characterize sameness for these products and their reference listed drugs.

We further object to many of the referenced concepts in the Luitpold petition presented as support for the requirement of identical physical and chemical parameters between generic and innovator iron sucrose preparations because Luitpold has taken these concepts out of context, and they are either ambiguous, misleading, or completely irrelevant to the discussion. Below, we describe specific examples of references in Luitpold's petition that raise these concerns.

⁸ Lawrence, R. 1998. Development and comparison of iron dextran products. *PDA J. Pharm. Sci. Technol.* 52:190-97.

⁹ Kudasheva, D.S., Lai, J., Ulman, A., and Cowman, M.K. 2004. Structure of carbohydrate-bound polynuclear iron oxyhydroxide nanoparticles in parenteral formulations. *J. Inorganic Biochem.* 98:1757-69.

Exhibit 8 (Vifor analysis¹⁰) in the Luitpold petition (p. 15) is characterized as representing certificates of analysis of “generic” iron sucrose API and finished dosage products. Given the extremely large range of average molecular weights ranging from 535 Da to 250,000 Da and a very large range of colloidal turbidities, these products obviously differ greatly, and in our view could not possibly be construed as generic products. Since the six samples analyzed are not identified in the exhibit tables as other than test products, it becomes impossible to verify any of the petition statements regarding purported relationships between such products and VENOFER®. We believe that inclusion of such data in the Luitpold petition is misleading and irrelevant.

Exhibits 9 (Sato 1997¹¹) and 10 (Sato 1998¹²) of the Luitpold petition (pp. 15-16) are purported as evidence that the Japanese iron sucrose product FESIN® has a clinically important toxicity (osteomalacia) not known to constitute a risk with VENOFER®. However, the reports of osteomalacia described with FESIN® were associated with dosing described in the article as “excessive” (many grams accumulated dose over several years). Therefore, it cannot be ascertained whether the toxicity is caused by the chemical composition and structure of the product or its prolonged and excessive administration. The authors themselves clearly relate this toxicity to “abusive infusion” and not poor or otherwise toxic product. We believe that inclusion of such data in the Luitpold petition is misleading and irrelevant.

The Luitpold petition (p. 17) cites a paper describing ineffectiveness of iron preparations to treat iron deficiency anemia (Exhibit 13: Mehta 1993¹³). This citation pertains to oral therapy with iron polymaltose. As this product is neither iron sucrose nor an injectable formulation, we believe that this exhibit is completely irrelevant to considerations of the efficacy of injectable iron sucrose, and to considerations of “sameness” of VENOFER® and generic iron sucrose products.

The Luitpold petition (p. 17) cites Exhibit 14 (Sunder-Plassmann 1996¹⁴) and discusses the importance of identity of physicochemical properties, such as colloidal structure and complex stability to iron kinetics and safety and effectiveness. However, this exhibit is a paper which presents serum iron and transferrin saturation data for four different doses of a single iron sucrose formulation, and has no data relative to structure, stability, or safety of various iron sucrose preparations. Statements in Exhibit 14 related to differential product stability relate to the comparison between iron sucrose and iron

¹⁰ Iron sucrose API and finished dosage forms: Results of Analysis, Vifor International, 2005.

¹¹ Sato, K., Nohtomi, K., Demura, H., Takeuchi, A., Kobayashi, T., Kazama, J., and Ozawa, H. 1997. Saccharated ferric oxide (SFO)-induced osteomalacia: in vitro inhibition by SFO of bone formation and 1,25-dihydroxy-vitamin D production in renal tubules. *Bone* Vol. 21:57-64.

¹² Sato, K., and Shiraki, M. 1998. Saccharated ferric oxide-induced osteomalacia in Japan: iron-induced osteopathy due to nephropathy. *Endocrine J.* 45:431-439.

¹³ Mehta, B.C. 1993. Ineffectiveness of iron polymaltose in treatment of iron deficiency anemia. *J. Assoc. Phys. India* 51:419-21.

¹⁴ Sunder-Plassmann, G., and Horl, W.H. 1996. Safety of intravenous injection of iron saccharate in haemodialysis patients. *Nephrol. Dial. Transplant.* 11:1797-1802.

gluconate, a comparison which is clearly irrelevant to the consideration of a generic form of VENOFER®. Furthermore, the paper's discussion which is relevant to toxicity relates to recipient factors (the hypothesized situation whereby administered iron could produce toxicity by exceeding the recipient's transferrin saturation) rather than a product's physicochemical characteristics. We believe that inclusion of such discussion in the Luitpold petition is misleading and irrelevant.

Finally, the Luitpold petition (pp. 22-23) cites data from Exhibit 15 (Fletes 2001¹⁵), a paper showing much higher (8-fold) adverse event rates for one iron dextran formulation compared to another, concluding, "This demonstrates how even a minor difference in the macromolecules of otherwise similar products significantly may affect their safety." However, the iron dextran products being compared differ substantially by molecular weight (96,000 vs. 265,000 Da), which is hardly the "minor" difference claimed by Luitpold. We believe that inclusion in the Luitpold petition of such discussion related to chemical similarities of innovator and generic iron sucrose preparations is misleading and irrelevant.

VII. FDA Should Reject Luitpold's Clinical Trial Argument

Luitpold's March 2005 petition includes a request that the Agency not approve as a 505(b)(2) application any product referencing VENOFER® as the reference listed drug unless the applicant conducts full-scale preclinical and clinical safety and effectiveness studies. We oppose -- and FDA should reject -- this request because it is overly restrictive. Whether clinical testing is required depends on the precise nature of the product and is properly a matter that should be decided on the basis of a discussion between the applicant and the Agency after consideration of all relevant information.

Luitpold's petition (p. 25) presents as a precedent for this request the 1,000 patient Phase IV safety study that FDA required for the approval of Luitpold's 505(b) VENOFER® application. That precedent is irrelevant. VENOFER® was an application for an iron formulation never previously approved by FDA. The safety study requirement for data, related in part to the potentially fatal adverse reaction of anaphylaxis, was appropriate because the drug had long been marketed ex-U.S. but without a good modern-day clinical database rather than, as stated in the petition, *in spite* of its long marketing history. We suggest that the requirement for such studies for new iron sucrose products should be negotiated with FDA on a case-by-case basis.

We object to the misleading use in the Luitpold petition of Exhibit 15. The publication in this exhibit (Fletes 2001¹⁵) (discussed on pp. 22-23) is cited as evidence that safety profiles of iron products can differ despite being "comparable with respect to their effectiveness based on pharmacokinetic and iron utilization...." This conclusion is

¹⁵ Fletes, R., Lazarus, J.M., Gage, J., and Chertow, G.M. 2001. Suspected iron dextran-related adverse drug events in hemodialysis patients. *Am. J. Kidney Dis.* 37:743-49.

misleading because the products with different safety profiles being compared in this study, DEXFERRUM® and INFed®, differ in molecular weight by nearly 3-fold (96,000 vs. 265,000 Da) as pointed out in the discussion of the paper. These products clearly are not chemically comparable. Furthermore, although not pointed out in Exhibit 15, these two iron dextran products also are not comparable with respect to pharmacokinetics as claimed on page 23 in the petition: Luitpold's own data¹⁶ show that these products differ by approximately 1.5-2 fold for both AUC and T_{max}.

We furthermore object to the use of quotations (p. 23 of the Luitpold petition) from Watson Pharmaceuticals' citizen petition 2004P-0070 concerning Ferrlecit® ferric gluconate complex to support the concept that "minor changes" in the manufacture of a product can have a negative impact on safety. The Watson petition cites an increase in adverse event frequency after a change of ingredient source in one instance and omitting preservative in another, stating, "Although the events cannot be definitely attributed to the change in Ferrlecit formulation, it is reasonable to suspect that it was a contributing factor." Regardless of whether or not the manufacturing changes were responsible for the altered safety profile in the case of Ferrlecit®, changes of source ingredients and changes in excipients in drug manufacture are common, and rarely require prospective clinical investigation. Safety surveillance activities are the established methodologies for determining whether minor manufacturing changes may have inadvertently created a clinical consequence. Rather than interpreting this change in Ferrlecit® adverse event frequency as a rationale for conducting full pre-market safety testing of generic iron sucrose, as presented in the Luitpold petition, this example serves to demonstrate the appropriate utility of post-market safety surveillance.

A very informative precedent exists for approval of a 505(b)(2) application of a parenteral iron product in the absence of pivotal clinical safety and efficacy data. Luitpold's DEXFERRUM® iron dextran injection was approved on the basis of a favorable iron utilization study, performing as well or better (Medical Reviewer conclusions¹⁷) than the iron dextran reference listed drug INFed® in a comparative study. In a pharmacokinetic comparison to INFed®, bioavailability did not fall within standard bioequivalence limits for AUC (only 1/20 subjects demonstrated bioequivalence according to standard criteria). As repeatedly pointed out by FDA reviewers, the molecular weights of these two drugs also differed greatly (nearly 3-fold, as described above), and particle sizes varied greatly. Yet despite the differences in products, the FDA considered that adequate evidence of safety of DEXFERRUM® had been achieved from only the limited numbers of subjects treated with a single dose DEXFERRUM® in the pharmacokinetic study or the 5-dose administration in the iron utilization study. Thus, in comparison with the marketed iron dextran product INFed® (the reference product in several comparative studies) DEXFERRUM®:

¹⁶ Summary Basis of Approval, DEXFERRUM®, p. 8.

¹⁷ Id. at p. 11.

- Has markedly different physicochemical characteristics from INFeD®;
- Is not bioequivalent to INFeD®;
- Could not possibly have been manufactured according to identical procedures, as deduced from the molecular differences; and
- Was approved without extensive clinical studies of efficacy and safety.

We maintain that the approval of DEXFERRUM® is a precedent in direct opposition to the stringencies listed in Luitpold's citizen petition 2005P-0095 for generic equivalents and pharmaceutical alternatives of iron sucrose injection.

C. ENVIRONMENTAL IMPACT

An environmental assessment report on the action requested in this petition is not required under 21 C.F.R. § 25.31.

D. ECONOMIC IMPACT

Pursuant to 21 C.F.R. §10.30(b), a statement of the effect of requested action on various economic indicators will be submitted only if requested by the Commissioner.

E. CERTIFICATION

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

Sincerely,


Mark S. Brown / CIA

cc Gary Buehler, Director, Office of Generic Drugs
Gregory Q. Mills, MD, Director, Division of Medical Imaging and Hematology
Products