



LUITPOLD

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VIA HAND DELIVERY

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
Docket 2005P-0095

Dear Sir/Madam:

Reference is made to our Citizen Petition, Docket 2005P-0095/CP1, filed on March 4, 2005. Reference is also made to the FDA acknowledgement letter, dated March 7, 2005; our correspondence, dated March 23, 2005; the Agency's interim response, dated August 31, 2005, and our amendment to this Petition, dated April 3, 2006.

This communication responds to comments submitted to our Petition by King & Spalding LLP, dated June 2, 2006. In its comments, King & Spalding supports the requests set forth in our Citizen Petition that the FDA withhold approval of any generic version of iron sucrose injection, USP unless the ANDA applicant meets all USP monograph requirements, conducts *in vivo* bioequivalence studies and provides an *in vitro* release test for demonstration of batch to batch bioequivalence.

However in regard to the Agency's acceptance of ANDA applications, King & Spalding opposes our requests that:

- That an ANDA applicant for iron sucrose injection demonstrate the identity of the manufacturing process of the active pharmaceutical ingredient (API) and the finished product to those of the RLD and its API; and
- That an ANDA applicant demonstrate its generic product and its API are identical in physicochemical properties and characteristics to our iron sucrose injection, USP, product Venofer® and its API.

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And, with regard to the Agency's acceptance of 505(b)(2) applications for Iron Sucrose Injection, USP, King & Spalding opposes our request:

- That the Agency not approve as a 505(b)(2) application any product referencing Venofer[®] as the referenced listed drug (RLD) unless the applicant conducts full scale preclinical and clinical safety and effectiveness studies.

Since the Agency's acceptance requirements for ANDA and 505(b)(2) applications differ, our response to King & Spalding's position on these issues is divided in two parts, Part I: ANDA Applications and Part II: 505(b)(2) Applications.

Part I: ANDA Applications:

In its opposition, King & Spalding argues that colloidal iron formulations by definition are heterogeneous and that imposing the requested restrictions to their production is incidental, irrelevant and technically impossible. King & Spalding reasons that iron sucrose, an iron colloid, cannot be defined as a single chemical entity¹ and that "minor manufacturing differences commonly occur during the production of marketed drugs without impacting quality or therapeutic characteristics."

Venofer[®] (Iron Sucrose Injection, USP) is simply its API in water for injection. Section 505(j) of the Federal Food, Drug and Cosmetic Act (the Act), provides the requirements for an ANDA. In the case of Venofer[®], an RLD with only one active ingredient, Section 505(j)(2)(A)(ii)(I) requires all ANDA applicants provide information to show that the active moiety of their new drug is the same as that of the RLD.

As noted Venofer[®] is an iron colloid; it is a macromolecule with a high molecular weight composed of an iron core complexed with the carbohydrate sucrose in water for injection. As explained in detail in our Citizen Petition, the final structure - and, hence, the physicochemical and

¹ King & Spalding's admission as to this fact support our arguments at page 2a of our Petition that with regard to complex non-traditional molecules guidelines should be established before approving generic equivalents of such products.

pharmacologic activity - of the macromolecule is highly dependent on the manufacturing practice. Given the complexity of the structure of the molecule, different manufacturing methods will produce different macromolecules. In this sense, these products are similar to products of a biological origin that are similarly complex macromolecules whose properties may be affected by change in the way they are made, resulting in similar, but not identical, substances. In this sense, generics of these products should be evaluated with the same principles applicable to such products.²

As with such products, therefore, major changes and even minor changes of its API or finished product must be evaluated to assure there are no significant differences from the processes of the drug product used in the injection's pivotal clinical trials.

In its request that the FDA should reject our manufacturing process "identity" argument, King & Spalding notes "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."

Luitpold objects to King & Spalding's statements that Luitpold provided misleading information in our Petition. To the contrary, we provided all information available to clearly describe and document the issues raised in our Petition.

The following three specific examples were provided by King & Spalding. Their first example is as follows:

"First, the 1968 Federal Register DESI notice statement (cited as exhibit 1: Federal Register 19686 on Luitpold 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 well established for all drugs. However, the Federal Register DESI statement is not in reference to generic products that are required to satisfy current USP criteria. Furthermore, since 1968, numerous technological advances

² See the Agency's decision on pharmaceutical alternatives of human powder hormone, Docket 2004P-0231/CP1, dated May 30, 2006 (also in Docket 2003P-0176/CP1, 2004P-0171/CP1 and 2004N-0355, in which, while approving the 505(b)(2) NDA for OMNITROPE, it did so based on the submission of safety and effectiveness data; consistent with that requested in our Petition.

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 formulation of iron sucrose, as stated in the Luitpold petition."

In response to this first example, Luitpold believes that it is important to note that acceptance of ANDA for generic drug is based on its pharmaceutical equivalence to the RLD. Pharmaceutical equivalence, under 21 C.F.R. § 320.1(c) means "drug products in identical dosage forms that contain identical amounts of **identical active drug ingredient...**" (emphasis added) Given the complexity of iron colloids, the pharmaceutical equivalence of one iron colloid to another is defined by both their physiochemical characteristics and manufacturing processes. If the manufacturing processes of the API and/or the drug product for a generic iron colloid differs significantly from that of its RLD it should not be accepted as an ANDA as while they may produce similar macromolecules, they will not be the same. While King & Spalding asserts that newer methods allow for an increased ability to evaluate iron colloids, they provide no proof or evidence that different manufacturing methods will produce an identical API and/or finished product. Absent such evidence, or evidence that the manufacturing process is identical, pharmaceutical equivalence cannot be demonstrated, bioequivalence cannot be assumed, and ANDA's are not an appropriate method for approval. This is consistent with regard to the Agency's evaluation of the OMNITROPE NDA, discussed in footnote 2 above.

King & Spalding's second example is as follows:

"Second, Luitpold's discussion of demonstrable structure/histotoxicity relationships as supported 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."

Geisser P, Baer M and Schaub E, "Structure/histotoxicity relationship of parenteral iron preparations." Arzneim.-Forsch./Drug Res.42(II), 12: 1439-1452, 1992 was referenced to support our statements that "[t]he 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.", "[f]or example, the stability of the complex is strongly dependent on the type of carbohydrate used.", and "[t]he release of iron from the complex is strongly dependent on the modification of the interior of the iron hydroxide core." See pages 10 and 11 of our petition.

King & Spalding's third example is as follows:

"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, 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."

In their third example, King & Spalding failed to fully comprehend the following paragraph from page 11 of our Petition:

"The manufacturing process is, therefore, critical to creation of these macromolecules and, hence, their stability and iron release rates. 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, merely meeting those specifications may not result in an API (or a finished product) whose safety and efficacy, as well as quality, is the same as the API used to make VENOFER®. To the contrary, because the manufacturing process 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 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 its manufacturing process is identical to that used to manufacture VENOFER® and its API, there can be no guarantee that the resulting macromolecule is the same and that the products are, therefore, of equivalent safety and efficacy."

The first sentence is not a direct reference to the *Geisser* article, but cumulative summation of the information provided up to this point of the Petition. With regard to King & Spalding's reference that the three batches of iron sucrose evaluated in the *Geisser* article showed minimal variability in degradation kinetics, it should be noted that, since this method was not specific enough for Venofer®, an improved method was developed and adopted. This was done in fulfillment of our NDA Phase IV commitment to establish an *in vitro* release test. This test method and examples are disclosed in US patent number 6,911,342; *Helenek, et al.* "Bioequivalence test for iron-containing formulations."

King & Spalding has requested that the FDA reject our physicochemical identity argument "because it's both unnecessary and technically impossible." They suggest that the Agency consider the FDA's draft Guidance for Industry, "ANDAs: Pharmaceutical Solid Polymorphs; Chemistry, Manufacturing, and Controls Information" as a means for accepting an ANDA where the API for the generic differs from that of the RLD, Venofer®.

We totally disagree. There is no basis for applying solid state polymorphism to an aqueous colloidal suspension. Polymorphism is a concept appropriate for **pharmaceutical solids**, not colloids of iron carbohydrates in liquid suspension as in iron sucrose injection. Not only does it relate to pharmaceutical solids, but it relates to minor variations in simple chemical crystalline substances with low molecular weight to which a water molecule or other solvent has been added to the crystal structure. There is simply no conceivable similarity between polymorphs and iron carbohydrate colloids in suspension.

As indicated above, Luitpold believes that their product should be evaluated in the same way as "generic" biologic

products. To this end, unless pharmaceutical equivalence can be shown, Luitpold requests that Agency follow the FDA's draft Guidance for Industry, "Applications Covered by Section 505(b) (2)." On page 8 of this draft Guidance for Industry, it states that a 505(b) (2) application may be accepted "for a change in active ingredient such as a different salt, ester, complex, chelate, clathrate, racemate, or enantiomer of an active ingredient in a listed drug containing the same active moiety." Such a request is consistent with the Agency's finding as to OMNITROPE referenced above.

King & Spalding's argues that Exhibit 8 of our Petition providing Vifor's analysis of six (6) generic iron sucrose API and products is misleading and irrelevant. Their reasoning is that the overall molecular weight of the six (6) products ranged from a molecular weight of 535 Daltons to 250,000 Daltons and that these samples are identified by an internal reference number.

King & Spalding fails to mention that four (4) of the six (6) samples analyzed by Vifor met Venofer®'s USP specifications for molecular weight and in the case where samples were identified in our April 3, 2006 addendum, King & Spalding still maintains the analysis of Feriv®, Hematin®, Fe-Back®, and Fe-Lib® is "irrelevant to a discussion of data requirements for a generic formulation of VENOFER® a drug product which fully complies with USP monograph specifications."

This testing of Feriv®, Hematin®, Fe-Back®, and Fe-Lib® included Venofer®'s *in vitro* release test for trivalent iron which is reported by LAZ as "kinetics of degradation (T₇₅)."
Their test results found significant differences between these four "generic" iron sucrose product and Venofer®.

As stated in our April 3, 2006 amendment to our Petition, "[t]hough these drug products are not purported to be related to any specific submission, this data is being provided to aid the Agency in its review of any pending or future ANDA and/or 505(b) (2) submissions for any generic version or other pharmaceutical alternative of VENOFER® (iron sucrose injection, USP)."

The fact that Feriv® meets Venofer®'s USP specifications for molecular weight but differs significantly in its polarography and kinetics of degradation (T₇₅) responses to that of

Venofer®, is not irrelevant because it demonstrates that molecular weight alone is not an indicator of pharmaceutical equivalence of two iron sucrose products.

Thus, Luitpold believes that unless an ANDA applicant for an iron sucrose injection product can demonstrate pharmaceutical equivalence by mere conformance to their USP monograph, by demonstration of identical manufacturing methods and/or physicochemical properties and characteristics, such applicants should be required to obtain approval of such product as 505(b)(2) applications.

Part II: 505(b)(2) Applications;

King & Spalding opposes our request that the Agency should not approve as a 505(b)(2) application any product referencing Venofer® as the RLD unless the applicant conducts full scale preclinical and clinical safety and effectiveness studies.

The FDA's draft Guidance for Industry, "Applications Covered by Section 505(b)(2)," describes a 505(b)(2) application as an application that contains full reports of investigations of safety and effectiveness but where at least some of the information required for approval comes from studies not conducted by or for the applicant and for which the applicant has not obtained a right of reference.

It is our opinion that clinical safety and effectiveness studies should be conducted for each proposed indication and or patient population. In addition, as the filing of a 505(b)(2) application referencing Venofer® as the RLD indicates a lack of pharmaceutical equivalence and hence bioequivalence and safety and effectiveness, a 505(b)(2) applicant should not have the right of reference Venofer®'s 1,000 patient Phase IV safety study.

King & Spalding's argues that the approval of Dexferrum's 505 (b)(2) application is a precedent in direct opposition to the specific requests listed in our petition as requirements for a 505(b)(2) petition. Luitpold disagrees. Iron dextran injection, USP, is a pre-1962 drug. Its approval was based on safety. There were no efficacy studies performed or required for its approval. It was DESI Reviewed and "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."

The approval of Dexferrum's 505(b)(2) application on its pharmacokinetics and iron utilization studies was appropriate and in compliance with the 1968 DESI notice "Drug Efficacy Study Implementation Regarding Certain Iron Preparations for Parenteral Use." Dexferrum's labeling bears the Agency's required black box warning for iron carbohydrates.

In the case of Venofer® we conducted extensive clinical safety and efficacy studies in support of our Venofer® NDA. Based on its proven safety, its labeling bears no black box warning.

Please note that the original labeling for Venofer® had a bolded warning on hypersensitivity and anaphylactoid reactions that was only changed after submission of a Phase IV safety study.

Any pharmaceutical alternative product approved through 505(b)(2) process should not be permitted to obtain labeling as to the degree of safety, and in particular, hypersensitivity and anaphylactoid reactions, unless it has conducted similar safety studies.

Furthermore, efficacy studies should be required. Luitpold disagrees that efficacy studies were not required for Dexferrum. Two clinical studies were submitted demonstrating its effectiveness and, as noted in the Agency's discuss on the Citizen Petition on human growth hormone, full scale efficacy studies are necessary to approve a 505(b)(2) application. Our requested relief is based on and supported by the Agency's decision with regard to those types of products.

* * * * *

As requested in our Petition, the Agency should establish guidelines for approval of parenteral iron colloids referencing VENOFER® as the RLD and other parenteral iron colloids, such as 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 process of the API and the finished product to those of 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 for each proposed indication;
- (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
- (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 appropriate to the amount and type of safety information about the product.

For other reasons discussed herein, and in our prior submission, we believe that until the Agency establishes such guidelines for parenteral iron colloid products, it should not approve any generic or pharmaceutical alternative of such product.

Sincerely,

Luitpold Pharmaceuticals, Inc.



Richard P. Lawrence
Director, Research and Development

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