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BY HAND DELIVERY

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

CITIZEN PETITION

AMAG Pharmaceuticals, Inc. (AMAG or "the Company"), the sponsor of Feraheme® (ferumoxytol) Injection, New Drug Application (NDA) 22-180, respectfully submits this Citizen Petition under 21 USC 355 and 21 CFR 10.30, among other provisions of law, to request that the Commissioner of Food and Drugs takes the actions described below with respect to any abbreviated new drug application (ANDA) for a generic version of Feraheme.

AMAG is a specialty pharmaceutical company primarily involved in the development and commercialization of nanoparticle iron therapeutic products such as Feraheme. The Company's core competencies include the ability to design macromolecular complexes for particular applications and to manufacture nanoparticles comprised of these complexes in controlled sizes with different chemically distinct iron oxide cores and complexed carbohydrates, depending on the application for which they will be used.

Feraheme is an iron replacement intravenous (IV) product approved on June 30, 2009, for the treatment of iron deficiency anemia in adult patients with chronic kidney disease.[1] The active ingredient in Feraheme – ferumoxytol – is highly complex, as are the manufacturing and quality-control processes required for its production.

In December 2012, the Food and Drug Administration (FDA or "the Agency") published a guidance document in draft form providing product-specific bioequivalence recommendations for generic versions of ferumoxytol injection (the Draft Guidance).[2] The Company does not

[1] *See* Approved Drug Products with Therapeutic Equivalence Evaluations (the "Orange Book") (33rd ed. 2013), Prescription Drug Product List, at 3-177; Feraheme Prescribing Information, attached at Tab 1, *available at* http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/022180s006lbl.pdf.

[2] Food and Drug Administration, Draft Guidance on Ferumoxytol (Dec. 2012), attached at Tab 2, http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM333051.pdf.

believe that the Draft Guidance contains standards that are adequate to ensure that proposed generic ferumoxytol products are pharmaceutically equivalent and bioequivalent to the reference listed drug (RLD). The Draft Guidance describes five general categories of *in vitro* studies that FDA recommends should be conducted to show "[s]ameness in physicochemical properties." It also recommends bioequivalence based on pharmacokinetic (PK) measurements of ferumoxytol-associated iron in plasma or serum. Scientific consensus, however, is that measurement of IV iron products such as ferumoxytol in plasma or serum is not an accurate means of establishing the bioavailability of these products at the site of drug action in the target tissue of the mononuclear phagocyte system, or reticular endothelial system (RES).[3]

The challenges involved in demonstrating pharmaceutical equivalence and bioequivalence for generic versions of nanoparticle IV iron products such as Feraheme are not theoretical. In the European Union (EU), a number of generic versions of Venofer® (iron sucrose injection) have been approved. As described further below, post-market studies have confirmed that these products are not therapeutically equivalent.

On March 17, 2011, the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) adopted a "Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications."[4] This Reflection Paper described the "current thinking of the CHMP" on the type of non-clinical studies necessary to support generic approvals of nanoparticle iron medicinal products. Among other things, the CHMP concluded that *in vitro* physicochemical characterization of the drug substance, and *in vivo* PK studies using the final drug product, may not be sufficient to ensure bioequivalence for nanoparticle iron medicinal products.[5]

In the US, FDA has approved only a single generic IV iron product. On March 31, 2011, FDA approved Nulecit™ (sodium ferric gluconate complex), a generic version of Ferrlecit® (sodium ferric gluconate complex). The Agency has not approved any generic versions of Venofer.

Nonetheless, on April 19, 2013 – driven by the EU experience with generic versions of Venofer and the EMA Reflection Paper – FDA took the highly unusual step of issuing a "Sources Sought Notice" that was intended to help FDA determine "the availability and

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[3] AMAG submitted comments to FDA recommending modifications to the Draft Guidance. *See* FDA-2007-D-0369-114 (Feb. 14, 2013), attached at Tab 3, http://www.regulations.gov/#!documentDetail;D=FDA-2007-D-0369-0114. As of the date of this present citizen petition, FDA has not proposed any changes to the Draft Guidance based on AMAG's comments.

[4] European Medicines Agency, *Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications* (Mar. 17, 2011) (the "EMA Reflection Paper"), attached at Tab 4, http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2011/04/WC500105048.pdf.

[5] *Id.*

capability of small businesses . . . to evaluate the therapeutic equivalence of generic sodium ferric gluconate iron complex Nulecit™ and its RLD Ferrlecit®."[6] On July 16, 2013, FDA took the additional step of issuing a solicitation for contract studies with the formal objective of evaluating the therapeutic equivalence of Nulecit and Ferrlecit, and to "address potential concerns regarding the quality of generic iron complex products."[7] Thus, it has become clear that FDA is preparing to enter into a contract with a third-party laboratory to perform rigorous analyses to confirm that Nulecit is therapeutically equivalent to Ferrlecit and, more broadly, to address concerns regarding FDA's approval criteria for generic iron complex products.

FDA's approval of Nulecit was based on an assumption that physicochemical characterization would ensure comparable tissue distribution and no more *in vivo* labile iron leakage from generic formulations than that from the RLD. However, in the Nulecit Contract Studies Solicitation, FDA acknowledged that the EMA has suggested "that generic iron formulations could have higher levels of labile iron," which could potentially lead to "direct cellular damage . . . possibly increasing the risk of atherosclerotic disease." Thus, FDA is now taking action to confirm, post-market, what the Agency had assumed premarket.

Although FDA's action is directed at Nulecit, it plainly has class-wide implications. Accordingly, AMAG requests that FDA refrain from approving any ANDA referencing Feraheme unless it first takes the following actions.

ACTIONS REQUESTED

For the reasons that follow, AMAG respectfully requests that the Commissioner takes the following actions:

(1) Refrain from approving any ANDA referencing Feraheme until the Nulecit Post-Market Contract Studies have been completed and have demonstrated that FDA's proposed pre-market approval standards for generic IV iron formulations are sufficient to ensure therapeutic equivalence, including comparable tissue distribution and no more *in vivo* labile iron leakage than the RLD; and

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[6] Therapeutic Equivalence of Generic Iron Complex Product, Solicitation No. FDA-SS-1116099 (Apr. 19, 2013) (the "Nulecit Sources Sought Notice"), attached at Tab 5. *Available at* https://www.fbo.gov/spg/HHS/FDA/DCASC/FDA-SS-1116099/listing.html.

[7] Evaluate the therapeutic equivalence of generic sodium ferric gluconate iron complex Nulecit™ and its RLD Ferrlecit®, Solicitation No. FDA-SOL-1120929 (Jul. 16, 2013) (the "Nulecit Contract Studies Solicitation"), attached at Tab 6. *Available at* https://www.fbo.gov/spg/HHS/FDA/DCASC/FDA-SOL-1120929/listing.html. The studies described in the Nulecit Sources Sought Notice and the Contract Studies Solicitation are hereafter referred to as the "Nulecit Post-Market Contract Studies."

(2) Require that any sponsors of proposed generic versions of Feraheme show that their products are equivalent to the RLD using:

a) A comparative study in patients using clinical endpoints; and

b) The additional assays described in the Nulecit Contract Studies Solicitation.

Each of these requests is discussed in detail below.

STATEMENT OF GROUNDS

I. BACKGROUND

A. Statutory and Regulatory Standards

1. Sameness

Under the abbreviated approval pathway for generic drugs established by the Hatch-Waxman amendments to the Food, Drug, and Cosmetic Act (FDCA), an applicant submitting an ANDA can avoid having to submit clinical studies to establish safety and effectiveness by relying instead on FDA's previous finding of safety and effectiveness for a reference product. In order to do so, the ANDA applicant must show, among other things, that the proposed generic product has the same active ingredient as the RLD.[8]

By regulation, FDA has defined "same as" to mean, among other things, "identical in active ingredient(s)."[9] FDA has discretion to determine what information is sufficient to demonstrate that a generic product has the same active ingredient as the RLD, and to establish standards that are product-specific.[10]

FDA cannot, however, override the statutory requirement that a generic contain "the same active ingredient," nor without a new rulemaking procedure can it override its regulation requiring "identical in active ingredient." Nor can FDA require as part of an ANDA new studies to address safety and effectiveness. It is well-established that where there are differences between the generic product and its reference product, or where clinical studies are required to

[8] 21 CFR 314.92(a)(1); *see also* 21 USC 355(j)(2)(A)(ii); 21 CFR 314.94(a)(5) (ANDA must contain "information to show that the active ingredient is the same as that of the [RLD]").

[9] 21 CFR 314.92(a)(1).

[10] *See, e.g., Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998).

ensure the safety or effectiveness of the generic, an ANDA is not permitted. Instead, the sponsor must submit its application as an NDA under section 505(b) of the FDCA.

2. Bioequivalence

An ANDA drug product is not generally required to be "the same" as the RLD in characteristics other than those specified in the statute, including in its formulation and method of manufacture. Because two different manufacturers making the same drug product may use different formulations, components, and manufacturing processes, the approved RLD and the proposed generic, even if they contain the same amount of active ingredient, have the potential to release or deliver different amounts of drug at different rates to the patient. Thus, studies are necessary to demonstrate bioequivalence to ensure that patients receive the same treatment whether they are dispensed the RLD or the generic substitute.[11]

Under the FDCA, a generic drug is considered bioequivalent to the RLD if "the rate and extent of absorption of the [generic] drug do not show a significant difference from the rate and extent of absorption of the [reference] drug when administered at the same molar dose of the therapeutic ingredient under similar experimental conditions in either a single dose or multiple doses."[12]

According to the Agency's implementing regulations, "FDA may require *in vivo* or *in vitro* testing, or both, to measure the bioavailabilty of a drug product or establish the bioequivalence of specific drug products."[13] FDA's regulations describe these methods in descending order of accuracy, sensitivity, and reproducibility. These methods include *in vivo* PK studies, *in vivo* pharmacodynamic effect studies, clinical endpoint studies, and *in vitro* studies.[14] Ultimately, under the statute and regulations, the choice of study design is based on the ability of the design to compare the drug delivered by the two products at the particular site of action of the drug.

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[11] *See generally* 21 CFR 320.24.

[12] 21 USC 355(j)(8)(B)(i).

[13] 21 CFR 320.24(a).

[14] By regulation, FDA has identified the following potential approaches to establishing bioequivalence: (1) *In vivo* PK studies measuring the concentration of the drug in an appropriate biological fluid, such as blood or plasma, or *in vitro* studies that have been correlated with and are predictive of human *in vivo* bioavailability data; (2) *In vivo* studies measuring the urinary excretion of the drug; (3) *In vivo* pharmacodynamic studies measuring effects associated with the delivery of the drug to the site of action; (4) *In vivo* comparative clinical studies that measure the effectiveness of the drug; (5) A currently available *in vitro* test that ensures human *in vivo* bioavailability; (6) Any other approach deemed adequate by FDA to establish bioequivalence. The regulation specifically states that the different methods (1) through (6) are listed "in descending order of accuracy, sensitivity, and reproducibility," and requires applicants to use "the most accurate, sensitive, and reproducible approach available." *See* 21 CFR 320.24(a), (b).

The preferred methodology, and what is typically used with drugs that achieve therapeutic effect through systemic absorption, is to perform *in vivo* PK studies that measure the rate and extent to which the active ingredient or active moiety is absorbed into the blood over time.[15] For absorbed and systemically acting drug products, the rate and extent of systemic absorption is usually the most sensitive, accurate, and reliable indicator of the rate and extent to which the active ingredient becomes available at the site of drug action. The determination of bioequivalence of drug products whose primary mechanism of action depends on systemic absorption, therefore, usually rests on a PK comparison of drug and/or metabolite concentrations in an accessible biologic fluid, such as blood, after administration of a single dose of each drug product to healthy volunteers.

But this is not always the case. FDA's rules also provide for "[a]n *in vivo* test in humans in which an appropriate acute pharmacological effect of the active moiety, and, when appropriate, its active metabolites, are measured as a function of time."[16] Likewise, the rules expressly provide for the use of "[w]ell-controlled clinical trials that establish the safety and effectiveness of the drug product, for purposes of measuring bioavailability, or appropriately designed comparative clinical trials, for purposes of demonstrating bioequivalence."[17] For a dosage form designed to deliver the active moiety to the bloodstream for systemic distribution, a clinical endpoint study can be used to show bioequivalence when pharmacokinetic and pharmacodynamic measurements are inapplicable, either because the analytics have not been developed, or because they are not predictive of bioavailability.[18]

3. *Therapeutic Equivalence*

One of the principle benefits of approval under an ANDA is that the approved product is considered therapeutically equivalent to the RLD and is given an "A" rating in the Orange Book. With an A rating in the Orange Book, the generic drug product would be eligible in most states to be automatically substituted for the approved reference product at the pharmacy level. The underlying premise is that drug products sharing the characteristics that must be demonstrated for ANDA approval may be substituted for the other "with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product."[19]

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[15] 21 CFR 320.24(b)(1)(i).

[16] 21 CFR 320.24(b)(3).

[17] 21 CFR 320.24(b)(4).

[18] *Id.*

[19] Orange Book, Preface at vii.

B. Parenteral Iron Products

1. Overview of Therapeutic Class

Feraheme is a complex, nanoparticle-based drug product intended for use in IV iron replacement therapy. It belongs to a class of products all of which consist of colloidal iron complexed with a carbohydrate, and formulated as a suspension for parenteral administration. The active ingredient in these products each consist of a colloidal crystal of polynuclear ferric oxyhydroxide encased within or bound to a carbohydrate that sequesters the iron within a soluble nanoparticle.

Nanoparticle IV iron is not a new therapeutic class. As far back as the 1950s, FDA had approved a number of iron dextran products for IV administration. As pre-1962 drugs, these iron dextran products were not required to demonstrate effectiveness.[20] However, iron dextran was subject to the subsequent Drug Efficacy Study Implementation (DESI) review process.[21] Under DESI review, iron dextran was "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."[22]

Importantly, the DESI review also concluded that "[t]he active components of preparations of this kind 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."[23] Thus, as early as 1968, FDA appreciated the fact that different sponsors' manufacturing processes are especially critical to the identity, and to the safety, of parenteral iron colloidal suspension products.

In 1974, FDA approved INFeD® (iron dextran injection). This was followed in 1981 by the approval of Proferdex (iron dextran injection). However, owing to the serious adverse event issues, including anaphylaxis and death, all iron dextran parenteral products are required to

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[20] Prior to 1962, drug sponsors did not need to demonstrate the effectiveness of their drug products. In 1962, Congress amended the FDCA to require that all new drugs, including drugs approved prior to 1962, must be shown to be effective based on "substantial evidence" derived from adequate and well controlled clinical studies. *See* Pub. L. No. 87-781, 76 Stat. 780 (1962). The FDCA as originally enacted in 1938 required only that they were safe for their intended uses. *See* Pub. L. No. 75-717, 52 Stat. 1040 (1938).

[21] 33 Fed. Reg. 9352 (June 26, 1968). For pre-1962 drugs that had been approved solely on the basis of safety, FDA established a program known as the DESI review process to evaluate the efficacy of these products. *See* 31 Fed. Reg. 9426 (July 9, 1966).

[22] 33 Fed. Reg. 9352.

[23] *Id.* In designating iron dextran as a "new drug," FDA was indicating that it was not generally recognized as safe or effective and that all products containing iron dextran as an active ingredient must be subject to the NDA approval process. *See* 21 USC 321(p).

include a package insert that contains a black box warning for the potential of fatal anaphylactic-type reactions.

At the present time, there are no generic iron dextran products approved in the United States. In 1991, Luitpold Pharmaceuticals, Inc., submitted an ANDA for iron dextran injection.[24] Owing to the discontinuation and withdrawal of early iron dextran products, INFeD was designated as the RLD for the Luitpold ANDA. This ANDA included a request for a waiver of *in vivo* bioequivalence studies. The Agency denied that request. Luitpold was therefore required to perform *in vivo* bioequivalence studies with INFed as the comparator drug, and ultimately to resubmit its application under 505(b)(2) of the FDCA. Specifically, Luitpold was required to perform a comparative study in patients undergoing hemodialysis for end-stage renal disease (open-label, two-way crossover) to assess PK and iron utilization. These studies failed to show bioequivalence.[25] FDA approved the product, under 505(b)(2), on February 23, 1996, as Dexferrum® (iron dextran injection). It is not A-rated to INFed.[26]

Around this time, FDA began to see the development of a new wave of IV iron products. In 1999, FDA approved Ferrlecit for the treatment of iron deficiency anemia in adult patients and in pediatric patients age 6 years and older with chronic kidney disease receiving hemodialysis who are receiving supplemental epoetin therapy. In 2000, FDA approved Venofer for the treatment of iron deficiency anemia in patients with chronic kidney disease. These "second generation" parenteral iron products – Ferrlecit and Venofer – do not carry the black box warning for anaphylactic reactions that accompanies iron dextran. They do, however, contain a warning of serious hypersensitivity reactions seen in post-marketing reporting, including anaphylactic-type reactions, some of which have been life-threatening and fatal.

Feraheme was approved on June 30, 2009. Like Venofer and Ferrlecit, Feraheme carries a similar warning regarding hypersensitivity reactions:

> Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported in patients receiving Feraheme. Observe patients for signs and symptoms of hypersensitivity during and after Feraheme administration for at least 30 minutes and until clinically stable following completion of each administration. Only administer the drug when personnel and therapies are immediately available for the treatment of anaphylaxis and other hypersensitivity reactions. Anaphylactic type reactions

[24] Dexferrum Approval Package, Dexferrum Review of Pharmacokinetics and Iron Utilization Studies (Nov. 28, 1995) at 1, attached at Tab 7.

[25] *See id.*, Dexferrum Review of Pharmacokinetics and Iron Utilization Studies (Nov. 28, 1995) at 10 ("The confidence intervals do not fall within the limits of 80% to 125% for AUC_{0-t} or for $AUC_{0-inf.}$").

[26] Orange Book (33rd ed. 2013), Prescription Drug Product List, at 3-234.

> presenting with cardiac/cardiorespiratory arrest, clinically significant hypotension, syncope, and unresponsiveness have been reported in the post-marketing experience. In clinical studies, serious hypersensitivity reactions were reported in 0.2% (3/1,726) of subjects receiving Feraheme. Other adverse reactions potentially associated with hypersensitivity (e.g., pruritus, rash, urticaria or wheezing) were reported in 3.7% (63/1,726) of these subjects.[27]

On March 31, 2011, FDA approved Nulecit – a generic version of Ferrlecit – under an ANDA.[28] Nulecit is the only parenteral iron product approved under the ANDA review process. There are no other generic IV iron products approved in the United States.[29]

As discussed further below, this class of products raises difficult issues with regard to defining "sameness" of active ingredient and in ensuring the safety of generic entrants. Of particular concern is the potential for serious anaphylactic-type reactions. For highly complex and incompletely characterized molecular entities with this known risk, there is potential for follow-on products to exhibit a greater risk of anaphylaxis attributable to process-related, manufacturing-dependent changes in the molecule. Such changes can be anticipated where a complex nanoparticle iron product is manufactured by a new and unrelated manufacturer, without the innovator's historical experience with the product or access to the innovator's database of chemistry, manufacturing, and controls information. An obvious challenge exists with regard to mitigating this risk – at the preapproval stage – through the ANDA pathway, under which there are strict limits on the submission and review of new clinical safety and effectiveness data.

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[27] Feraheme Package Insert, 5.1 WARNINGS AND PRECAUTIONS, Hypersensitivity Reactions.

[28] A citizen petition was submitted on behalf of Watson Pharma, Inc., the sponsor of Ferrlecit, on February 13, 2004. FDA responded to the petition and approved the generic product on the same day. FDA Citizen Petition Response, Docket No. FDA-2004-P-0494 (Mar. 31, 2011). FDA granted the petition with respect to the request that the physicochemical characteristics of the generic product be the same as those of Ferrlecit, but denied it in all other material respects, including Watson's argument that it was not possible to fully characterize the active ingredient and therefore not possible to adjudicate a finding of "sameness;" that the generic product's manufacturing process would need to be "the same" as Ferrlecit's; and that clinical endpoint studies to show safety and efficacy would otherwise be required. *Id.* at 2-3.

[29] Unlike in Europe, there have not been any generic versions of Venofer approved in the United States. A citizen petition was submitted on behalf of Venofer's sponsor, Luitpold, on March 3, 2005, and remains pending. Citizen Petition, Docket No. FDA-2005-P-0319 (Mar. 3, 2005). The petition has been supplemented on five occasions, most recently on July 18, 2012. Among other things, Luitpold has requested that FDA refrain from approving any ANDA referencing Venofer unless the generic applicant can adequately demonstrate that the processes used to manufacture the finished generic product, as well as the API, are identical to the manufacturing processes used to manufacture Venofer, and that the physicochemical characteristics of the generic product, including its colloidal structure, are identical to Venofer.

2. EU Venofer

In the EU, a number of generic versions of Venofer have been approved. Post-market studies have confirmed that these products are not therapeutically equivalent. In the published studies and commentary, the generic iron sucrose products are often referred to as iron sucrose "similar" (ISS). Despite their complexity, however, they were approved as conventional generics based on pharmaceutical equivalence and comparative pharmacokinetics. These products are therefore considered interchangeable with one another and with the innovator product in accordance with EU and Member state law.

In one retrospective study, however, hemodialysis patients receiving the branded originator (or innovator) iron sucrose product, Venofer (IS_{ORIG}), were switched to an iron sucrose generic.[30] Although the hemodialysis patients had been stable with IS_{ORIG} treatment, switching to an ISS "was associated with significant reduction in [hemoglobin] level and reduced iron indices despite an increase in i.v. iron dose." The study concluded that "[t]he switch from the originator IS to an ISS preparation led to destabilization of a well-controlled population of [hemodialysis] patients" and that "[p]rospective comparative clinical studies are required to prove that ISS are as efficacious and safe as the originator i.v. [iron sucrose]."[31]

This study also hypothesized that clinical differences between the originator iron sucrose product and the generic iron sucrose arose because "the kinetics of iron dissociation differ between the two complexes, affecting the pattern of iron distribution and storage."[32] This hypothesis speaks directly to the need to characterize the pharmacokinetics and distribution of iron replacement IV products in target tissues and organs, beyond just measurements of the iron replacement IV products in serum or plasma.

Notably, for patients included in the above study, substitution of the innovator product for the generic was made automatically at the hospital pharmacy without physician or patient knowledge or consent. In a further study, three patients in one facility who had been stable on Venofer without complication for 3-12 months were switched to a generic iron sucrose product. Again, the patients were prescribed the innovator product, Venofer, and substitution was made automatically at the hospital pharmacy level.[33] Within one hour of infusion with generic product "all three patients experienced adverse events such as urticaria, headache, hypovolaemic

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[30] J. Rottembourg, *et al.*, *Do two intravenous iron sucrose preparations have the same efficacy*, Nephrol. Dial. Transplant. (2011) 26: 3262, 3263, attached at Tab 8.

[31] *Id.* at 3262.

[32] *Id.* at 3266.

[33] J. Stein, *et al.*, *Clinical case reports raise doubts about the therapeutic equivalence of an iron sucrose similar preparation with iron sucrose originator*, Curr. Med. Res. Opin. (2012) 28: 241, 241-42, attached at Tab 9.

dysregulation and peripheral oedema," and "[o]ne patient experienced severe hypovolaemic dysregulation, collapsed and was hospitalised for one day."[34]

Additional nonclinical studies in a rat model have also suggested that iron sucrose generics may lead to increased oxidative stress and inflammation relative to the originator iron sucrose preparation.[35] Even when one of the iron sucrose generics met the physicochemical reference values of iron sucrose, use of the iron sucrose generic resulted in an elevated level of oxidative stress, "demonstrating that similar physico-chemical properties do not ensure similar toxicological effects."[36] The study attributed these variations to possible differences in the manufacturing process between the two manufacturers, leading to subtle structural differences, and concluded that "the significant differences observed for most of the ISSs compared to the IS_{ORIG}, raise potential safety concerns on the interchangeability of these i.v. iron preparations and suggest that careful non-clinical and clinical evaluations of the safety and efficacy of ISSs should be performed before exposing vulnerable patients to potential additional sources of oxidative stress and inflammation."[37]

3. *EMA Reflection Paper*

Evidence from post-market studies on generic versions of Venofer and other similar studies led the EMA to recommend more stringent approval standards for generic iron-based nanoparticle medicinal products. Specifically, on March 17, 2011, the EMA's CHMP adopted a "Reflection paper on non-clinical studies for generic nanoparticle iron medicinal product applications," representing the "current thinking of the CHMP" on the type of non-clinical studies necessary to support generic approvals of nanoparticle iron medicinal products.[38]

Importantly, the CHMP concluded that measurement of generic nanoparticle iron medicinal product in plasma was insufficient to assess bioequivalence to the RLD. The CHMP arrived at this conclusion by discussing how the specific characteristics of nanoparticles distinguished them from small molecule drugs in ways that affect their pharmacokinetic profile and pattern of distribution within organs and tissues. For example, variations in "mean/median size," "size distribution," "the accuracy of methods employed for nano-sizing," and the "coat or core or both" of the nanoparticle were all cited as examples of characteristics that can impact nanoparticle distribution.[39]

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[34] *Id.* at 242.

[35] J. Toblli, *et al.*, *Comparison of Oxidative Stress and Inflammation Induced by Different Intravenous Iron Sucrose Similar Preparations in a Rat Model*, Inflammation & Allergy – Drug Targets (2012) 11: 66, 76, attached at Tab 10.

[36] *Id.*

[37] *Id.*

[38] EMA Reflection Paper, *supra* note 4.

[39] *Id.* at 3.

Variations in these nanoparticle characteristics between the generic and RLD are significant, because the resulting differences in the PK profile and pattern of distribution of the generic may adversely impact its safety and efficacy relative to the reference drug.

The EMA therefore concluded that "for iron-based nanoparticle medicinal products, physico-chemical characteristics comparison as well as pharmacokinetic measurements in humans based on plasma concentration may not be sufficient to ensure a comparable safety and efficacy between the reference product and the generic. . . . For the comparison of generic and reference [nanoparticle iron] medicinal products data on time dependent plasma levels alone are of limited value as they may conceivably fail to detect relevant differences in the tissue distribution of iron."[40]

The EMA Reflection Paper recommended the following comparative studies and assays be required for all generic nanoparticle IV iron products: (1) Fraction of free iron in the product and short term stability of the nanoparticles in plasma; (2) Uptake of the nanoparticles in the RES; (3) Degradation of the nanoparticles in the cells of the RES and release of iron from the RES; (4) Uptake of iron in pharmacological and toxicological target tissues after degradation of the nanoparticles; and (5) Direct uptake of the nanoparticles or partially-degraded nanoparticles in target tissues circumventing the RES.[41]

4. *Nulecit Post-Market Contract Studies*

On April 19, 2013, FDA took the highly unusual step of initiating the process to solicit a third-party contractor to conduct a rigorous three-year evaluation of whether the approved generic Ferrlecit product, Nulecit, is in fact therapeutically equivalent to Ferrlecit.[42] On July 16, 2013, FDA took the additional step of issuing a formal solicitation for such studies.[43] These studies are intended to "address potential concerns regarding the quality of generic iron complex

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[40] *Id.* at 3, 5.

[41] *Id.* at 4.

[42] FDA has used this process on a limited number of occasions where significant, or potentially significant, concerns exist regarding the therapeutic equivalence of an approved generic drug. For example, the same contract solicitation process was used to initiate post-market studies on generic bupropion 300 mg extended-release tablets. *See* FDA Update: Budeprion XL 300 mg Not Therapeutically Equivalent to Wellbutrin XL 300 mg (Oct. 3, 2012), http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm322161.htm. These studies ultimately confirmed that the generic product was not therapeutically equivalent to the RLD, causing it to be withdrawn from the market. *Id.* This in turn has led to a further Sources Sought Notice in order to solicit contract study to understand the scientific basis underlying the failure of the 300 mg bupropion tablets. Investigation of inequivalence of bupropion hydrochloride extended release tablets: in vitro metabolism quantification, Solicitation No. FDA-SS-1116086 (May 2, 2013), attached at Tab 11. *Available at* https://www.fbo.gov/spg/HHS/FDA/DCASC/FDA-SS-1116086/listing.html.

[43] Nulecit Contract Studies Solicitation, *supra* note 7.

products."[44] Directed at Nulecit for the obvious reason that it is the only approved generic parenteral iron product, the studies are critical to the class as a whole. This was made expressly clear by the Agency when it noted the following generally applicable concerns:

> There are a number of parenteral iron complex products available in North America: iron sucrose, sodium ferric gluconate, iron dextran, and ferumoxytol. All parenteral iron products are colloids comprising a continuous aqueous medium and particles of carbohydrate protected iron oxyhydroxide.
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> After intravenous administration, iron colloid particles are processed by phagocytes and iron ions are delivered to the lysosomes within the cell as part of the intracellular labile iron pool. The phagocyte uptake and biodistribution of iron complex particles depend upon their physicochemical properties. If iron is not needed immediately, it is stored in the form of ferritin or hemosiderin. When the iron is needed in the body, iron is released from the cell and transferrin binds iron ions and delivers them to their destination. If transferrin is oversaturated or if the iron complex product is so unstable that iron is spontaneously released at a rate that exceeds transferrin binding capacity, non-transferrin bound iron (NTBI) is formed in the plasma. NTBI can be toxic to cells as it acts as a catalyst in the formation of free radicals from reactive oxygen species.[45]

Further, referring directly to the EMA Reflection Paper, FDA states "that generic iron formulations could have higher levels of labile iron, leading to the formation of a greater amount of [NTBI] *in vivo* than the RLD that would potentiate oxidative stress and inflammation, then resulting in direct cellular damage and possibly increasing the risk of atherosclerotic disease."[46]

The Agency then states that its approval of Nulecit was based on an assumption that "physicochemical characterization tests including in-vitro labile iron determination would ensure comparable tissue distribution and no more in vivo labile iron leakage from generic formulations than that from RLD."[47] However, the Agency has apparently concluded that further studies are necessary in order to confirm, post-market, what the Agency had assumed premarket. Specifically, the contract studies are needed to investigate iron tissue distribution in animals and compare NTBI levels between brand and generic products in hemodialysis patients in order to confirm the adequacy of the Agency's approval criteria. In particular, FDA will require the contractor to perform three types of studies:

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[44] *Id.* at 2.

[45] *Id.* at 1.

[46] *Id.*; Nulecit Sources Sought Notice, *supra* note 6.

[47] Nulecit Contract Studies Solicitation, *supra* note 7, at 1.

(1) *In vitro* phagocytosis assays to compare RES uptake of RLD and generic.

(2) An evaluation of the time-dependent iron content in the major target organ (e.g., plasma, RES, target tissues) and a comparison of biodistribution of RLD and generic in appropriate animal models.

(3) A prospective, randomized, 2-way crossover study to compare plasma NTBI levels in hemodialysis patients treated with generic and RLD.

The Agency then instructs the contractor to "[c]onduct [s]tatistical analysis to determine whether there are any significant differences between generic and RLD in tasks 1-3 above."[48]

Regarding the prospective clinical study, FDA made clear that it will entail collecting the marketed brand and generic sodium ferric gluconate products and comparing them in terms of potency, impurity, and other drug product quality attributes. The contractor will then be required to develop bioanalytical methods to determine plasma NTBI, conduct the clinical trial, and evaluate and compare not only plasma NTBI, but also "the oxidative stress and toxicity caused by generic and RLD using in vitro and in vivo biomarkers;" the contractor must also "[m]onitor any side effects or adverse reactions during the study period."[49]

FDA indicated that it still has confidence in the validity of its current approval standards for this class of generic products based on equivalence in product characteristics and *in vivo* PK studies. Nulecit has not been withdrawn from the market and for now it retains its A rating to Ferrlecit. Indeed, subsequent to the publication of the Sources Sought Notice but just prior to the formal solicitation notice, as a signal of the Agency's current faith in the current approval standard, it issued a draft bioequivalence guidance for generic versions of Ferrlecit.[50] The new guidance accords with the standard described in the Draft Guidance for generic versions of Feraheme, and presumably with the standard used to approve Nulecit. Through its actions with regard to the Nulecit Post-Market Contract Studies, however, the Agency has now tacitly acknowledged that its generic approval standards for IV iron products may need to be more rigorous. For that reason, FDA is preparing to commission its own comprehensive set of studies – expected to take 3 years to complete – in order to confirm that generic Ferrlecit products are the same as the RLD.

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[48] *Id.* at 3.

[49] *Id.*

[50] Food and Drug Administration, Draft Guidance on Sodium Ferric Gluconate Complex (Jun. 2013), *available at* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm. FDA had not previously issued a product-specific bioequivalence recommendation for Ferrlecit.

C. Feraheme

Feraheme is the most recent nanoparticle IV iron to be approved by FDA. Feraheme's active ingredient, ferumoxytol, was developed as a "third generation" IV iron product, to address some of the clinical limitations of first and second generation IV iron products. These include: (1) the ability to safely administer larger doses and deliver the target therapeutic dose with fewer administrations; and (2) an increased PK half-life and distinct tissue distribution from previously approved active ingredients.

Ferumoxytol is a large and complex chemical entity, with a molecular weight greater than any FDA-approved nanoparticle-iron therapeutic product currently on the market. The apparent relative molecular weight of ferumoxytol is approximately 750 kDa, exceeding that of all other nanoparticle IV iron products including INFeD, Dexferrum, Ferrlecit, and Venofer.[51]

Notably, ferumoxytol is far larger than monoclonal antibodies (mAbs), which typically have a molecular weight of approximately 150 kDa. Yet for mAbs, methods of physicochemical characterization are relatively well-established. The primary structure of a mAb can be determined with precision, and the analytics for determining secondary, tertiary, and quaternary structure are well described. Ferumoxytol, by contrast, is much less well characterized. This leaves reproducibility of the structure very much a function of manufacturing processes and controls, with critical attention required with respect to starting materials and intermediates. The product is therefore intimately linked to the particular sponsor's manufacturing process.

While ferumoxytol has not been fully characterized, at the molecular level, ferumoxytol exhibits the properties of an extremely large chelating complex. Ferumoxytol is comprised of a carboxymethylated ligand (polyglucose sorbitol carboxymethylether (PSC)) bound to a ferric-ferrous-oxide substrate. Normally a chelating complex is characterized by the presence of two or more separate bindings between a polydentate (multiple bonded) ligand and a single central atom. Here, the complex is thought to comprise separate bindings between multiple polydentate ligands (PSC) and a multiply bonded, predominantly ferric-oxide core (the substrate). Accordingly, the chelating function in ferumoxytol is believed to be provided by the carboxymethyl groups which decorate the carbohydrate backbone of the PSC molecule. In this regard, PSC is thought to form an electronegative chelating-type agent relative to the ferric core, exhibiting a high number of metal-ligand coordination points. PSC therefore coordinates with the ferric substrate and forms a stable complex with multiple points of anchorage between the ligand and the core. The resulting active ingredient is a stable non-stoichiometric form of magnetite (superparamagnetic iron oxide) complexed with PSC. The overall colloidal particle size is about 29-49 nm in diameter. The estimated chemical formula of AMAG's ferumoxytol is

[51] Lewis J.M., *et al.*, *Comparison of Free Iron in Ferumoxytol with Other Iron Therapeutics*, Poster session presented at: American Society of Nephrology (ASN) Renal Week, November 2003, San Diego, CA, attached at Tab 12.

$Fe_{5874}O_{8752}C_{11719}H_{18682}O_{9933}Na_{414}$ with an apparent relative molecular weight of approximately 750 kDa.

Critically, however, the structure of ferumoxytol has not been fully elucidated. To a great extent the product remains incompletely characterized. The predominant barriers to characterizing the structure adequately relate directly to its size and complexity and to its particular chemical and physical properties. Instead, carefully controlled manufacturing conditions are essential to the proper formation of the total complex as well as both intermediates of the ferumoxytol complex, *i.e.*, its crystalline iron core and its carbohydrate coating.

The integration of the PSC component into the active ingredient isolates the bioactive iron of ferumoxytol from plasma until the complex enters the macrophages of the RES. In other words, the iron in ferumoxytol is not released, and does not become bioavailable, until the complex is resident within vesicles inside macrophage cells in the liver, spleen, and bone marrow, *i.e.*, the site of hematopoiesis (red blood cell generation). Once released intracellularly, ferumoxytol's iron then enters the intracellular storage iron pool (*e.g.*, ferritin) or is transferred to plasma transferrin for transport to erythroid precursor cells for incorporation into hemoglobin.

Ferumoxytol therefore remains intact until taken up by macrophages of the RES with little release of potentially toxic free iron. If the iron was released in the blood immediately after injection, severe adverse reactions would take place. Because free iron is toxic and causes oxidative stress, in normal iron metabolism the Fe atom is at all times sequestered within molecular complexes, *e.g.*, ferritin, hemoglobin, transferrin, ferroportin – all metal-ion binding protein complexes. Ferumoxytol exhibits this sequestering function, forming a stable complex with the ferric substrate to arrive intact at the target RES cells. However, present analytics cannot fully predict the stability of the complex after IV administration based on structural analysis alone. As detailed below, additional forms of testing are required to ensure that nanoparticle IV iron products such as ferumoxytol have their desired *in vivo* effects.

II. ARGUMENT

A. FDA Must Refrain From Approving Any More Generic IV Iron Products Until The Results Of The Nulecit Post-Market Studies Are Known

1. Greater certainty regarding the approval standards of generic IV iron products is necessary

Nanoparticle IV iron products belong to a growing class of non-biologic, complex drugs (NBCDs). A key concern with approving generic products in this class is that the active ingredients can be inordinately difficult to characterize. Furthermore, for many of these

products, important structural attributes may be linked to a particular manufacturer's manufacturing process and process controls, as is the case with many biologics.

Accordingly, there can be uncertainty about the degree of "sameness" of a generic copy of a product in this class (an issue that does not arise for less complex, small-molecule drugs, where "sameness" is based on straightforward chemical identity and is often self-evident). Nonetheless, FDA has asserted its authority to approve generic versions of drug products with increasingly complex active ingredients. For example, in July 2010, FDA approved a generic version of Lovenox (enoxaparin sodium), a highly complex, low molecular weight heparin.[52] In its citizen petition response regarding this decision, FDA appeared to affirm principles first laid out in 1998, when the Agency approved a generic version of Pergonal (menotropins) – a protein-based hormonal preparation approved under an NDA.[53] These decisions articulate a framework for approving generic versions of drugs even when the active ingredient has not been fully characterized.[54] "Complete chemical identification" and "complete characterization" are not required.[55] Rather, in these cases the Agency has approved a generic when the active ingredients can be "adequately characterized," and provide a sufficient basis upon which to adjudicate "sameness."[56]

The complexity of the reference drug's active ingredient does not relieve the generic applicant from proving that its product contains "the same" active ingredient. While FDA's decision to approve generic Lovenox indicates a willingness on the part of the Agency to approve a generic version of a drug that is not fully characterized, it must still be possible to "adequately characterize" the drug. "Adequate characterization" must include specific criteria for establishing the identity of the active ingredient and for establishing sameness and bioequivalence, taking into account the inherent complexity of the molecule and its mode of therapeutic action.

As exemplified by its approval of generic Lovenox, the relevant general questions underlying the Agency's capacity to approve a generic version of a non-biological, complex drug, are: (a) to what extent is physicochemical testing capable of characterizing the active ingredient; (b) to what extent are *in vitro* and *in vivo* assays available and capable of generating meaningful sameness and bioequivalence data such that therapeutic equivalence can be assured;

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[52] Orange Book (33rd ed. 2013), Prescription Drug Product List, at 3-152.

[53] *See* FDA Citizen Petition Response, Docket No. FDA-2003-P-0273 (Jul. 23, 2010) (the "Lovenox Petition Response"); FDA Citizen Petition Response, Docket No. FDA-1992-P-0029 (formerly Docket No. 92P-0487) (Jun. 17, 1997).

[54] Lovenox Petition Response at 2-3.

[55] *Id.* at 26, 45.

[56] *Id.* at 2-3.

(c) are additional clinical data required; and (d) does FDA have the authority to review such data within the confines of the ANDA review process?

Residual uncertainty about sameness and bioequivalence for NBCDs is a fundamentally important regulatory issue. Follow-on approval for this class of products is governed by the Hatch-Waxman amendments to the FDCA[57] enacted for small-molecule generics, and not the newer Biologics Price Competition and Innovation Act (BPCIA) that provides an abbreviated pathway for more complex follow-on biologics (or biosimilars).[58] The BPCIA contains an expectation that residual uncertainties in the identity of a biosimilar – in the closeness of match between the test and reference products – will be addressed with new clinical data.[59] For a generic drug approved under the FDCA, however, there is no such expectation. In fact, beyond what's required to show that two drugs are bioequivalent, new clinical data is generally not permitted.[60]

Furthermore, the approval of a generic entails a finding of therapeutic equivalence, meaning that the generic product can be substituted for the RLD. Under the BPCIA, there is no automatic finding of therapeutic equivalence or comparable safety. For a generic drug to be eligible for a rating of therapeutic equivalence (*i.e.*, an "A" rating), FDA must find that the generic product "can be substituted with the full expectation that the substituted product will produce the same clinical effect and safety profile as the prescribed product."[61] Physicians, pharmacists and the wider community consider an "A" rating to mean that a generic drug is fully substitutable for the RLD. In approving the ANDA and making a finding of therapeutic equivalence, the Agency must conclude that there are no differences between the RLD and the generic, or that such differences are so minor that they will not alter the safety or efficacy of the product in any way.[62]

As discussed in section I.B.2 above, these issues are immediate and non-theoretical. The generic iron sucrose products approved in the EU in some cases have resulted in severe adverse events on switching from the innovator product, Venofer, to the generic. These generic versions of Venofer are often referred to as "similars" in order to denote the complexity of the active

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[57] Drug Price Competition and Patent Term Restoration Act of 1984, Pub. L. No. 98-417, 98 Stat. 1585 (1984).

[58] Pub. L. No. 111-148, §§ 7001-7003 (2010).

[59] 42 USC 262(k)(2)(A)(i)(I)(cc).

[60] Other than what is required to show bioequivalence, new clinical data cannot be required in an ANDA. If new clinical investigations are required to independently establish the safety or effectiveness of the new product, or where labeling must be substantially changed to describe differences between the generic and the RLD, the ANDA approval pathway is not available. The applicant would instead need to submit a new drug application under 505(b) supported by original safety and efficacy studies to the extent required.

[61] Orange Book, Preface at vii.

[62] 21 CFR 314.94(a)(9)(ii).

ingredient and the problem of certainty regarding pharmaceutical equivalence. Nonetheless, despite their complexity, the products were approved as conventional generic drugs on the basis of pharmaceutical equivalence and comparative pharmacokinetics. Moreover, they were subject to automatic substitution at the hospital pharmacy level without physician or patient knowledge.

Public health, and the public's faith in the system for approving generic versions of these forms of complex drug products, demands a secure foundation for determining therapeutic equivalence for this class of products. Accordingly, FDA must not approve any further generic IV iron products until the results of the Nulecit Post-Market Studies are known.

2. *A reasonable moratorium on further approval of generic IV irons is required*

Uncertainty regarding pharmaceutical equivalence or bioequivalence for a complex drug product approved under an ANDA is a critical regulatory issue. All new drugs approved by FDA require a finding of safety and efficacy. Although the approval criteria for generic drugs are different than for new drugs, generic drug products must also be safe and effective for their intended uses. Where the RLD is particularly complex and where there is controversy surrounding how to characterize the active ingredient and what kinds of data would suffice to show bioequivalence, the ANDA approval pathway comes under strain – particularly so when there are safety issues relating to the complexity of the active ingredient and to its manufacture.

There is currently a question mark over FDA's approval standards for generic versions of nanoparticle IV iron products. It is unclear whether physicochemical characterization of the active ingredient and conventional PK analysis provide a sufficient basis to determine that a generic IV iron product is "the same as" and bioequivalent to the RLD.

FDA has limited experience approving generic versions of complex IV iron products. And, as illustrated by the EU experience with this class of products, current standards and regulatory science based around physicochemical characterization and pharmacokinetics may not be able to assure therapeutic equivalence.

Through its action regarding Nulecit – in formally soliciting post-market contract studies – FDA has tacitly acknowledged this controversy. Driven by the EU experience with generic versions of Venofer and the EMA's Reflection Paper on generic nanoparticle iron, FDA took the extraordinary measure of initiating the process to solicit a three year study program intended to confirm that Nulecit – approved on the basis of physicochemical characterization and PK studies – is in fact therapeutically equivalent to Ferrlecit. In the Nulecit Sources Sought Notice as it was originally published, FDA expressly stated that "[t]he approval standards for generic iron

complex products ***have been controversial***."[63] Though FDA later amended the Sources Sought Notice by removing this particular phrase, the acknowledgement of the controversy remains implicit in the final version and in the Nulecit Contract Studies Solicitation. Although it removed terms such as "controversy" and "controversial," FDA expressly acknowledged the finding of the EMA "that generic iron formulations could have higher levels of labile iron," which could potentially lead to "direct cellular damage ... possibly increasing the risk of atherosclerotic disease."[64]

This is a real and non-theoretical public health issue. Because of the acute safety concerns associated with these products, FDA must not approve any more ANDAs for nanoparticle IV iron products – including ferumoxytol – until the controversy is resolved. Namely, FDA must await the results of the Nulecit Post-Market Studies. Until those studies have been completed and have validated FDA's assumptions regarding the therapeutic equivalence of two IV iron products based on physicochemical characterization and pharmacokinetics, a reasonable moratorium on further approvals based on those assumptions is required. Such a measure is not only reasonable, it is necessary in order to protect public health and the public's confidence in the generic drug approval process.

B. FDA Must Not Approve An ANDA For A Generic Version Of Feraheme Without Adequate Proof Of Bioequivalence And Equivalent Safety

1. ANDAs for generic ferumoxytol must include data showing bioequivalence from clinical endpoint studies in hemodialysis patients

As detailed in AMAG's comments on the December 2012 Draft Guidance providing bioequivalence recommendations for generic versions of ferumoxytol, we do not believe that the Guidance provides sufficiently rigorous standards for ANDA approval.[65] AMAG does agree with the Agency that the assays and studies described in the Draft Guidance should be included

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[63] The original version of the Nulecit Sources Sought Notice is attached at Tab 13, *available at* https://www.fbo.gov/spg/HHS/FDA/DCASC/FDA-SS-1116099/listing.html (emphasis added). The original synopsis was published at 11:13 AM on April 19, 2013. The modified version was published at 12:06 PM the same day. Both versions remain available on the Federal Business Opportunities website.

[64] Nulecit Contract Studies Solicitation, *supra* note 7, at 1.

[65] In its recommendation for establishing "sameness in physicochemical properties" between generic ferumoxytol and Feraheme, the Draft Guidance lists five types of assessments that should be included in the characterization: (1) iron core characterizations including but not limited to core size determination, iron oxide crystalline structure and iron environment; (2) composition of carbohydrate shell; (3) magnetic properties; (4) particle morphology; and (5) labile iron determination under physiologically relevant conditions. The Draft Guidance also provides for a polydispersity match for particle size distribution and for a qualitative and quantitative evaluation of the "stoichiometric ratios of polyglucose sorbitol carboxymethylether, iron, and other relevant components." For *in vivo* bioequivalence, it recommends PK measurements of ferumoxytol-associated iron in plasma or serum, and that data be collected on transferrin-bound iron in serum.

in all ANDAs for proposed generic ferumoxytol products. But while necessary, these studies are not in themselves sufficient, particularly in reference to aspects of the product that may affect clinical safety.

As reported in the literature[66] and as recognized by the EMA,[67] measurement of nanoparticle IV iron products in plasma or serum is an insufficient means of measuring bioavailability for these products due to the inability of these measurements to detect differences in iron distribution in tissues and organs. Uncertainty regarding this sufficiency is implicitly acknowledged by FDA in the Nulecit Contract Studies Solicitation. Accordingly, post-market studies are now being planned to determine whether the active ingredient is localized to the target tissue to the same rate and extent as the innovator product.

There is no clear evidence that ferumoxytol-associated iron in plasma or serum correlates with bioavailability at the site of action in the cells of the RES.[68] Likewise, measurement of transferrin-bound iron in serum is problematic because of the inability to differentiate between endogenous transferrin-bound iron and the ferumoxytol fraction. Moreover, transferrin-bound iron does not correlate with bioavailability at the site of drug action. While more direct measurement of the uptake of ferumoxytol by the target tissues of the RES provides important evidence, AMAG does not believe that these data provide a sufficient basis upon which to make a finding of bioequivalence.

Given the complex issues regarding pharmaceutical equivalence as applied to ferumoxytol, and given the complex way it is taken up and compartmentalized within the target tissues, a clinical endpoint study to demonstrate bioequivalence must be required. Until there is reasonable scientific consensus that pharmaceutical equivalence and comparable pharmacokinetics provide an adequate basis for approval of ANDAs for complex nanoparticle IV iron products – a condition currently lacking because the Nulecit Post-Market Studies have not been completed – comparative evaluation of safety and effectiveness provides the most reliable

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[66] *See* Stein *et al.*, *supra* note 33, at 241-42; Toblli *et al.*, *supra* note 35, at 76; Rottembourg *et al.*, *supra* note 30, at 3262; J. Toblli, *et al.*, *Differences Between Original Intravenous Iron Sucrose and Iron Sucrose Similar Preparations*, Arzneimittelforschung (2009) 59: 176, 189, attached at Tab 14.

[67] EMA Reflection Paper, *supra* note 4, at 3, 5.

[68] The Draft Guidance recommended that bioequivalence be based on ferumoxytol-associated iron in plasma or serum. Scientific consensus, however, is that measurement of IV iron products such as ferumoxytol in plasma or serum is not an accurate means of establishing the bioavailability of these products at the site of drug action in the target tissue of the RES. While FDA has included in the Draft Guidance a recommendation that data should also be collected on transferrin-bound iron in serum, transferrin-bound iron is not an appropriate or reliable biomarker for either the pharmacokinetics or pharmacodynamics of ferumoxytol. Assays measuring transferrin-bound iron in serum cannot differentiate between endogenous transferrin-bound iron and the ferumoxytol fraction. Moreover, transferrin-bound iron does not correlate with bioavailability at the site of drug action. Accordingly, it cannot provide meaningful data regarding the bioequivalence or therapeutic equivalence of two different ferumoxytol products.

means of assessing the bioequivalence of ferumoxytol. Specifically, an evaluation of hematologic response, safety, and effectiveness is – at present – the only reliable surrogate for the rate and extent of absorption of ferumoxytol, and its availability at the site of drug action.

A clinical bioequivalence study with safety and effectiveness endpoints is further warranted because of the particular safety concerns that are associated with this class of drugs. As discussed above, this class of products raises difficult issues with regard to defining "sameness" of active ingredient and in making a finding of therapeutic equivalence. Of particular concern in this respect is the potential risk of immunogenicity present with this class of drugs. Serious hypersensitivity reactions, including anaphylactic-type reactions, some of which have been life-threatening and fatal, have been reported with IV iron products. Ferumoxytol carries highlighted warnings of this rare but serious potential adverse event. For highly complex and incompletely characterized molecular entities with known risk of anaphylaxis, there is potential for follow-on products to exhibit a greater risk of anaphylaxis attributable to alterations in the molecule. Such alterations must be anticipated where the product is manufactured by an unrelated manufacturer, without access to the innovator's chemistry, manufacturing, and controls data. Moreover, these alterations may not be susceptible to physicochemical characterization.

AMAG's request is entirely consistent with FDA's treatment of other products with potential safety and/or tolerability issues.[69] As the Agency has often recognized, it is proper for a generic manufacturer to be required to address the safety of its product. FDA must ensure that all drug products marketed in the United States are safe and effective. A generic drug product is not relieved of this requirement. While the Hatch-Waxman Act created an abbreviated approval pathway for generic drug products, this did not alter (and FDA remains bound by) the fundamental purpose underlying the FDCA: to ensure that all drug products marketed in the United States are safe and effective. FDA must require ANDA applicants to establish that the proposed generic will have "the same . . . safety profile" as the reference product in all respects.[70]

For example, if the proposed generic product includes a different inactive ingredient, the Agency must conclude that the different inactive ingredient will not alter the safety or efficacy of the product.[71] Similarly, to the extent the manufacturing process or other factors may affect the safety or effectiveness of the product, these must be evaluated. A generic product, like

[69] For example, the bioequivalence recommendation for terconazole vaginal suppository includes a requirement for a clinical endpoint bioequivalence study with detailed instructions, including reporting requirements for adverse events (AEs): "[t]he report of AEs should include date of onset, description of the AE, and date of resolution. This information is needed to determine if the incidence and severity of adverse reactions is different between the test product and RLD." FDA Draft Guidance on Terconazole (Jun. 2010), http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM199677.pdf.

[70] Orange Book, Preface at vii.

[71] 21 CFR 314.94(a)(9)(ii).

the innovator product, must be safe and effective as labeled, and not misbranded or adulterated.[72] Within limits the Agency has recognized it is proper for a generic manufacturer to be required to address these issues independently.[73]

For many systemically acting drugs, *in vivo* bioequivalence studies provide an adequate demonstration to ensure "the same . . . safety profile."[74] This is because for most systemically acting drugs, safety and tolerability are based on, or originate with, the concentration of the active drug substance (or a relevant metabolite) in systemic circulation. Accordingly, a systemic pharmacokinetic assay can usually ensure the same safety profile. For Feraheme, however, this is not the case. Because of the uncertainty regarding therapeutic equivalence based on physicochemical characterization and PK studies, and the acute safety concerns relating to potential for anaphylactic-type reactions, a more extensive clinical evaluation is required.

Thus, FDA must refrain from approving any ANDA referencing Feraheme that does not include a comparative clinical trial with safety and effectiveness endpoints for purposes of demonstrating bioequivalence. Specifically, as detailed in AMAG's comments on the Draft Guidance, this would be a single-dose, randomized, *in vivo* study in adult patients with chronic kidney disease suffering from iron deficiency anemia. The study should evaluate total hematologic response (hemoglobin, ferritin, iron, and transferrin saturation). It should also include a systematic comparative evaluation of incidence and severity of adverse reactions.

2. *ANDAs for generic ferumoxytol must contain data showing equivalence in phagocytic uptake, biodistribution, and plasma NTBI*

Because of the uncertainty regarding the ability of physicochemical characterization and conventional bioequivalence studies to be relied on in support of IV iron products, AMAG requests that sponsors of ANDAs for generic ferumoxytol products should be required to conduct clinical endpoint bioequivalence studies. Similarly, FDA must not approve any generic versions of Feraheme unless the ANDA includes the additional forms of data described in FDA's notices for the Nulecit Post-Market Contract Studies.

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[72] 21 USC 355(d); 21 USC 355(j)(2), (4); 21 USC 331(a); 21 USC 352.

[73] FDA has broad authority to request test results from an ANDA sponsor in order to assess the manufacture, processing and packing of the drug product as these may affect the quality and purity of the product. *See* 21 USC 355(j)(4); 21 CFR 314.127(a)(1); *sanofi-aventis v. FDA et al.*, 842 F. Supp. 2d 195, 207-11 (D.D.C. 2012). *See also Serono Laboratories, Inc. v. Shalala*, 158 F.3d 1313 (D.C. Cir. 1998) (the Agency has broad discretion to determine the kinds of data it needs to make the expert assessment it is entrusted to make); *sanofi-aventis*, 842 F. Supp. 2d at 203, 204.

[74] Orange Book at vii.

All products within this class of drugs are structurally and compositionally complex. Aspects of this complexity are related to specific, proprietary manufacturing processes. Additionally, the degree to which clinical "sameness" can be assumed based on physicochemical characterization and conventional bioequivalence data is not well understood. FDA's action with regard to Nulecit is a case in point. Additional clinical and preclinical data must therefore be required.

In addition to containing all of the other data required under section 505(j) of the FDCA, ANDAs referencing Feraheme must include the following comparative studies: (1) *in vitro* phagocytosis assays to compare RES uptake; (2) an evaluation of the time-dependent iron content in the major target organ (*e.g.*, plasma, RES, target tissues) and comparison of biodistribution in appropriate animal models; and (3) a prospective, randomized, 2-way crossover study to compare plasma NTBI levels in hemodialysis patients.

Because FDA has initiated the process for requesting these post-approval studies to confirm that Nulecit is, in fact, equivalent to Ferrlecit, FDA should take a consistent approach with this class of drugs and require exactly the same type of studies in support of proposed generic ferumoxytol products.

A key requirement, however, is that these studies must be completed as a condition of ANDA approval and not *post-hoc*. An important consideration regarding this requested action is therefore whether such studies can be required for ANDA approval. In the preamble to the regulations implementing 505(j), FDA stated that "[t]he ANDA applicant relies on a prior agency finding of safety and effectiveness based on the evidence presented in a previously approved new drug application. If investigations on a drug's safety or effectiveness are necessary for approval, an ANDA is not permitted."[75]

AMAG recognizes that in granting summary judgment in favor of the government in litigation following FDA's approval of a generic version of Lovenox, the district court held that FDA has reasonably broad discretion to request that an ANDA include study data, including non-clinical immunogenicity assays, to ensure the quality and purity of its product.[76] Nonetheless, a clinical study designed to address, *de novo*, a core issue of safety and effectiveness, goes well beyond the limited nonclinical studies that were the subject of that case.

Furthermore, even if FDA permits ANDA applicants to demonstrate bioequivalence by using the clinical endpoint bioequivalence study described in the previous section, and the

[75] 57 Fed. Reg. 17950, 17953 (April 28, 1992).

[76] *Sanofi-aventis v. FDA et al.*, 842 F. Supp. 2d 195, 207-11 (D.D.C. 2012); see also Government Memorandum in Opposition to Preliminary Injunction at 11-12 ("Sandoz provided data to satisfy CDER's concerns about the potential for impurities to affect immunogenicity. . . . FDA did not require clinical testing.")

Nulecit post-market study criteria proposed above, it still may be necessary for generic sponsors to take additional steps to ensure that their products are as safe as Feraheme. The only way to demonstrate that a generic ferumoxytol product does not pose a greater risk of serious hypersensitivity reactions than Feraheme may be through an adequately powered clinical investigation designed specifically to evaluate relative immunological risk, and to establish the risk of switching from one product to the other. And if new clinical investigations are required to independently establish the safety and effectiveness of a generic ferumoxytol product, the applicant would need to submit a 505(b)(2) NDA.

III. CONCLUSION

A growing body of evidence from the scientific literature and clinical experience with iron sucrose products in the EU supports the need for a more rigorous assessment of generic ferumoxytol. If a generic ferumoxytol product is not adequately characterized and shown to be both pharmaceutically equivalent and bioequivalent to the RLD, patients may receive a product that is less safe and effective than Feraheme itself. For these reasons, AMAG respectfully requests that FDA refrain from approving any ANDAs referencing Feraheme without first taking the action requested above.

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ENVIRONMENTAL IMPACT

The actions requested in this petition are subject to categorical exclusion under 21 CFR 25.31.

ECONOMIC IMPACT

Information on the economic impact of this proposal will be submitted upon request of the Commissioner.

CERTIFICATION

I certify that, to my 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) I have taken reasonable steps to ensure that any representative data and/or information which are unfavorable to the petition were disclosed to me. I further certify that the information upon which I 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: April 19, 2013. If I received or expect to receive payments, including cash and other forms of consideration, to file this information or its contents, I received or expect to receive those payments from the following persons or organizations: None, other than my compensation as an employee of AMAG. I verify under penalty of perjury that the foregoing is true and correct as of the date of the submission of this petition.[77]

Respectfully submitted,

Steve Caffé, M.D.
Chief Development & Regulatory Officer

Enclosures

Cc: Kathleen Uhl, M.D.
Acting Director, Office of Generic Drugs

[77] AMAG is not aware of any ANDA or 505(b)(2) applications referencing Feraheme that are pending before FDA. Accordingly, this petition is not subject to section 505(q) of the FDCA. However, in accordance with FDA guidance, AMAG is including with this petition the certification described under section 505(q). *See* 21 USC 355(q)(1)(H); Guidance for Industry, Citizen Petitions and Petitions for Stay of Action Subject to Section 505(q) of the Federal Food, Drug, and Cosmetic Act (Jun. 2011). Consistent with the statute, this petition cannot be subject to 505(q) unless there is an ANDA or 505(b)(2) application that references Feraheme pending before the Agency as of the date of submission of this petition.