DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
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JUN 5 2015

Peter S. Reichertz
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1300 I Street, NW, 11th Floor East
Washington, DC 20005-3314

Re: Docket No. FDA-2013-P-1294

Dear Mr. Reichertz:

This letter responds to the citizen petition dated September 30, 2013, that you submitted on behalf of Luitpold Pharmaceuticals, Inc. (Petition). The Petition requests that the Food and Drug Administration (FDA or the Agency) require that any new drug application (NDA) or supplement to an NDA (sNDA) of any injectable form of iron for the treatment of iron deficiency anemia (IDA) outside of chronic kidney disease (CKD) be approved only if the clinical studies supporting such approval contain objectively and prospectively derived data that the patients in the pivotal clinical study or studies are intolerant to or have had an unsatisfactory response to oral iron during a run-in period. The Petition also requests that FDA require that any injectable iron product be contraindicated for use in patients with a previous history of allergic reaction to iron products and/or in patients with allergies to two or more classes of drugs if the pivotal study or studies submitted for approval of such a drug product excluded such patients. FDA has carefully considered the information submitted in your Petition. For the reasons described below, the Petition is denied.

I. BACKGROUND

A. Injectafer (ferric carboxymaltose injection)

Luitpold Pharmaceuticals, Inc., holds approved NDA 20-3565 for Injectafer (ferric carboxymaltose injection). Injectafer is an iron replacement product indicated for the treatment of iron deficiency anemia in adult patients who have intolerance to oral iron or who have had an unsatisfactory response to oral iron and for adult patients who have non-dialysis dependent chronic kidney disease.

The clinical study that supported the approval of Injectafer for treatment of IDA outside of CKD had a design that included a 14-day run-in period to allow for inclusion into the study of patients who had either an unsatisfactory response to oral iron or who poorly tolerated oral iron based on objectively and prospectively derived data.[1] Specifically,

[1] The study design also provided for the inclusion of subjects who met the other eligibility criteria, but for whom their physician considered the 14-day run-in to be inappropriate.

consenting patients at least 18 years of age who met eligibility criteria were given a 14-day run-in of oral ferrous sulfate, 325 milligrams (mg) three times daily. All participants returned on day 7 of the run-in phase to assess compliance (via pill counts) and tolerance of oral iron. Study participants who responded adequately to oral iron during run-in were not randomized. Participants who had an inadequate response to oral iron or an inability to tolerate oral iron were assigned to a study group.[2] In addition, patients who had a prior allergic response to intravenous (IV) iron or multiple drug allergies were not excluded from the study.[3]

B. NDA and sNDA Approval Requirements

The Federal Food, Drug, and Cosmetic Act (FD&C Act) and FDA regulations require that a person seeking to market a new drug that is not a generic copy of any already approved drug submit an NDA for that drug. A person seeking to market an already approved drug for a new indication also must submit a marketing application for approval of that indication. NDAs and sNDAs are submitted under section 505(b)(1) of the FD&C Act and approved under section 505(c) of the FD&C Act. NDAs and sNDAs generally contain, among other things, extensive scientific data demonstrating the safety and effectiveness of the drug for the indication for which approval is sought.

NDA and sNDA applicants must provide "substantial evidence" of effectiveness for claimed indications in their applications. As stated in section 505(d) of the FD&C Act, "substantial evidence" means:

> evidence consisting of adequate and well-controlled investigations, including clinical investigations, by experts qualified by scientific training and experience to evaluate the effectiveness of the drug involved, on the basis of which it could be fairly and responsibly concluded by such experts that the drug will have the effect it purports or is represented to have under the conditions of use prescribed, recommended, or suggested in the labeling or proposed labeling thereof.

The Agency generally requires at least two adequate and well-controlled studies, each convincing on its own, to establish effectiveness for the approval of an NDA. The Agency's guidance for industry, *Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products*, outlines our current thinking on acceptable approaches.[4] The characteristics of adequate and well-controlled clinical investigations are described in FDA's regulations at 21 CFR 314.126.

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[2] Onken, J.E., et al., "A multicenter, randomized, active controlled study to investigate the efficacy and safety of intravenous ferric carboxymaltose in patients with iron deficiency anemia," *Transfusion*, doi: 111/trf.12289, 2013.

[3] Id. at Table S1.

[4] This guidance is available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

C. Product Labeling Requirements

The Agency's regulations at 21 CFR 201.57 describe specific requirements for the content and format of labeling for human prescription drug products, including the CONTRAINDICATIONS section (21 CFR 201.57(c)(5)).[5] By regulation, the CONTRAINDICATIONS section:

> must describe any situations in which the drug should not be used because the risk of use (e.g., certain potentially fatal adverse reactions) clearly outweighs any possible therapeutic benefit. Those situations include use of the drug in patients who, because of their particular age, sex, concomitant therapy, disease state, or other condition, have a substantial risk of being harmed by the drug and for whom no potential benefit makes the risk acceptable. Known hazards and not theoretical possibilities must be listed (e.g., if severe hypersensitivity to the drug has not been demonstrated, it should not be listed as a contraindication).[6]

FDA guidance provides recommendations for when a drug should be contraindicated.[7] The guidance states that a drug should be contraindicated "only in those clinical situations for which the risk from use clearly outweighs any possible therapeutic benefit." Both observed and anticipated adverse reactions can serve as the basis for a contraindication. The guidance gives examples of clinical situations for which a contraindication may be appropriate, including use of a drug in patients with known hypersensitivity when severe hypersensitivity reactions have been observed to occur with the drug.

II. DISCUSSION

A. Clinical Study Requirements for Approval of NDAs and sNDAs for Injectable Iron

In your Petition, you request that FDA approve NDAs or sNDAs of injectable iron products for treatment of IDA outside of CKD only if the approval is based on pivotal clinical studies that include a run-in period where patients take oral iron to confirm intolerance or unsatisfactory response to oral iron or similarly prospectively captured data that provides objective evidence the patients in such studies have such conditions

[5] FDA regulations at 21 CFR 201.80 address the requirements for the content and format of labeling for human prescription drug products that are not subject to 21 CFR 201.57. Any new NDA or sNDA that would be submitted for an injectable iron product would be subject to 21 CFR 201.57.

[6] 21 CFR 201.57(c)(5).

[7] Guidance for industry on *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drugs and Biological Products – Content and Format* (October 2011) at 8-10. This guidance is available at http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

(Petition at 1).[8] You claim that the Agency required Luitpold to collect data to identify on an objective and prospective basis the patient population of poor responders and those intolerant of oral iron (Petition at 3) and that use of a 14-day oral iron run-in period is the only method to collect such data (Petition at 7). You assert that it would be arbitrary and capricious to approve an NDA or sNDA for any injectable iron product for use in a population that has an unsatisfactory response to, or is intolerant of, oral iron that does not require objective data that the patient population studied meets the patient population to be treated (Petition at 10-12).

To be approved by FDA, every NDA and sNDA must demonstrate that the drug product at issue is safe and effective under section 505 of the FD&C Act. Accordingly, FDA will apply the same statutory and regulatory requirements for approval of other injectable iron products for treatment of IDA outside of CKD that the Agency applied to Injectafer.

As noted in your Petition, given the safety risks associated with the product, FDA required Luitpold to demonstrate that patients included in the Injectafer study for treatment of IDA outside of CKD were intolerant of or had an unsatisfactory response to oral iron based on objective data and evidence (Petition Ex. 3 ("The requirements of a clearly documented need for Injectafer is mandatory to help offset the demonstrated risks for the product.")). We do not agree, however, that FDA required Luitpold to use a run-in period, as the Petition suggests (Petition at 3 ("The design of this study, as required by the Agency, included a 14 day run-in period . . . ."); id. at 10). Luitpold proposed using a run-in approach to address the Agency's concern that clinical studies of Injectafer identify a study population of patients intolerant of or poor responders to oral iron using objective data supported by documentation given the safety risks associated with the product in clinical trials and the Agency agreed that a run-in approach appeared to be reasonable (Petition Ex. 8).

As was the case for Injectafer, any decision about the acceptability of clinical trials for other injectable iron products for use to treat IDA outside of CKD will be based on our

[8] We interpret your Petition as requesting that FDA approve an NDA or sNDA for IDA outside of CKD only if the approval is based on a pivotal clinical study with a run-in period. In some places, you seem to request FDA base approval on a clinical trial *either* with a run-in period *or* with similarly prospectively captured data to provide objective evidence regarding the study population (Petition at 1 (stating that FDA should require that any NDA or sNDA of an injectable form of iron for the treatment of IDA outside of CKD "be approved only if the clinical studies supporting such approval contain objectively and prospectively derived data that the patients in the pivotal clinical study or studies are intolerant to or have had an unsatisfactory response to oral iron"); id. (stating that FDA should approve any NDA or sNDA of injectable iron for the treatment of IDA outside of CKD "[o]nly if the approval is based on pivotal clinical studies that include a necessary run-in period where patients take oral iron to confirm intolerance to, or unsatisfactory response to, oral iron or similarly prospectively captured data that provides objective evidence the patients in such studies have such conditions"). However, you claim that a run-in period is the "only method to conduct a study to collect objective, not subjective, data that" a population intolerant of or unresponsive to oral iron would be studied (id. at 7; see also id. at 12 (stating that FDA should not approve any NDA or sNDA "for treatment of IDA in patients intolerant to or who have had unsatisfactory response to oral iron unless the applicant has objectively proven by a run-in period that the patients in the pivotal trial(s) reflect the population to be treated")).

scientific experience and expertise regarding the product and applicable legal standards. The Agency will take into consideration the risks and benefits of the proposed product, as described in the NDA or sNDA, as well as our evaluation of current relevant scientific data and information.

We believe that a run-in period with oral iron is the most reliable way to identify, based on objective data and evidence, a patient population that is intolerant of or that has an unsatisfactory response to oral iron, because a run-in period ensures that there will be detailed documentation of patients' intolerance of or unsatisfactory response to oral iron. However, we decline to require such a study. Applicants may propose to conduct clinical studies with alternative approaches to objectively collect data on the patient population that is intolerant of oral iron or that has an unsatisfactory response to oral iron. For example, detailed documentation of intolerance of oral iron or an unsatisfactory response to oral iron based on review of patients' medical records could potentially be used to identify an appropriate study population.[9] FDA will consider the evidence supporting an NDA or sNDA and make a decision regarding its acceptability on a case-by-case basis, as described above.[10]

For the reasons set forth above, we deny your request not to approve an NDA or sNDA for injectable iron for the treatment of IDA outside of CKD unless the applicant uses a run-in study design to demonstrate that patients are intolerant of or have had an unsatisfactory response to oral iron.

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[9] We acknowledge that medical record review has its limitations. For example, evaluation of unsatisfactory response to oral iron using medical record review may be difficult given the high noncompliance rate with oral iron treatment and the fact that medical record review does not provide for collection of hemoglobin levels following oral iron treatment as is the case with a run-in study design. Use of medical record review also may be limited by the fact that "intolerance" is a term subject to interpretation. And even if "intolerance" is adequately defined, the signs and symptoms of oral iron treatment and duration of side effects may not be documented in sufficient detail in medical records to allow adequate evaluation of intolerance.

[10] You also claim that approval of an injectable iron product for treatment of IDA in patients intolerant of oral iron or who have an unsatisfactory response to oral iron based on evidence from a different study design, i.e., that is not based on a clinical trial with an oral iron run-in period, would be arbitrary and capricious action by the Agency (Petition at 10-11). We disagree. The case you cite in support of your position, *Bracco Diagnostics, Inc. v. Shalala*, 963 F.Supp. 20 (D.D.C. 1997), addressed the evaluation of products under two different regulatory schemes by two different Centers at FDA. The situation here, however, involves the evaluation of products under the same regulatory standard, by the same Center at FDA. We agree that the same legal standard for approval must be met for any such products in the circumstances at hand. Section 505(d) of the FD&C Act requires that, in order to obtain approval, a new drug must be shown to be safe and effective for its proposed use(s). As discussed above, each NDA or sNDA is reviewed on an individual basis, considering the risks and benefits of that particular drug and the data contained in the application. In conducting this review, FDA relies on its scientific and regulatory expertise to determine whether the statutory requirements are met. While all NDAs and sNDAs must meet the same standard of safety and efficacy, this does not mean either that FDA must require all applications to use the same scientific approach and methodology to do so, or that it is arbitrary and capricious if the Agency determines that a different scientific approach and methodology is appropriate and satisfies the statutory requirements.

B. Product Labeling Requirements

In your Petition, you request that FDA require any injectable iron product be contraindicated for use in patients with previous history of allergic reaction to iron products and/or for use in patients with allergies to two or more classes of drugs if the pivotal study or studies submitted for approval of such a drug product excluded such patients (Petition at 2). You state that patients who are intolerant or allergic to other injectable irons or who have multiple drug allergies are vulnerable to serious drug reactions (Petition at 13). You claim that unless a product has been shown to be safe to use in those populations based on clinical evidence, its use in those populations should be contraindicated (Petition at 15).

As described above, the contraindications section of human prescription drug labeling must describe any situations in which the drug should not be used because the risk of use clearly outweighs any possible therapeutic benefit.[11] Both observed adverse reactions and anticipated adverse reactions can provide the basis for a contraindication under the conditions set forth in the guidance for industry, *Warnings and Precautions, Contraindications, and Boxed Warning Sections of Labeling for Human Prescription Drug and Biological Products – Content and Format*. Currently approved injectable iron products are contraindicated in patients with known hypersensitivity to the drug,[12] and a contraindication was recently added to one product in patients with a history of allergic reaction to any intravenous iron product based on the evaluation of reported cases of

[11] 21 CFR 201.57(c)(5).

[12] See labeling approved August 8, 2009, for DexFerrum (iron dextran injection, USP) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/040024s022lbl.pdf ("CONTRAINDICATIONS: Hypersensitivity to the product. All anemias not associated with iron deficiency."); labeling approved August 12, 2009, for INFeD (iron dextran injection, USP) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017441s171lbl.pdf ("CONTRAINDICATIONS: Hypersensitivity to the product. All anemias not associated with iron deficiency."); labeling approved August 25, 2011, for Ferrlecit (sodium ferric gluconate complex in sucrose injection) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020955s013s015lbl.pdf (listing as a contraindication "Known hypersensitivity to sodium ferric gluconate or any of its components."); labeling approved March 29, 2013, for Venofer (iron sucrose injection, USP) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/021135s023lbl.pdf (listing as a contraindication "Known hypersensitivity to Venofer."); labeling approved March 16, 2015, for Feraheme (ferumoxytol) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022180s011s013lbl.pdf (listing as a contraindication "Known hypersensitivity to Feraheme or any of its components."); labeling approved July 25, 2013, for Injectafer (ferric carboxymaltose injection) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2013/203565s000lbl.pdf (listing as a contraindication "Hypersensitivity to Injectafer or any of its components."). To the extent that there are approved ANDAs for any of these drug products, they would be required to include the same contraindications in their labeling (20 CFR 314.94(a)(8)).

anaphylactic reactions, including deaths, that occurred after the product was approved.[13] Two products also have boxed warnings related to the risk for anaphylactic-type reactions,[14] and a boxed warning was recently approved to strengthen the existing warning regarding the risk of serious, potentially fatal allergic reactions for another product.[15]

As it does with all applications, FDA will carefully review any submitted NDAs and sNDAs for injectable iron products for the treatment of IDA on a case-by-case basis and determine whether similar and/or additional contraindications are necessary. Although our decisions about the contraindications required to be in a product's labeling may be informed by concerns reflected in the design of the pivotal study or studies, the ultimate decision will be made based on available clinical evidence in accordance with the statute and regulations at 21 CFR 201.57(c)(5).[16] Accordingly, FDA denies your request to require that any injectable iron product be contraindicated for use in patients with previous history of allergic reaction to iron products and/or for use in patients with allergies to two or more classes of drugs if the pivotal study or studies submitted for approval of such a drug product excluded such patients.

[13] See labeling approved March 16, 2015, for Feraheme (ferumoxytol) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022180s011s013lbl.pdf (listing as a contraindication "History of allergic reaction to any intravenous iron product."); FDA Drug Safety Communication (March 30, 2015), at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm440479.htm.

[14] See labeling approved August 8, 2009, for DexFerrum (iron dextran injection, USP) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/040024s022lbl.pdf; labeling approved August 12, 2009, for INFeD (iron dextran injection, USP) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/017441s171lbl.pdf.

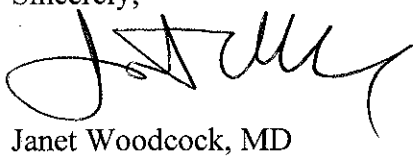
[15] See labeling approved March 16, 2015, for Feraheme (ferumoxytol) at http://www.accessdata.fda.gov/drugsatfda_docs/label/2015/022180s011s013lbl.pdf

[16] This is what happened for Feraheme, where FDA strengthened the warnings and made changes to the prescribing instructions based on its evaluation of serious adverse reactions, including deaths, reported after the product was approved. See FDA Drug Safety Communication (March 30, 2015), at http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm440479.htm.

III. CONCLUSION

For the reasons set forth above, the Petition is denied.

Sincerely,



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