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September 23, 2008

FEDERAL EXPRESS

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

Re: **CITIZEN PETITION - Labeling for Ferumoxytol Should Be the Same as Other Iron Dextran IV Products and Approval of any NDA for Ferumoxytol for Iron Deficiency Anemia in Patients with Non-Dialysis Dependent Chronic Kidney Disease and Patients Undergoing Dialysis Should be Based on the Types of Studies Required for Approval of Other IV Iron Products for Similar Indications**

Dear Sir/Madam:

On behalf of Luitpold Pharmaceuticals, Inc., ("Luitpold"), One Luitpold Drive, P.O. Box 9001, Shirley, NY 11967, the undersigned submits this Petition pursuant to 21 C.F.R. § 10.30. The Petition requests that the Commissioner of Food and Drugs ("the Commissioner") require that approval of any NDA for ferumoxytol for use in treating iron deficiency anemia be conditioned upon the same safety and effectiveness requirements as all other intravenous (IV) iron replacement products and that the labeling for ferumoxytol conform to the labeling of other iron dextran IV products. These conditions are necessary to (1) ensure there are adequate safety and effectiveness data to support product approval; (2) minimize the risk of serious and life-threatening adverse events that, although rare, have been associated with products containing or derived from iron dextran; and (3) ensure that FDA complies with its legal mandate to treat similarly situated parties in a similar manner.

FDA 2008.P.0524

A. ACTION REQUESTED

Luitpold requests that the Commissioner take the following specific actions:

- The Commissioner require, as a condition of approval, that an NDA for ferumoxytol contain the same rigorous clinical trial data in support of safety and effectiveness that have been required for all other IV iron replacement products.
- The Commissioner require, as a condition of approval, that the ferumoxytol labeling be required to bear the same information as that of all other IV iron dextran products, including, without limitation (a) the black box warning relating to the risk of anaphylactic-type reactions associated with these products; (b) a requirement to administer a test dose prior to administration; and (c) a limitation as second line therapy to oral iron.

B. STATEMENT OF GROUNDS

BACKGROUND

1. Ferumoxytol NDA

As a result of a review of publicly available information, Luitpold has become aware that AMAG Pharmaceuticals, Inc. ("AMAG") (formerly Advanced Magnetics, Inc.) submitted to the U.S. Food and Drug Administration (FDA) an NDA for the use of ferumoxytol as an intravenous (IV) iron replacement therapeutic in chronic kidney disease (CKD) patients in December 2007. AMAG has reported that the user fee date for FDA's review of the NDA is late October 2008. See www.amagpharma.com.

AMAG, which describes itself as a "developer of superparamagnetic iron oxide nanoparticles used in pharmaceutical products," touts ferumoxytol as one of its key product candidates. AMAG is reportedly developing ferumoxytol for use as an IV iron replacement therapeutic for the treatment of iron deficiency anemia in CKD patients". See AMAG's Transition Report on Form 10-Q, filed June 14, 2007; see also AMAG's website at www.amagpharma.com. AMAG further touts its "proprietary nanoparticle technology" as providing the platform for its development and commercialization of therapeutic iron compounds to treat anemia, as well as "novel imaging agents" to aid in the diagnosis of cancer and cardiovascular disease.¹

¹ See AMAG's Form 10-Q Quarterly Report, filed on Nov. 7, 2007 (for quarterly period ended Sept. 30, 2007), at www.sec.gov (SEC Edgar Filing Information).

AMAG reports that it has completed all four of its planned pivotal Phase III clinical studies for ferumoxytol as an IV iron replacement therapeutic in CKD patients. According to AMAG, two of the studies were identical efficacy and safety studies, each of which enrolled 304 non-dialysis dependent CKD patients comparing two doses of 510 mg ferumoxytol to daily oral iron. The third completed study was a safety study in 750 non-dialysis dependent CKD and dialysis-dependent CKD patients comparing a single dose of 510 mg ferumoxytol to placebo. The final Phase III study was a 230 patient multi-center efficacy and safety study in hemodialysis-dependent CKD patients comparing two doses of 510 mg ferumoxytol to daily oral iron.² One of these studies was just published in the *Journal of the American Society of Nephrology*.³

2. Ferumoxytol

Ferumoxytol is a parenteral iron colloid that holds the parenteral iron nanoparticles suspended in aqueous solution. These nanoparticles 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.⁴ The core itself is polynuclear (i.e., containing multiple nuclei of iron, OH, and O₂ groups in lattice form), and the carbohydrate coating is similarly polymeric. The mean volume diameter (MVD) of its colloidal particle is approximately 21 nm.⁵

Ferumoxytol is a polyglucose, as indicated by its chemical name: polyglucose sorbitol carboxymethyl ether-coated non-stoichiometric magnetite. The non-stoichiometric magnetite of ferumoxytol is an ultrasmall superparamagnetic iron oxide (USPIO) that, for stability, must be coated with a semi-synthetic carbohydrate. Notably, and as discussed in further detail below, this coating is a hydrogenated and carboxymethylated dextran.⁶

3. Parenteral Iron Colloids

Currently, three parenteral products consisting of iron colloids are approved by FDA and listed in FDA's *Approved Drug Products with Therapeutic Equivalence Evaluations* (the

² Ibid.

³ Spinowitz BS, et al. (2008): Ferumoxytol for treating iron deficiency anemia in CKD. *J Am Soc Nephrol* 19(8): 1599-605. See Exhibit 1.

⁴ Danielson BG. (2004): Structure, chemistry and pharmacokinetics of intravenous iron agents. *J Am Soc Nephrol* 15:S93-98. See Exhibit 2.

⁵ U.S. Patent No. 6,599,498 B1, Groman et. al. (7/29/03) column 25, example 31. Heat stable colloidal iron oxides coated with reduced carbohydrates and carbohydrate derivatives.

⁶ The coating is a mixture of synthetic glucose polymers that deliver a core of iron molecules in the ferric state to the reticuloendothelial system for subsequent use in erythropoiesis and other metabolic processes.

“Orange Book”). These preparations are iron dextran injection, USP; sodium ferric gluconate complex in sucrose injection; and iron sucrose injection, USP. These complex formulations were developed to improve the utility of non-heme iron for treatment of iron deficiency anemia, which if uncomplexed with carbohydrate, would hydrolyze and polymerize.⁷ Each of these preparations contains ferric iron as the active ingredient. The iron colloid in each of these products is composed of ferric chloride, and, thus, unlike the composition of ferumoxytol, is homogenous. In contrast, the iron colloid of ferumoxytol is composed of a mixture of both ferric chloride and ferrous chloride.⁸

Because parenteral iron replacement products are not true solutions but instead colloidal suspensions, they pose special safety considerations and concerns. The safety and efficacy of these complexes are critically dependent on the nature of the iron hydroxide core, the nature of the carbohydrate shell, and the way the two are complexed.⁹ Differences in core size and carbohydrate chemistry can also determine pharmacological and biological differences, including clearance rate after injection, iron release rate *in vitro*, early evidence of iron bioactivity *in vivo*, and maximum tolerated dose and rate of infusion.

Because the products are polymeric, there can be significant variation in the sizes of the iron core and the complete saccharide-bound complexes. Consequently, there are variations in clearance after injection, variations in iron release *in vitro* and release/utilization *in vivo*, and variations in maximal tolerated dose. Also, the release of iron from the complex depends on the

⁷ Funk F, Long GJ, 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. See Exhibit 3.

⁸ Thus, the composition of ferumoxytol is readily distinguishable from all of the IV iron replacement products that have been approved by FDA and that have a longstanding history of clinical use in the U.S. and elsewhere in the world. All FDA-approved IV iron replacement products are homogenous, consisting of an iron core composed of ferric chloride. The iron core of ferumoxytol, however, is heterogenous, consisting of a mixture of both ferric and ferrous chloride. Since an iron replacement product with this heterogenous composition has never been approved by FDA, the long-term clinical effects of this product are uncertain. Such uncertainty is further increased by the use of AMAG's “proprietary nanotechnology” to produce its ferumoxytol product. As FDA's Nanotechnology Task Force has reported recently, particular attention must be paid to “the composition and surface characteristics of nanoscale materials that may come in context with biological systems.” *Nanotechnology, A Report of the U.S. Food and Drug Administration Nanotechnology Task Force*, July 25, 2007, p. 9. Indeed, as also noted by FDA's Nanotechnology Task Force, “[s]everal recent scientific reviews conclude that the state of knowledge for biological interactions of nanoscale materials is generally in need of improvement to enhance risk assessments and better support risk management decisions.” *Id.* at 13.

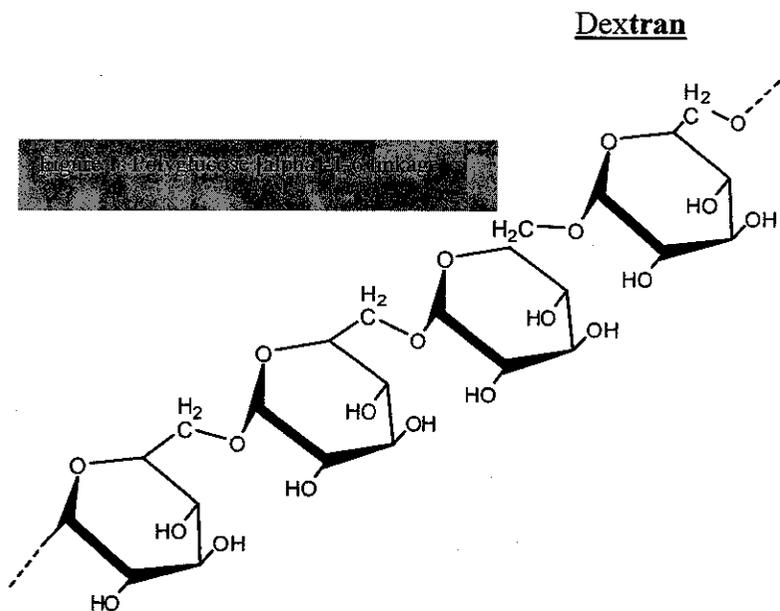
⁹ Geisser P, Baer M and Schaub E (1992): Structure/histotoxicity relationship of parenteral iron preparations *Arzneim-Forsch Drug Res* 42 (II), 12: 1439-1452. See Exhibit 4.

modification of the interior of the iron hydroxide core. And, finally, the type of carbohydrate used affects the stability and toxicity of the product.¹⁰

ARGUMENT

1. Ferumoxytol is a dextran derivative.

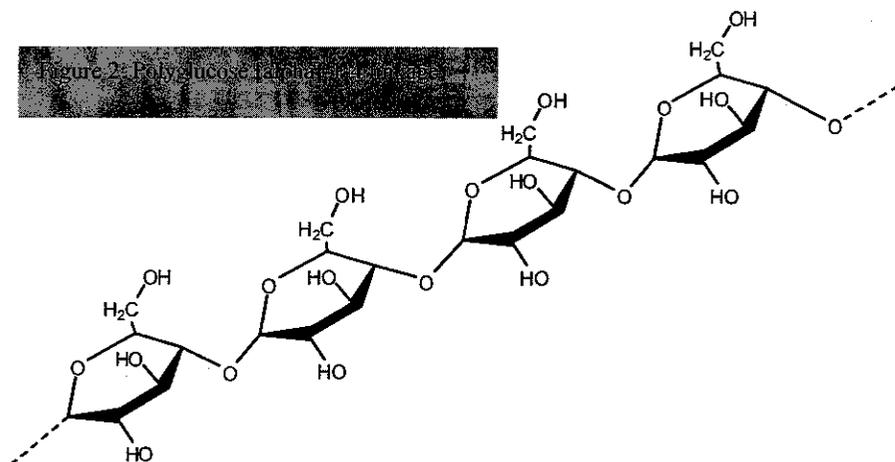
Ferumoxytol, which contains carboxy dextran, is a dextran derivative. Specifically, it is an ultrasmall superparamagnetic iron oxide (USPIO) mixed-valence compound stabilized with a hydrogenated and carboxymethylated dextran. What distinguishes it from dextrin and other polyglucoses is that the oxygen in dextran derivatives is bonded to the sixth carbon on glucose (i.e., a [alpha]-1-6 linkage) rather than the fourth carbon (i.e., a [alpha]-1-4 linkage) as illustrated below in figures 1 and 2 (rotated 180° to highlight the structural differences).¹¹



¹⁰ Ibid.

¹¹ Merck Index, Thirteenth Edition, pp. 519, 520 and 1567

Dextrin



Dextrin is primarily composed of polyglucose with a [alpha]-1-4 linkage. However, it is derived from starch, a mixture of amylose and amylopectin that may contain approximately 4% polyglucose [alpha]-1-6 linkages.

The patents licensed by AMAG clearly indicate that that the manufacturing process for ferumoxytol begins with iron dextran and ends with a dextran, albeit what is described as a "reduced dextran". See, U.S. Patent No. 6,599,498 ("Heat stable colloidal iron oxides coated with reduced carbohydrates and carbohydrate derivatives"). This patent is replete with references to "reduced dextran." See, e.g., Claim No. 3 (a reduced dextran as the reduced polymer of glucose which is used in the iron complex); Claim No. 6 (a method of carboxyalkylating a reduced polysaccharide by carboxymethylation, wherein the reduced polysaccharide is a reduced dextran); Claim No. 16 (a reduced polysaccharide iron oxide complex, wherein reduced polysaccharide is a reduced dextran); Claim No. 17 (a carboxymethyl reduced dextran as the carboxyalkylated reduced dextran); Claim No. 18 (citing a carboxyalkylated reduced dextran that comprises at least app. 750 micromole of carboxyl groups per gram of polysaccharide); Claim No. 19 (a carboxyalkylated reduced dextran comprising at least approximately 900 micromole of carboxyl groups per gram of polysaccharide); Claim No. 20 (a carboxyalkylated reduced dextran comprising at least approximately 1,100 micromole of carboxyl groups per gram of polysaccharide).

It is well-established that a dextran can elicit an anaphylactic response – sometimes fatal – when administered intravenously.¹² Notably, there are no claims in the patent, nor any other information, that provides any assurance whatsoever that the finished “reduced dextran” product contains no unmodified/free dextran.¹³ Yet, it is the total absence of any unmodified/free dextran that is required to adequately protect patients administered ferumoxytol from the risk of anaphylactic shock associated with dextran. It is this same unequivocal demonstration of the complete absence of any unmodified/free dextran that is required for ferumoxytol to be properly excluded from FDA’s labeling requirements for IV iron dextran-containing products.

Regardless of whether the dextran molecule is further manipulated to produce the final compound (ferumoxytol), the manipulated molecule still appears to contain the epitope (or points/conformational region) recognized by the dextran antibody. Consequently, it is entirely possible that the same mechanism in humans that triggers recognition of dextran prior to manipulation will operate to similarly recognize the dextran in ferumoxytol in its “reduced” form.

At least one study in the publicly available scientific literature finds that ferumoxytol does contain residual carboxydextran and does react with dextran antibodies. According to Simon, Vopelius-Feld, et al.,¹⁴ a monoclonal body (“MAB”) against dextran effectively localizes ferumoxytol in histologic sections of synovium in rats with experimental immune complex arthritis. The antigen that the MAB localizes would appear to be the dextran in the ferumoxytol complex. These findings indicate that AMAG cannot possibly show that there is no cross-reactivity between their complex and dextran: clearly, there are shaped epitopes which the MAB recognizes. Whether the finding is clinically significant is impossible to determine based on the limited clinical data available to date, and, thus, the marketing of this product would pose an unacceptable risk to patients, unless the product contains labeling to warn of the risk.¹⁵

¹² Briseid G and Briseid K, et al. (1980): Dextran-induced anaphylactoid reaction in mN: altered reactivity of high molecular weight and kininogen. *Acta Pharmacol Et Toxicol* 47:119-126. See also, Ljungström KG, et al. (1983): Adverse reactions to dextran in Sweden 1970-1979. *Acta Chir Scand* 149:253-262. See Exhibits 5 and 6.

¹³ Instead, the patent only claims that the reduced dextran is “less immuno-responsive” than iron dextrans produced by methods other than those purportedly used by AMAG. Given the severity of consequences of anaphylaxis that may be triggered by the intravenous administration of dextran, the mere claim of “less immunoresponsive” is simply not adequate. The quantity of dextran remaining in the final product cannot be definitively determined because all analytical methodologies are limited to their lower limit of detection. Therefore, the total absence of dextran cannot be assured in a product derived from dextran.

¹⁴ Simon S, Vopelius-Feld J, et al. (2006): Ultrasmall supraparamagnetic iron oxide enhanced magnetic resonance imaging of antigen-induced arthritis.” *Investigative Radiology* 41:45-51. See Exhibit 7.

¹⁵ For similar reasons, the approval of any NDA for ferumoxytol should, **at an absolute minimum**, contain appropriate REMS requirements, including Medication Guides, Physician Certification and Patient Registries.

It is also important to note that according to information publicly available, AMAG appears to rely, in large part, on data from a rat paw edema study as support for its claim that ferumoxytol – as a “reduced dextran” – does not pose the risk of an anaphylactic-type reaction as can be triggered by other iron dextrans. Specifically, AMAG contends that ferumoxytol has low immunoreactivity based on results of anaphylaxis studies and low cross-reactivity to anti-dextran antibodies.

Notably, however, the results of animal models are a poor predictor of the potential for anaphylactic-type reactions in humans. Several animal models have been employed for many years to test for hypersensitivity drug allergies mediated by IgE in humans. None of the methods described are considered reliable nor are they recommended. Modifications of these methods are included to measure rat paw edema as an indicator of systemic anaphylactic response to dextrans and other substances. Such assays include the passive cutaneous anaphylaxis assay, the active cutaneous anaphylaxis assay and the active systemic anaphylaxis assay.¹⁶ An additional rat paw edema assay described by Squire, et al in 1955 has been used to screen for analgesic properties of new drugs, not for anaphylaxis.

FDA has cautioned that when conducting these studies, negative findings should not be interpreted to indicate an experimental drug cannot produce anaphylactic reactions in humans.¹⁷ Indeed, in this Guidance, FDA explicitly states that the PCA, ACA, and ASA assays are not recommended for the routine safety evaluation of INDs.

In summary, because ferumoxytol retains the dextran epitopes that are antigenic and may contain unmodified/free dextran, the product must be classified as an iron dextran and should contain the same labeling warning as to anaphylactic reactions and the requirement for a test dose. Even its own patents declare that it does contain dextran. Thus, AMAG's NDA for ferumoxytol should be subjected to all of FDA's labeling and all other approval requirements applicable to iron dextran IV products.

¹⁶ Squire JR, et al. (1955): Dextran: Its Properties and Use in Medicine; Voorhees AB, et al. (1951): Reactions of albino rats to injections of dextran. *Proceedings of the Society for Experimental Biology and Medicine*. 76(2):254-56; and Hanna CH, et al. (1957): Effect of ether and barbiturate anesthesia on the reaction of rats to dextran and of dogs to polyvinylpyrrolidone. *Am J Physiol* 191:615-20.

¹⁷ FDA Guidance for Industry, “Immunotoxicity Evaluation of Investigational New Drugs” (citing Choquet-Kastylevsky G and Descotes J (1988): Value of Animal Models for Predicting Hypersensitivity Reactions to Medicinal Products. *Toxicology* 129, 27-35).

2. Since ferumoxytol is an injectable iron product, NDA approval should be conditioned upon satisfying the same safety and efficacy requirements as have been applied to all other injectable iron products.
 - a. The NDA should be subjected to the same rigorous clinical trial data requirements as other NDAs for this same class of products.
 - (1) Ferumoxytol study and designs did not allow a fair comparison to oral iron.

The ferumoxytol, Venofer® and Injectafer® NDD-CKD trials all utilized comparable amounts of administered IV iron (approximately 1,000 mg). However, the total amount of oral iron administered to control patients was dramatically different between the programs. The ferumoxytol clinical development program is reported to have utilized only a 21 day course of oral iron administering Ferro-Sequels® (iron as ferrous fumarate), 2 tablets twice daily for 21 days for a total of 200 mg of elemental iron daily. This results in a total oral iron dose of 4,200 mg. Spinowitz Ibid., at. In contrast, the oral iron regimen:

- in the Injectafer® (ferric carboxymaltose)¹⁸ and Venofer® (iron sucrose) non-dialysis dependent chronic kidney disease (NDD-CKD) clinical trials¹⁹ required 8 weeks of 195 mg of elemental iron daily as ferrous sulfate for a total oral iron dose of 10,920 mg; and
- in the Injectafer iron non-CKD clinical development program required 6 to 12 weeks of 195 mg of elemental iron daily as ferrous sulfate for a total oral iron dose of 8,190 to 16,380 mg²⁰

Bioavailability data on the various oral iron compounds are limited; however an isotope study by Jacobs et. al. 1984²¹ suggested that oral bioavailability of ferrous sulfate may be up to four times greater than ferrous fumarate. The mean absorption rate of 50 mg of elemental ferrous sulfate was 39.92% (SD 13.42) vs. 10.25% (6.89) following 100 mg of ferrous fumarate. These doses parallel the individual oral iron doses administered in the clinical trials; ferrous sulfate 65 mg tid and ferrous fumarate 100 mg bid. Assuming either a conservative 10%

¹⁸ See Briefing Package at www.fda.gov/ohrms/dockets/ac/cder08.html#drugsafetyriskmgmt and Summary Basis of Approval, S-008, NDA-21-135 available on www.fda.gov.

¹⁹ Van Wyck DB, et al. (2006). A randomized, controlled trial comparing IV iron sucrose to oral iron in anemic patients with non-dialysis dependent CKD. *Kidney Int.* 2005 Dec; 68(6):2846-56. See Exhibit 8.

²⁰ See Briefing Package, footnote 18.

²¹ Jacobs P, et al. Oral iron therapy in human subjects, comparative absorption between ferrous salts and iron polymaltose. *J Med* 1984;15(5-6):367-77. See Exhibit 9.

absorption rate or the rates from the Jacobs study for both the fumarate and sulfate oral iron products predicts an unfair comparison of oral to IV iron in the ferumoxytol trials (see Table I) as the ratio of the oral to IV iron dose was substantially lower in the ferumoxytol trials.

Table 1

	TOTAL DOSE IV IRON	TOTAL ELEMENTAL DOSE ORAL IRON	PREDICTED ORAL IRON ABSORBED DOSE (10% absorption rate)	Oral to IV iron ratio	PREDICTED ORAL IRON ABSORBED DOSE (absorption rate per Jacobs study)	Oral to IV iron ratio
Ferumoxytol*	1,020 mg	4,200 mg (fumarate)	420 mg	42%	430 mg	41%
Venofer®	1,000 mg	10,920 mg (sulfate)	1,092 mg	109%	4,359 mg	436%
Injectafer®	1,200 mg**	10,920 mg (sulfate)	1,092 mg	91%	4,359 mg	363%

* per protocol: ** mean calculated dose from NDD-CKD clinical trial

On multiple occasions during the conduct of the Venofer® and Injectafer® development programs, FDA has stated to Luitpold that superiority in efficacy would not be demonstrated based on changes in hemoglobin stemming from lower administered oral iron doses due to patient non-compliance. In fact Luitpold was consistently reminded that oral iron “must be given every opportunity to work” supporting the fact that the total dose of administered oral iron is critical to FDA’s efficacy evaluation.

As an example, the Agency initially refused to approve Luitpold’s Venofer® product for treatment of iron deficiency in pre-dialysis CKD patients, because it did not believe the Company had sufficiently demonstrated efficacy. Luitpold was required to do another efficacy study to demonstrate the effectiveness of the product using a robust control. See Medical Officer’s Reviews of S-008, NDA 21-135, available on FDA’s website. And this was for a product that had already been approved (for treatment of iron deficiency in hemodialysis patients) and which had been marketed worldwide for over 50 years by that time and was the subject of extensive published literature. Here, AMAG has apparently requested approval based on efficacy studies using, in essence, a placebo rather than an active control – as had been required of other IV iron products.

Based on these facts, the ferumoxytol NDD-CKD study design did not allow a fair comparison to oral iron. In his review of the Spinowitz et. al. article just published, Hürl pointed

out this discrepancy, stating it was not surprising that **high dose IV** iron was found superior to low dose oral iron, and the discrepancies with data comparing other IV products to oral iron.²²

The published clinical trials for ferumoxytol indicate that FDA did not require AMAG as sponsor to apply as rigorous an active control in the study design, and given the poor bioavailability of the control, there is no assurance that ferumoxytol is effective at all given the inadequate comparator utilized. Furthermore, the Agency did not require AMAG to use the same type of strict standard as a comparison as it did for Venofer®, Injectafer® and Ferrlecit®. FDA should require ferumoxytol to be studied against an adequate dose of a more bio-available oral iron for a longer period of time.

- (2) Ferumoxytol study designs did not allow for a fair safety comparison to Venofer® and Injectafer®.

The ferumoxytol NDD-CKD clinical trials utilized a **30 day** or shorter period for monitoring of treatment emergent adverse events following the last dose of study drug.²³ In contrast the Injectafer® and Venofer® NDD-CKD clinical trials required a 56 day safety monitoring period. The trial for Ferrlecit® (sodium ferric gluconate complex in sucrose injection) involved 40 or 50 days. See approved package insert.

During the development of Injectafer®, FDA repeatedly suggested the need for **long-term** and **multiple dose** safety studies. As a result, Luitpold conducted a safety and efficacy study in NDD-CKD patients and a second study, in this same population, consisting of a 44 week long safety extension study to support the approval of Injectafer®. Three deaths, one at day 35, one at day 46 and one at day 98 occurred in these studies of this multi-morbid population. Despite the extended time period between dosing and the occurrence of the events, FDA maintained that these deaths were pertinent to the overall numerical imbalance in deaths and contributed to FDA's safety concerns regarding the product.²⁴ It goes without saying that there will likely be more deaths in any study of multi-morbid populations as the study is conducted for a longer periods of time. Not requiring the ferumoxytol development program to investigate the long term and repeat dose safety of this product limits the data available for the Agency to consider and potentially places patients at risk for adverse events and death.

²² Hörl WH (2008): Comparing the efficacy of intravenous iron and oral iron in non-dialysis patient with chronic kidney disease. Published online on August 18, 2008 at www.nature.com/clinicalpractice/doi.10.1038/ncpheph0913. See Exhibit 10.

²³ Spinowitz at 604. See *infra*, at n. 3.

²⁴ It should also be noted that there were 31 deaths in the ferumoxytol trial – 16 with the product and 15 without. While there was not a death imbalance, the absolute number of deaths in the ferumoxytol studies is significantly greater than the number in Ferrlecit® and Venofer® trials. Such a safety signal cannot be ignored.

FDA should require AMAG to conduct, prior to approval, long term safety studies – of the type and length required of Luitpold for Injectafer® and other IV iron products.

- b. Since ferumoxytol is a dextran derivative, a black box warning concerning the risk of life-threatening anaphylactic shock is required.
 - (1) FDA requires a black box warning for iron dextran injection products.

As noted previously, three types of intravenous iron preparations are currently approved for use in the U.S.: iron dextran (InFeD, Watson Pharma, Inc.; Dexferrum, American Regent, Inc.), sodium ferric gluconate complex in sucrose (Ferrlecit; Watson Pharma, Inc.) and iron sucrose (Venofer, American Regent). Of the three parenteral iron preparations currently listed in FDA's Orange Book, only iron dextran injection USP is a drug marketed in the U.S. prior to 1962. As a pre-1962 drug, iron dextran injection was reviewed in the Drug Efficacy Study Implementation or DESI Review. (See 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 its DESI notice, FDA concurred with the findings of the National Academy of Sciences – National Research Council, Drug Efficacy Study Group, that the pre-1962 iron dextran parenteral drugs 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.

Notably, however, the DESI review also concluded that: "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)).

To this day, the serious concern with toxicities associated with these compounds – including anaphylaxis and death – has led FDA to require the package insert labeling for all iron dextran IV products sold in the U.S. to contain a black box warning of the potential of fatal anaphylactic type reactions. The same caution must be extended to ferumoxytol.

That warning currently²⁵ reads as follows:

WARNING

THE PARENTERAL USE OF COMPLEXES OF IRON AND CARBOHYDRATES HAS RESULTED IN ANAPHYLACTIC-TYPE REACTIONS. DEATHS ASSOCIATED WITH SUCH ADMINISTRATION HAVE BEEN REPORTED. THEREFORE, [TRADE NAME OF PRODUCT] SHOULD BE USED ONLY IN THOSE PATIENTS IN WHOM THE INDICATIONS HAVE BEEN CLEARLY ESTABLISHED AND LABORATORY INVESTIGATIONS CONFIRM AN IRON DEFICIENT STATE NOT AMENABLE TO ORAL IRON THERAPY. BECAUSE FATAL ANAPHYLACTIC REACTIONS HAVE BEEN REPORTED AFTER ADMINISTRATION OF IRON DEXTRAN INJECTION, THE DRUG SHOULD BE GIVEN ONLY WHEN RESUSCITATION TECHNIQUES AND TREATMENT OF ANAPHYLACTIC AND ANAPHYLACTOID SHOCK ARE READILY AVAILABLE.

The black box warning should appear in the labeling until such time, if any, that (1) sufficient data exist to demonstrate that ferumoxytol contains no dextran or dextran derivatives; or (2) sufficient post-marketing data exist to demonstrate that ferumoxytol can be distinguished from all other dextran products in a clinically meaningful way that obviates the need for a black box warning. As discussed below, AMAG has already reported a serious anaphylactic reaction and severe hypotension resulting in hospitalization of a NDD-CKD subject participating in one of the ferumoxytol clinical trials.

- (2) Anaphylaxis reactions to dextran antibodies are rare so data from ferumoxytol clinical trials are insufficient to assess incidence rate.

The limitations in the pre-market clinical trial data make it impossible to assess the safety profile of ferumoxytol with regard to the risk of anaphylactic shock. The small number of human exposures in the clinical trials is manifestly inadequate for the task.

There are several reasons for this fact: (a) the clinical trials are small, and the rate of the reaction even smaller; (b) the clinical trials present only limited exposure as compared with

²⁵ FDA has informally proposed that the warnings and directions for use – to require a test dose, for example, before each dose – be changed for IV iron dextran products. Any such changes should apply to ferumoxytol as well.

repeated dose studies and post-market use; and (c) clinical trials *may* have excluded reactive patients, the very subpopulation most susceptible to anaphylactic shock due to a dextran derivative such as ferumoxytol.

According to publicly available information, the pre-market safety profile for ferumoxytol will consist only of a Phase III clinical trial database of approximately 1,600 CKD patients, which AMAG reportedly submitted in support of its NDA.²⁶ Given the rate of occurrence for dextran-induced anaphylaxis, these 1,600 non-excluded patients provide an inadequate basis for assessing, with the requisite certainty for a potentially fatal reaction: the actual risk that ferumoxytol will trigger an anaphylactic event. Since the rate of anaphylactic reaction to dextran antibodies is relatively rare, it is simply not possible to reach conclusions about risk from a sample size of 1,600 patients. The limitations in the premarket clinical trial data are made all the more apparent when this small pre-market safety profile is compared against the millions of patients who have been treated with approved IV and oral therapies in the U.S. for years.

Moreover, FDA permitted AMAG to exclude from the Phase III clinical trial those patients with "known allergies to iron products or to 2 or more classes of drugs."²⁷ This is in stark contrast to the Venofer® and Injectafer® development program where protocols allowed such patients participation in the trials. Excluding patients that have had previous allergic reactions to intravenous iron compounds severely biases the safety results and lessens the overall probability that a severe allergic reaction will be detected in the trial. If the severe allergic reactions (anaphylaxis, severe hypersensitivity reaction, etc. – those reactions of most concern when administering intravenous irons) is indeed caused by the formation of an antibody to the iron products, then enrolling only patients that are either naïve to IV iron products or do not experience allergic reactions will limit the detection of such events. The result will be a reported, and presumably labeled, safety profile that is not representative of the product, placing patients at risk, once the product is commercially marketed.

As noted previously, when looking for a relatively low incidence problem such as the case with anaphylactoid shock related to IV iron dextran products, studying 1,500 or 1,600 patients over the short duration of a clinical trial is simply inadequate to assess the safety risk. Yet, notwithstanding this limitation, AMAG's report of its own safety study of ferumoxytol demonstrates that ferumoxytol, too, carries the risk of anaphylactoid shock, similar to other IV iron dextran-containing products. See supra, at 15-16.

²⁶ See www.amagpharma.com.

²⁷ Bolton WK et al., Ferumoxytol as an intravenous iron replacement therapy: efficacy results from two phase iii studies in subjects with chronic kidney disease (CKD) not on dialysis. Poster, American Society of Nephrology Meeting (Nov. 2007); Besarab A, et al. Ferumoxytol as an intravenous iron replacement therapy: safety results from two phase III studies in subjects with chronic kidney disease (CKD) not on dialysis. Poster, American Society of Nephrology Meeting (Nov. 2007). See www.amagpharma.com.

(3) Patient safety requires a “black box” warning for ferumoxytol.

Although AMAG claims that ferumoxytol has been developed to minimize potential immunogenic reactions such as those that have been observed with currently marketed iron dextran products, patient safety requires this product to bear a black box warning. The warning should remain until if and when there has been sufficient patient exposure and safety data collected to either (1) establish that ferumoxytol contains no dextran polysaccharides; or (2) to establish that there is some other clinically meaningful demonstration that ferumoxytol can be readily distinguished from all other dextran-containing parenteral iron supplements so as to obviate the need for a black box warning to alert physicians and patients to the risk of serious and life-threatening anaphylactoid reactions.

A black box warning is a labeling statement concerning unique risks associated with use of a drug, particularly those events that may lead to serious injury or death. 21 C.F.R. § 201.57(e). This type of warning is designed to highlight special or serious problems so as to ensure the continued safe use of the product. FDA reserves black box warnings for serious and life-threatening risks that can best be minimized by conveying critical information to the prescribing physician in a highlighted manner. It is designed to help a physician prescribe a drug that may be associated with serious side effects in a way that maximizes its benefits and minimizes its risks.²⁸

Given that the anaphylactic-type reactions that may result from iron dextran or dextran derivatives can sometimes – albeit rarely – be fatal, a black box warning should be required for ferumoxytol until sufficient post-marketing data has been collected to demonstrate with the requisite degree of certainty that such risk does not exist. It is well-established that iron agents sometimes cause anaphylaxis and this occurs at different rates between different carbohydrates. The allergic reactions can include dyspnea, wheezing, chest pain, hypotension, urticaria, and/or angioedema, and they can be both serious and life-threatening.

What is not yet specifically known is how and why these allergic reactions occur. Although the mechanism of allergic anaphylactic reactions is still poorly understood, the reaction is thought to be attributable to the dextran portion of the molecule, since that is *known* to be antigenic.²⁹ Thus, it is not possible to rule out the risk that use of ferumoxytol – a dextran derivative – will trigger a life-threatening anaphylactic shock reaction in some patients.

Indeed, such risk has been noted in a Poster titled, “Evaluation of the Safety of Intravenous Ferumoxytol for Iron Replacement Therapy in Chronic Kidney Disease (CKD),”

²⁸ 44 Fed. Reg. 37434 (June 26, 1979); 51 Fed. Reg. 43900 (12/5/86).] www.fda.gov/medwatch/report/DESK/actions.htm.

²⁹ Fishbane S (2003): Safety in iron management. AJKD 41(6) Suppl. J (June): S-18-26, at 18-19. See Exhibit 11.

which AMAG presented at the April 2007 NFK Spring Clinical Meeting in Orlando, Florida, Specifically, AMAG reported the following. The study was a double-blind crossover safety study of 750 patients total (randomized 1:1 to ferumoxytol to placebo). Of the 750 cohort, about 60% of the patients were CKD patients not on dialysis and 40% were NDD-CKD. The study was intended to provide data to support ferumoxytol as a safe, tolerable, and convenient rapid IV agent. However, there was one subject reported to have had two related serious adverse events: anaphylactoid reaction with severe hypotension. This occurrence in such a limited clinical setting further underscores the need for ferumoxytol labeling to bear the same black box warning as any other dextran or dextran derivative product as a way to ensure that physicians are aware of the need for immediate access to emergency support to report to any serious anaphylactic reaction triggered by an IV injection of ferumoxytol. Indeed, AMAG itself has acknowledged that “[c]ertain serious adverse reactions and side effects are often associated with iron replacement therapeutics such as ferumoxytol.”

In addition, evidence suggests that an anaphylactic reaction triggered by dextran antibodies is not a dose-related reaction.³⁰ Thus, even assuming for the sake of argument that the ferumoxytol for which AMAG seeks FDA approval contains “only” some trace quantity of dextran, there is insufficient data based on clinical trials alone from which to conclude that there is no risk that such trace amount could trigger an anaphylactic reaction. In other words, the issue is not “how much” dextran that ferumoxytol may contain, but instead whether it contains any dextran. If so, its labeling should be required to contain the same black box warning that all other dextran-containing iron injection products are required to contain. Any definitive determination as to the risk that ferumoxytol will trigger a life-threatening type anaphylaxis reaction will only be made after extensive post-market use of ferumoxytol.³¹

In sum, FDA currently requires the labeling of all iron dextran injectable products approved for marketing in the U.S. to contain a black box warning for the risk of life-threatening anaphylactic reactions. Since ferumoxytol is a dextran derivative, FDA should require that it bear the same black box warning as all other iron dextran products. The public health and safety demands it.

- c. A test dose should be required prior to use of ferumoxytol.

FDA requires the labeling for iron dextran products to instruct that a test dose be given to the patient prior to the administration of the first therapeutic dose. For example, the

³⁰ Walters, BAJ and Van Wyck DB (2005): Benchmarking iron dextran sensitivity: reactions requiring resuscitative medication in incident and prevalent patients. *Nephrol Dial Transplant*. Jul; 20(7):1438-42. Epub 2005 Apr 19. See Exhibit 12.

³¹ See AMAG's 10-Q Report, filed on Nov. 7, 2007 (for quarterly period ended Sept. 30, 2007.), at www.sec.gov (SEC Edgar Filing Information).

“Administration” Section of the labeling for INFED® (Iron Dextran Injection USP) states for either an IV or intramuscular injection:

1. Intravenous Injection – PRIOR TO RECEIVING THEIR FIRST IN INFED THERAPEUTIC DOSE, ALL PATIENTS SHOULD BE GIVEN AN INTRAVENOUS TEST DOSE OF 0.5 mL. (See PRECAUTIONS: General.) THE TEST DOSE SHOULD BE ADMINISTERED AT GRADUAL RATE OVER AT LEAST 30 SECONDS. Although anaphylactic reactions known to occur following INFED administration are usually evident within a few minutes, or sooner, it is recommended that a period of an hour or longer elapse before the remainder of the initial therapeutic dose is given.

Individual doses of 2 mL or less may be given on a daily basis until the calculated total amount required has been reached. INFED is given undiluted at a **slow gradual rate** not to exceed 50 mg (1 mL) per minute.

2. Intramuscular Injection – PRIOR TO RECEIVING THEIR FIRST INFED THERAPEUTIC DOSE, ALL PATIENTS SHOULD BE GIVEN AN INTRAMUSCULAR TEST DOSE OF 0.5 mL. (See PRECAUTIONS: General.) The test dose should be administered in the same recommended test site and by the same technique as described in the last paragraph of this section. Although anaphylactic reactions known to occur following INFED administration are usually evident within a few minutes or sooner, it is recommended that at least an hour or longer elapse before the remainder of the initial therapeutic dose is given.

If no adverse reactions are observed, INFED can be given according to the following schedule until the calculated total amount required has been reached. Each day's dose should ordinarily not exceed 0.5 mL (24 mg of iron) for infants under 5 kg (11 lbs); 1.0 mL (50 mg of iron) for children under 10 kg (22 lbs); and 2.0 mL (100 mg of iron) for other patients.

Ferumoxylol labeling should be required to contain this same instruction.³² Should FDA determine that there is no longer a scientific basis for requiring a test dose prior to a therapeutic

³² Should the Agency decide to require a test dose prior to each administration of an IV iron dextran, as it has informally proposed, it should do so for ferumoxylol as well.

dose of an iron dextran replacement product, then the labeling for other iron dextran products should be permitted to omit this information.

Notably, the absence of an adverse reaction with a test dose does not preclude the possibility of an iron dextran-related ADE with ongoing administration. As noted previously, this type of serious adverse reaction to iron dextran may be induced by relatively low doses.

- d. Ferumoxytol labeling should be required to specify that its use is limited to second-line therapy.

FDA requires the labeling for iron dextran products to specify that its use is limited to second line therapy to oral iron products. The "Indications and Usage" section of labeling for INFeD® and DexFerrum® (Iron Dextran Injection USP) states that each product is indicated for treatment of patients with documented iron deficiency "in whom oral administration is unsatisfactory or impossible." The labeling for ferumoxytol should be required to contain this same information.

Indeed, given that there are already two IV iron products approved for treatment of iron deficiency anemia in hemodialysis patients, and one in pre-dialysis CKD, the approval of another IV iron product which has not been studied against an active control or for a sufficient period of time to develop adequate information as to safety has to be seriously questioned. Not only were both ferric gluconate and iron sucrose studied more vigorously, but each had been marketed for an extensive time outside of the U.S. prior to approval over 40 to 50 years. Given the deaths which occurred in the clinical studies of ferumoxytol, and its potential risk of anaphylaxis (not present with other IV iron products), one has to question the risk-benefit - and hence the rationale for approval - of such a product for even a second line indication.

3. FDA is required to treat similarly situated parties in a similar manner.

Not only does public safety demand that ferumoxytol be required to comply with the same approval and labeling requirements as applied to all other dextran products, but so does the legal mandate that FDA treat similarly situated parties similarly. It is 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)). FDA requires product class labeling for IV iron dextran products. Such requirements include a black box warning, a test dose requirement, and use of a second line therapy. Because it, too, is a dextran or dextran derivative, these same labeling requirements should also be required for ferumoxytol. To fail to impose such requirements would be arbitrary, capricious, and contrary to law.

“Government is at its most arbitrary when it treats similarly situated people differently.” Etelson v. OPM, 684 F.2d 918, 926 (D.C. Cir. 1982). This bedrock principle has been applied time and again to ensure that people who are subject to the same legal standards are, to the fullest extent possible, treated the same. See, e.g., Airmark Corp. v. FAA, 758 F.2d 685, 692 (D.C. Cir. 1985) (striking down agency decision where “different decisional criteria” were applied to “similarly situated carriers,” resulting in a lack of “[e]lementary even-handedness”); NLRB V. Washington Star Co., 732 F.2d 974, 977 (D.C. Cir. 1984) (“The present sometimes-yes, sometimes-no, sometimes maybe policy...cannot, however, be squared with our obligation to preclude arbitrary and capricious management....”).

It is a principle that is readily applicable to the regulation of drugs and other FDA-regulated products, particularly where sponsors are vying to compete in the same market. For example, in United States v. Diapulse Corp. of America, 748 F.2d 56 (2d Cir. 1984), the court struck down FDA’s disparate treatment of two similarly situated medical devices, where one sponsor (Diapulse) sought to modify its device to match one that had been approved by FDA for another sponsor (United Medical Equipment). The court enjoined FDA from refusing to approve Diapulse’s product, while allowing the other to remain on the market, emphasizing that “[r]eference to administrative discretion or expertise is not a license to a regulatory agency to treat like cases differently.” Id. at 62; see also, United States v. Undetermined Quantities...Exachol, 716 F. Supp. 787 (S.D.N.Y. 1989) (rejecting FDA’s refusal to apply its policy on health claims for food product evenly across similarly situated products).

The clearest expression of this principle – and the one that dictates the outcome of this petition – is found in Bracco Diagnostics, Inc. v. Shalala, 963 F. Supp. 20 (D.D.C. 1997). There, plaintiffs alleged that FDA had decided to regulate some ultrasound contrast agents as medical devices and others as drugs, for no apparent reason. See id. at 24. That decision – in and of itself – may have passed muster, had FDA not been “apparently applying very different standards to assess the safety and effectiveness of essentially identical products.” Id.

In the words of the court, “[t]he disparate treatment of functionally indistinguishable products is the essence of the meaning of arbitrary and capricious.” Id. at 28.

The injectable iron product currently marketed in the U.S. and the proposed ferumoxytol drug product are similarly situated and functionally indistinguishable for purposes of establishing the safety and effectiveness of the respective products. It is incumbent upon FDA to apply the applicable legal standard product class labeling and all other approval requirements, including the amount of safety data and the same degree of effectiveness data in a consistent manner.

4. Conclusion

For the foregoing reasons, Luitpold respectfully requests that FDA impose the same labeling requirements for an NDA for ferumoxytol as have been imposed on all other IV iron

dextran products. Such requirements include (1) that inclusion of the same black box warning and (2) all of the other labeling information such as test dose that FDA requires for other dextran-containing IV iron replacement products until such time, if any, that sufficient data exist to demonstrate that ferumoxytol contains no dextran or dextran derivatives, or that sufficient post-marketing data exist to demonstrate that ferumoxytol can be distinguished from all other iron dextran products in a clinically meaningful way. Furthermore, FDA should not approve any NDA for ferumoxytol unless and until AMAG submits the type and amount of safety and efficacy data FDA has required and is requiring for other IV iron products.

C. ENVIRONMENTAL IMPACT

According to 21 C.F.R. § 25.31(a), this petition qualifies for a categorical exclusion from the requirement for submission of an environmental assessment.

D. ECONOMIC IMPACT

According to 21 C.F.R. § 10.30(b), information on economic impact is to be submitted only when requested by the Commissioner following review of the petition.

E. CERTIFICATION

The undersigned certify that, to their best knowledge and belief: (a) this petition includes all information and views upon which the petition relies; (b) this petition includes representative data and/or information known to the petitioner which are unfavorable to the petition; and (c) we have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to us. We further certify that the information which we have based the action requested herein first became known to the party on whose behalf this petition is submitted on or about the following date: August 19, 2008. If we received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, we received or expect to receive those payments from the following persons or organizations: Luitpold Pharmaceuticals, Inc., One Luitpold Drive, P.O. Box 9001, Shirley, NY 11967. We verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.

Respectfully submitted,



Peter S. Reichertz



Deborah M. Shelton

for SHEPPARD MULLIN RICHTER & HAMPTON LLP

Attachments