

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-180

**ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS**

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/10
See OMB Statement on Page 3.

**PATENT INFORMATION SUBMITTED UPON AND
AFTER APPROVAL OF AN NDA OR SUPPLEMENT**

**For Each Patent That Claims a Drug Substance
(Active Ingredient), Drug Product (Formulation or
Composition) and/or Method of Use**

NDA NUMBER

22-180

NAME OF APPLICANT/NDA HOLDER

AMAG Pharmaceuticals, Inc.

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME

Feraheme (TM)

ACTIVE INGREDIENT(S)

ferumoxytol

STRENGTH(S)

30 milligrams of iron per milliliter

DOSAGE FORM

Injectable

APPROVAL DATE OF NDA OR SUPPLEMENT

30 June 2009

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) within thirty (30) days after approval of an NDA or supplement or within thirty (30) days of issuance of a patent as required by 21 CFR 314.53(c)(2)(ii) at the address provided in 21 CFR 314.53(d)(4). To expedite review of this patent declaration form, you may submit an additional copy of this declaration form to the Center for Drug Evaluation and Research "Orange Book" staff.

For hand-written or typewriter versions of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

7553479

b. Issue Date of Patent

6/30/2009

c. Expiration Date of Patent

3/8/2020 (extendable)

d. Name of Patent Owner

AMAG Pharmaceuticals, Inc. (formerly known as
Advanced Magnetics, Inc.)

Address (of Patent Owner)

100 Hayden Avenue

City/State

Lexington, MA

ZIP Code

02421

FAX Number (if available)

(617) 499-3362

Telephone Number

(617) 498-3300

E-Mail Address (if available)

ifarmer@amaenharma.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

Address (of agent or representative named in 1.e.)

City/State

ZIP Code

FAX Number (if available)

Telephone Number

E-Mail Address (if available)

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

No

For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
N/A

2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

2.7 If the patent referenced in 2.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
- the answer to 2.2 is "Yes" and the answer to 2.3 is "No," or,
- the answer to 2.3 is "Yes" and there is no response to 2.4, or,
- the answer to 2.5 or 2.6 is "Yes."
- the answer to 2.7 is "No."

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.37? Yes No

3.2 Does the patent claim only an intermediate? Yes No

3.3 If the patent referenced in 3.1 is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.) Yes No

FDA will not list the patent in the Orange Book as claiming the drug product if:

- the answer to question 3.1 is "No," or,
- the answer to question 3.2 is "Yes," or,
- the answer to question 3.3 is "No."

4. Method of Use

Sponsors must submit the information in section 4 for each approved method of using the approved drug product claimed by the patent. For each approved method of use claimed by the patent, provide the following information:

4.1 Does the patent claim one or more approved methods of using the approved drug product? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product? Yes No

4.2a If the answer to 4.2 is "Yes," identify the use with specific reference to the approved labeling for the drug product. Use: (Submit indication or method of use information as identified specifically in the approved labeling.)

4.2b If the answer to 4.2 is "Yes," also provide the information on the indication or method of use for the Orange Book "Use Code" description.

Use: (Submit the description of the approved indication or method of use that you propose FDA include as the "Use Code" in the Orange Book, using no more than 240 total characters including spaces.)

FDA will not list the patent in the Orange Book as claiming the method of use if:

- the answer to question 4.1 or 4.2 is "No," or
- If the answer to 4.2 is "Yes" and the information requested in 4.2a and 4.2b is not provided in full.

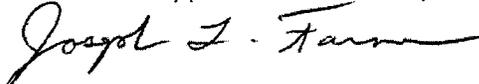
5. No Relevant Patents

For this NDA or supplement, there are no relevant patents that claim the approved drug substance (active ingredient) or the approved drug product (formulation or composition) or approved method(s) of use with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product. Yes

6. Declaration Certification

6.1 *The undersigned declares that this is an accurate and complete submission of patent information for the NDA or supplement approved under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.*

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (Attorney, Agent, Representative or other Authorized Official) (Provide Information below)	Date Signed
	07/20/2009

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Joseph L. Farmer	
Address c/o AMAG Pharmaceuticals, Inc. 100 Hayden Avenue	City/State Lexington, MA
ZIP Code 02421	Telephone Number (617)498-3320
FAX Number (if available) (617)499-3362	E-Mail Address (if available) jfarmer@amagpharma.com

The public reporting burden for this collection of information has been estimated to average 5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

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Feraheme (TM)

ACTIVE INGREDIENT(S)

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30 milligrams of iron per milliliter

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APPROVAL DATE OF NDA OR SUPPLEMENT

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For each patent submitted for the approved NDA or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this NDA or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number

6599498

b. Issue Date of Patent

7/29/2003

c. Expiration Date of Patent

3/8/2020 (extendable)

d. Name of Patent Owner

AMAG Pharmaceuticals, Inc. (formerly known as
Advanced Magnetics, Inc.)

Address (of Patent Owner)

100 Hayden Avenue

City/State

Lexington, MA

ZIP Code

02421

FAX Number (if available)

(617) 499-3362

Telephone Number

(617) 498-3300

E-Mail Address (if available)

jfarmer@amagpharma.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

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f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?

Yes

No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?

Yes

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For the patent referenced above, provide the following information on each patent that claims the drug substance, drug product, or method of use that is the subject of the approved NDA or supplement. FDA will not list patent information if you file an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing. FDA will consider an incomplete patent declaration to be a declaration that does not include a response to all the questions contained within each section below applicable to the patent referenced above.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the approved NDA or supplement? Yes No

2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA? Yes No

2.3 If the answer to question 2.2 is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b). Yes No

2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in 2.3.
N/A

2.5 Does the patent claim only a metabolite of the approved active ingredient? (Complete the information in section 4 below if the patent claims an approved method of using the approved drug product to administer the metabolite.) Yes No

2.6 Does the patent claim only an intermediate? Yes No

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Patent also includes direct product claims.

FDA will not list the patent in the Orange Book as claiming the drug substance if:

- the answers to 2.1 and 2.2 are "No," or,
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- the answer to 2.7 is "No."

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the approved drug product as defined in 21 CFR 314.3? Yes No

3.2 Does the patent claim only an intermediate? Yes No

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Patent also includes direct product claims.

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4. Method of Use

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4.1 Does the patent claim one or more approved methods of using the approved drug product? Yes No

4.2 Patent Claim Number(s) (as listed in the patent) Does (Do) the patent claim(s) referenced in 4.2 claim an approved method of use of the approved drug product? Yes No

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Joseph L. Farmer Date Signed
07/20/2009

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Check applicable box and provide information below.

<input checked="" type="checkbox"/> NDA Applicant/Holder	<input type="checkbox"/> NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
<input type="checkbox"/> Patent Owner	<input type="checkbox"/> Patent Owner's Attorney, Agent (Representative) or Other Authorized Official
Name Joseph L. Farmer	
Address c/o AMAG Pharmaceuticals, Inc. 100 Hayden Avenue	City/State Lexington, MA
ZIP Code 02421	Telephone Number (617)498-3320
FAX Number (if available) (617)499-3362	E-Mail Address (if available) jfarmer@amagpharma.com

The public reporting burden for this collection of information has been estimated to average 5 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
Office of Chief Information Officer (HFA-710)
5600 Fishers Lane
Rockville, MD 20857

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

EXCLUSIVITY SUMMARY

NDA # 22-180

SUPPL # N/A

HFD # 160

Trade Name Feraheme

Generic Name Ferumoxytol

Applicant Name AMAG Pharmaceuticals, Inc.

Approval Date, If Known pending

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3, SE4, SE5, SE6, SE7, SE8

505(b)(1)

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

N/A

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years

e) Has pediatric exclusivity been granted for this Active Moiety?

YES NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# 20-416

Feridex I.V.

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)
IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of

summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

- (c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Study 62,745-5 "A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in Hemodialysis Patients who are Receiving Supplemental Erythropoietin Therapy"

Study 62,745-6 "A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in chronic kidney disease patients not on dialysis"

Study 62,745-7 "A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in chronic kidney disease patients not on dialysis"

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1

YES

NO

Investigation #2

YES

NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

same as #2(c)

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1 !
IND # 62,745 YES ! NO
! Explain:

Investigation #2 !
IND # 62,745 YES ! NO
! Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not

identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1
!
!
YES ! NO
Explain: ! Explain:

Investigation #2
!
!
YES ! NO
Explain: ! Explain:

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

Name of person completing form: Hyon-Zu Lee
Title: Project Manager
Date: June 9, 2009

Name of Office/Division Director signing form: Rafel Dwaine Rieves, M.D.
Title: Division Director

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Rafel Rieves

6/12/2009 12:58:46 PM

PEDIATRIC PAGE
(Complete for all filed original applications and efficacy supplements)

NDA/BLA#: 22-180 Supplement Number: N/A NDA Supplement Type (e.g. SE5): N/A

Division Name: Division of Medical Imaging and Hematology Products (DMIHP) PDUFA Goal Date: 10/19/08 Stamp Date: 12/19/2007

Proprietary Name: Feraheme

Established/Generic Name: ferumoxytol

Dosage Form: Injection

Applicant/Sponsor: AMAG Pharmaceuticals, Inc.

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):

- (1) _____
- (2) _____
- (3) _____
- (4) _____

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): 1

(Attach a completed Pediatric Page for each indication in current application.)

Indication: Treatment of iron deficiency anemia in patient with Chronic Kidney Disease

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
- No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
- Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)
- (Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
- Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input checked="" type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. 1 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/>	Other	__ yr. 1 mo.	1 yr. 11 mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdcrpmhs@fda.hhs.gov) OR AT 301-796-0700.

pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> Other	2 yr. __ mo.	2 yr. __ mo.	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____						

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: N/A

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population	minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	_____ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population	minimum	maximum
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	_____

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpmhs@fda.hhs.gov) OR AT 301-796-0700.

pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:					
Population		minimum	maximum	Extrapolated from:	
				Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	_____	<input type="checkbox"/>	<input type="checkbox"/>

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

(Revised: 6/2008)

NOTE: If you have no other indications for this application, you may delete the attachments from this document.

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: _____

Q1: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
- No. Please proceed to the next question.

Q2: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
- No: Please check all that apply:
 - Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 - Deferred for some or all pediatric subpopulations (Complete Sections C)
 - Completed for some or all pediatric subpopulations (Complete Sections D)
 - Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 - Extrapolation in One or More Pediatric Age Groups (Complete Section F)

(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: **(check, and attach a brief justification for the reason(s) selected)**

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):
 Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit [*]	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

* Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (Note: if studies are partially waived on this ground, this information must be included in the labeling.)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.)

Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Section C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so,

proceed to Section F).. Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for some or all pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
Population	minimum	maximum	Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	_____	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____						

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

† Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	_____	Yes <input type="checkbox"/>	No <input type="checkbox"/>

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	_____

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or existing appropriate labeling, this Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	_____	<input type="checkbox"/>	<input type="checkbox"/>

b(4)

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

{See appended electronic signature page}

Regulatory Project Manager

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE PEDIATRIC AND MATERNAL HEALTH STAFF at 301-796-0700

(Revised: 6/2008)

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cdcrpmhs@fda.hhs.gov) OR AT 301-796-0700.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Hyon Z Lee
6/23/2009 11:04:37 AM

1.3.3 DEBARMENT CERTIFICATION

AMAG Pharmaceuticals, Inc., hereby certifies that it did not and will not use, in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this New Drug application (NDA 22-180) for ferumoxytol injection.



Terri Clark
Vice President, Clinical Operations
AMAG Pharmaceuticals, Inc.

Oct 02, 2007
Date

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION ¹		
NDA # 22-180 BLA #	NDA Supplement # N/A BLA STN #	If NDA, Efficacy Supplement Type: N/A
Proprietary Name: Feraheme Established/Proper Name: ferumoxytol Dosage Form: Injection		Applicant: AMAG Pharmaceuticals, Inc. Agent for Applicant (if applicable): N/A
RPM: Hyon-Zu Lee, Pharm.D.		Division: HFD-160
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p> <p>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</p>
❖ User Fee Goal Date Action Goal Date (if different)		June 29, 2009 June 30, 2009
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions (specify type and date for each action taken)		<input type="checkbox"/> None CR (Oct. 17, 2008, Dec. 22, 2008)
❖ Promotional Materials (accelerated approvals only) Note: If accelerated approval (21 CFR 314.510/601.41), promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see guidance www.fda.gov/cder/guidance/2197dft.pdf). If not submitted, explain _____		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

❖ Application ² Characteristics	
Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only): 2 <input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies <input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC Comments: _____	
❖ Date reviewed by PeRC (<i>required for approvals only</i>) If PeRC review not necessary, explain: _____	December 17, 2008
❖ BLAs only: <i>RMS-BLA Product Information Sheet for TBP</i> has been completed and forwarded to OBPS/DRM (<i>approvals only</i>)	<input type="checkbox"/> Yes, date
❖ BLAs only: is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No
❖ Public communications (<i>approvals only</i>)	
• Office of Executive Programs (OEP) liaison has been notified of action	X Yes No
• Press Office notified of action (by OEP)	X Yes No
• Indicate what types (if any) of information dissemination are anticipated	<input type="checkbox"/> None <input type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input type="checkbox"/> CDER Q&As <input checked="" type="checkbox"/> Other : burst

² All questions in all sections pertain to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	X No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	X No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	X No <input type="checkbox"/> Yes If yes, NDA # and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	X Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification?

Yes No

(Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If "Yes," skip to question (4) below. If "No," continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If "No," continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If "Yes," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If "No," continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
CONTENTS OF ACTION PACKAGE	
❖ Copy of this Action Package Checklist ³	Included
Officer/Employee List	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	X Included
Documentation of consent/non-consent by officers/employees	X Included
Action Letters	
❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Action(s) and date(s) CR: October 17, 2008 CR: December 22, 2008, AP: June 30, 2009
Labeling	
❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	June 18, 2009
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	December 17, 2007
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Medication Guide/Patient Package Insert/Instructions for Use (<i>write submission/communication date at upper right of first page of each piece</i>)	<input type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use X None

³ Fill in blanks with dates of reviews, letters, etc.
Version: 9/5/08

<ul style="list-style-type: none"> • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) 	N/A
<ul style="list-style-type: none"> • Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version) 	N/A
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	N/A
<ul style="list-style-type: none"> • Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable 	N/A
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date at upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> • Most-recent division proposal for (only if generated after latest applicant submission) 	
<ul style="list-style-type: none"> • Most recent applicant-proposed labeling 	June 16, 2009
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	X RPM September 10, 2008 X DMEDP March 4, 2009, June 12, 2009, June 18, 2009 X DRISK September 23, 2008 X DDMAC September 12, 2008 <input type="checkbox"/> CSS X Other reviews DMIHP: June 19, 2008 MHT: September 18, 2008
❖ Proprietary Name <ul style="list-style-type: none"> • Review(s) (<i>indicate date(s)</i>) • Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) 	Reviews: May 9, 2008, September 23, 2008, December 17, 2008, June 9, 2009, Letter: September 18, 2008, email: December 17, 2008
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	RPM (June 2, 2008), Clin Pharm (Feb. 19, 2008), CMC (Jan. 18, 2008)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	X Included
❖ Application Integrity Policy (AIP) Status and Related Documents www.fda.gov/ora/compliance_ref/aip_page.html	
<ul style="list-style-type: none"> • Applicant in on the AIP 	<input type="checkbox"/> Yes X No
<ul style="list-style-type: none"> • This application is on the AIP <ul style="list-style-type: none"> ○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>) ○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes X No <input type="checkbox"/> Not an AP action
❖ Pediatric Page (<i>approvals only, must be reviewed by PERC before finalized</i>)	X Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	X Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies	<input type="checkbox"/> None
<ul style="list-style-type: none"> • Outgoing communications (<i>if located elsewhere in package, state where located</i>) 	Email: December 15, 2008, December 19, 2008, June 2, 2009

⁴ Filing reviews for other disciplines should be filed behind the discipline tab.
Version: 9/5/08

• Incoming submissions/communications	December 16, 2008, June 3, 2009, June 9, 2009
❖ Postmarketing Commitment (PMC) Studies	X None
• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)	
• Incoming submission documenting commitment	
❖ Outgoing communications (<i>letters (except previous action letters), emails, faxes, telecons</i>)	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings	
• PeRC (<i>indicate date; approvals only</i>)	<input type="checkbox"/> Not applicable December 17, 2008
• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)	X Not applicable
• Regulatory Briefing (<i>indicate date</i>)	X No mtg
• Pre-NDA/BLA meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg July 20, 2007
• EOP2 meeting (<i>indicate date</i>)	<input type="checkbox"/> No mtg October 9, 2003
• Other (e.g., EOP2a, CMC pilot programs)	None
❖ Advisory Committee Meeting(s)	X No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available	
Decisional and Summary Memos	
❖ Office Director Decisional Memo (<i>indicate date for each review</i>)	X None
Division Director Summary Review (<i>indicate date for each review</i>)	<input type="checkbox"/> None October 19, 2008, June 23, 2009
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	X None
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	None
• Clinical review(s) (<i>indicate date for each review</i>)	October 10, 2008, December 18, 2008
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	X None
❖ Safety update review(s) (<i>indicate location/date if incorporated into another review</i>)	See MO review dated October 7, 2008 (pages 48-108)
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	See MO review dated October 7, 2008 (page 10)
❖ Clinical reviews from other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	<input type="checkbox"/> None QT/IRT: July 15, 2008
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	X Not needed

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management	<ul style="list-style-type: none"> Review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) REMS Memo (<i>indicate date</i>) REMS Document and Supporting Statement (<i>indicate date(s) of submission(s)</i>) 	<input type="checkbox"/> None September 23, 2008 N/A N/A
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)		<input type="checkbox"/> None requested October 14, 2008
Clinical Microbiology <input checked="" type="checkbox"/> None		
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None		
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)		X None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)		X None
Statistical Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None October 8, 2008
Clinical Pharmacology <input type="checkbox"/> None		
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)		X None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)		X None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None October 9, 2008
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)		X None
Nonclinical <input type="checkbox"/> None		
❖ Pharmacology/Toxicology Discipline Reviews		
• ADP/T Review(s) (<i>indicate date for each review</i>)		X None
• Supervisory Review(s) (<i>indicate date for each review</i>)		X None
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)		<input type="checkbox"/> None NDA: October 6, 2008, December 16, 2008
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)		X None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)		X No carc
❖ ECAC/CAC report/memo of meeting		X None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)		X None requested
CMC/Quality <input type="checkbox"/> None		
❖ CMC/Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) (<i>indicate date for each review</i>)		X None
• Branch Chief/Team Leader Review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None Memo: October 17, 2008
• CMC/product quality review(s) (<i>indicate date for each review</i>)		<input type="checkbox"/> None January 18, 2008, August 29, 2008, October 9, 2008, December 18, 2008, June 17, 2009
• BLAs only: Facility information review(s) (<i>indicate dates</i>)		<input type="checkbox"/> None

<ul style="list-style-type: none"> ❖ Microbiology Reviews <ul style="list-style-type: none"> • NDAs: Microbiology reviews (sterility & pyrogenicity) <i>(indicate date of each review)</i> • BLAs: Sterility assurance, product quality microbiology <i>(indicate date of each review)</i> 	September 16, 2008 <input type="checkbox"/> Not needed
<ul style="list-style-type: none"> ❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i> 	X None
<ul style="list-style-type: none"> ❖ Environmental Assessment (check one) (original and supplemental applications) 	
<ul style="list-style-type: none"> X Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i> 	See CMC review dated August 29, 2008
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>	
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>	
<ul style="list-style-type: none"> ❖ NDAs: Methods Validation 	<input type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested X Not needed
<ul style="list-style-type: none"> ❖ Facilities Review/Inspection 	
<ul style="list-style-type: none"> • NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i> 	Date completed: October 16, 2008, November 17, 2008, May 6, 2009 X Acceptable <input type="checkbox"/> Withhold recommendation
<ul style="list-style-type: none"> • BLAs: <ul style="list-style-type: none"> ○ TBP-EER ○ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i> 	Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation Date completed: <input type="checkbox"/> Requested <input type="checkbox"/> Accepted <input type="checkbox"/> Hold

Appendix A to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Hyon Z Lee
6/30/2009 06:17:25 PM

Lee, Hyon-Zu

From: Greeley, George
Sent: Tuesday, June 23, 2009 10:24 AM
To: Lee, Hyon-Zu
Cc: Stowe, Ginneh D.
Subject: NDA 22-180

Importance: High

Hi Hyon-Zu,

The [redacted] (ferumoxytol) partial waiver/deferral and plan was reviewed by the PeRC PREA Subcommittee on December 17, 2008. The Division recommended a partial waiver from 0-2 years because too few children with disease/condition to study and a deferral from 2- → years because the product is ready for approval in adults. The PeRC agreed with the Division to grant a partial waiver and deferral for this product.

The PeRC requested that the pediatric page be modified to at the waiver section to note a waiver granted from [redacted] months and that the you uncheck the box "Other Appropriate Reason" under the deferral section. b(4)

Thank you.

George Greeley
Regulatory Health Project Manager
Pediatric and Maternal Health Staff
Office of New Drugs
FDA/CDER
10903 New Hampshire Ave.
Bldg #22, Room 6467
Silver Spring, MD 20993-0002
301.796.4025

 Please consider the environment before printing this e-mail.

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Hyon Z Lee
6/29/2009 05:48:48 PM
CSO

MEMORANDUM OF TELECONFERENCE

Date: June 9, 2009

Time: 1:30 – 2 PM

Location: White Oak Bldg 22, Rm 2157

Application: NDA 22-180: Feraheme (ferumoxytol) Injection

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products

Rafel Rieves, M.D., Division Director

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology

Min Lu, M.D., M.P.H., Medical Reviewer

Jyoti Zalkikar, Ph.D., Statistical Team Leader

Satish Misra, Ph.D., Statistical Reviewer

Ira Krefting, M.D., Associate Director for Safety

Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

Diane Leaman, Safety Project Manager

And

External Constituent Attendees and Titles:

AMAG Pharmaceutical, Inc.

Mohammed Salem, Ph.D., R.A.C., V.P. of Regulatory Affairs

Lee Allen, M.D., Ph.D., Chief Medical Officer & Senior V.P. of Clinical Development

Brian Pereira, M.D., President & C.E.O.

Louis Brenner, M.D., Senior V.P.

Robert Brenner, M.D., Senior V.P. of Medical Affairs

Annamaria Kausz, M.D., Senior Director of Clinical Research

William Strauss, M.D., Executive Director of Medical Affairs

Ratna Lingamaneni, Ph.D., R.A.C., Director of Regulatory Affairs

The Division had a teleconference on June 2, 2009 with the sponsor to discuss the labeling and items tying into the postmarketing commitment (PMC) for ferumoxytol. The sponsor sent their follow up edits on the labeling via email on June 3, 2009 and the Division sent edits back to the sponsor on June 8, 2009.

teleconference on June 9, 2009, the sponsor sent the following email:

Also, before the

b(4)

"Dear Ms. Lee:

Thank you for your edits to the PI, and we will incorporate them into a red line revision as you requested today. We do feel that the suggestion to only show asterisks for the primary endpoints in the efficacy table (Table 3) would be misleading to physicians, because it suggests that the other endpoints are not statistically significant. This is incorrect and the data support the statistical significance of all primary and secondary endpoints. Therefore, we request the asterisks remain on both the primary and secondary endpoints. Let's plan to also follow-up on this request and finalize our label discussion at the end of today's meeting on the PMC study.

Thanks,
Mohammed Salem"

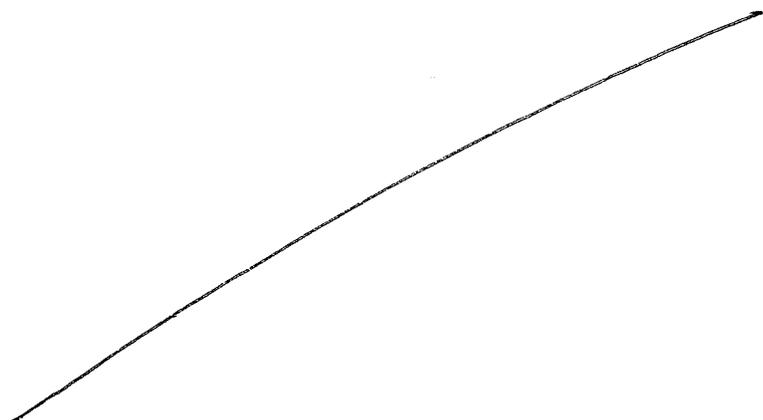
The Division set up the teleconference to discuss the above sponsor's comment and the proposed PMC.

The Division stated the following:

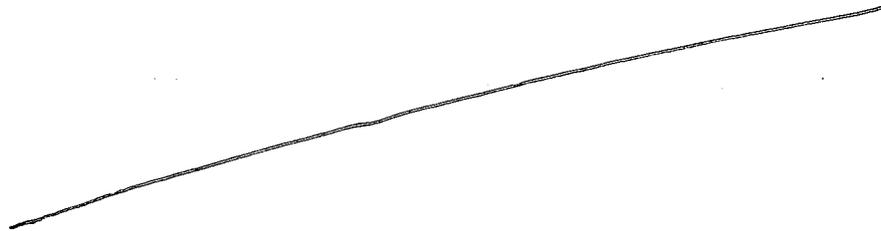
- We concur with the asterisks for the primary endpoint, but not for the secondary endpoints in Table (Changes from Baseline to Day 35 in Hemoglobin, Transferrin Saturation and Ferritin (Intent to Treat Population)) under the Clinical Studies section.

The sponsor asked if it is acceptable if they define the asterisks as " $p \leq 0.001$ for main efficacy endpoint" and show the asterisks only for the primary endpoint.

The Division responded that it is acceptable.



b(4)



b(4)

The Division responded that the pending items are the labeling, PMRs and the response to the citizen petition.

The teleconference concluded.

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/s/

Hyon Z Lee
6/22/2009 10:10:27 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-180

DISCIPLINE REVIEW LETTER

AMAG Pharmaceuticals, Inc
Attention: Mohammed Salem, Ph.D., RAC
100 Hayden Avenue
Lexington, MA 02421

Dear Dr. Salem:

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Feraheme™ (ferumoxytol) Injection.

We also refer to your submission dated March 30, 2009.

The Division of Medication Error and Prevention Analysis (DMEPA) has completed the review of your proposed labeling and has the following recommendation:

A. Container Label and Carton Labeling

We note that the circular blue and green logo is more prominent than the strength presentation. We recommend deleting this logo or at a minimum decrease the size and relocate the logo away from the proprietary name, established name, and product strength so that the most prominent information on the container label and carton labeling is the proprietary name, established name, and product strength.

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Kyong Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

James Moore
6/15/2009 09:24:03 AM

PMR/PMC Development Template

This template should be completed by the PMR/PMC Development Coordinator and included for each PMR/PMC in the Action Package.

PMR/PMC Description: PMR #1 To conduct a clinical trial in pediatric patients aged 2 to <18 years who have iron deficiency anemia and who are receiving either hemodialysis or peritoneal dialysis. In addition to any other items, the trial will obtain pharmacokinetic (PK), pharmacodynamic (PD) and safety data from at least 50 patients exposed to ferumoxytol. In this trial, patients will be randomized to oral iron (25 patients) or one of two dose ferumoxytol dose regimens (25 patients in each dose cohort). endpoints will consist of PK, PD, comparisons of hemoglobin changes and safety summaries.

PMR/PMC Schedule Milestones: Final protocol Submission Date: 12/2009
 Study/Clinical trial Completion Date: 04/2013
 Final Report Submission Date: 10/2013
 Other: _____

1. During application review, explain why this issue is appropriate for a PMR/PMC instead of a pre-approval requirement. Check type below and describe.

- Unmet need
- Life-threatening condition
- Long-term data needed
- Only feasible to conduct post-approval
- Prior clinical experience indicates safety
- Small subpopulation affected
- Theoretical concern
- Other

The pre-approval studies have demonstrated an acceptable benefit/risk profile for the ferumoxytol in adult patients who have iron deficiency anemia and who are receiving hemodialysis or peritoneal dialysis to support labeling in this population. Though the safety and appropriate dosing regimen of ferumoxytol have not been studied in clinical trials in pediatric patients who have iron deficiency anemia and who are receiving either hemodialysis or peritoneal dialysis, it is reasonable to permit marketing of this product for use in adults while study of the use of the drug in pediatric patients is underway.

2. Describe the particular review issue and the goal of the study/clinical trial. If the study/clinical trial is a FDAAA PMR, describe the risk. If the FDAAA PMR is created post-approval, describe the "new safety information."

The goal of the clinical trial is to identify an appropriate dosing regimen and obtain safety information of ferumoxytol in pediatric patients aged 2-<18 years who have iron deficiency anemia and who are receiving either hemodialysis or peritoneal dialysis.

3. If the study/clinical trial is a PMR, check the applicable regulation.
If not a PMR, skip to 4.

-- Which regulation?

- Accelerated Approval (subpart H/E)
- Animal efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

-- If the PMR is a FDAAA safety study/clinical trial, does it: (check all the apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
 - Identify an unexpected serious risk when available data indicate the potential for a serious risk?

-- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk.
- Analysis using Pharmacovigilance system?
Do not select the above study/clinical trial type if: the new Pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk.
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk.
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is to be a pharmacokinetic (PK), pharmacodynamic (PD) and safety study in pediatric patients aged 2 to <18 years who have iron deficiency anemia and who are receiving either hemodialysis or peritoneal dialysis. In addition to any other items, the trial will obtain data from at least 50 patients exposed to ferumoxytol. In this trial, patients will be randomized to oral iron (25 patients) or one of two dose ferumoxytol dose regimens (25 patients in each dose cohort). Endpoints will consist of PK, PD, comparisons of hemoglobin changes and safety summaries.

Required

- Observational pharmacoepidemiologic study

Continuation of Question 4

- Registry studies
 - X Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - X Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safety drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- X Other
A pharmacokinetic (PK), pharmacodynamic (PD) and safety study
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- X Does the study/clinical trial meet criteria for PMRs or PMCs?
 - X Are the objectives clear from the description of the PMR/PMC?
 - X Has the applicant adequately justified the choice of schedule milestone dates?
 - X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- X *This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*
-

(signature line for BLAs)

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Diane V Leaman
6/12/2009 10:10:25 AM
CSO

Ira Krefting
6/17/2009 04:05:53 PM
MEDICAL OFFICER

3. If the study/clinical trial is a **PMR**, check the applicable regulation.
If not a PMR, skip to 4.

-- Which regulation?

- Accelerated Approval (subpart H/E)
- Animal efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

-- If the PMR is a FDAAA safety study/clinical trial, does it: (check all the apply)

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

-- If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:

- Analysis of spontaneous postmarketing adverse events?
Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk.
- Analysis using Pharmacovigilance system?
Do not select the above study/clinical trial type if: the new Pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk.
- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?
Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk.
- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The study is to be a pharmacokinetic (PK), pharmacodynamic (PD) and safety study in pediatric patients aged 2 to <18 years who have iron deficiency anemia and chronic kidney disease that does not require dialysis. In addition to any other items, the trial will obtain data from at least 50 patients exposed to ferumoxytol. In this trial, patients will be randomized to oral iron (25 patients) or one of two dose ferumoxytol dose regimens (25 patients in each dose cohort). Endpoints will consist of PK, PD, comparisons of hemoglobin changes and safety summaries.

Required

- Observational pharmacoepidemiologic study

- Registry studies

Continuation of Question 4

- X Primary safety study or clinical trial
 - Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
 - Thorough Q-T clinical trial
 - Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
 - Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
 - X Pharmacokinetic studies or clinical trials
 - Drug interaction or bioavailability studies or clinical trials
 - Dosing trials
 - Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)
-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
 - Pharmacoepidemiologic study not related to safety drug use (e.g., natural history of disease, background rates of adverse events)
 - Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
 - Dose-response study or clinical trial performed for effectiveness
 - Nonclinical study, not safety-related (specify)
-
- X Other
a pharmacokinetic (PK), pharmacodynamic (PD) and safety study
-

5. Is the PMR/PMC clear, feasible, and appropriate?
- X Does the study/clinical trial meet criteria for PMRs or PMCs?
 - X Are the objectives clear from the description of the PMR/PMC?
 - X Has the applicant adequately justified the choice of schedule milestone dates?
 - X Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- X This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

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Diane V Leaman
6/12/2009 10:41:11 AM
CSO

Ira Krefting
6/17/2009 04:06:26 PM
MEDICAL OFFICER

Information	eCTD Location
1. Post-marketing commitment study – Study synopsis and Timelines	5.3.5.1- Reports of efficacy and safety studies [CKD] and related information of controlled clinical studies pertinent to the claimed indication
2. Timelines for the two Pediatric Research Equity Act (PREA) post-marketing requirements: Revised Clinical trial completion dates	1.9.6 – Other correspondence regarding pediatric study plans

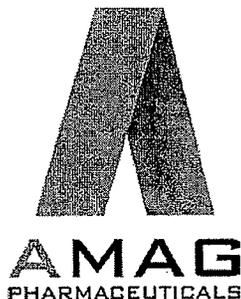
The structure of this amendment conforms to current eCTD specifications. The entire submission is approximately 1.86 MB and is being submitted through FDA Electronic Submission Gateway (ESG). All files in this electronic submission have been verified to be virus free using Norton Antivirus Program Version: 8.1.0.825, Scan Version: 4.2.0.7, and Virus Definition File 6/8/2009 rev. 7.

Please contact me directly by telephone at (617) 498-3332, by fax at (617) 499-3360, or by e-mail at msalem@amagpharma.com should you have any questions or require additional information.

Sincerely,



Mohammed A. Salem, Ph.D., RAC
Vice President, Regulatory Affairs



FERUMOXYTOL NDA 22-180

Correction to Amendment No. 0026

**RESPONSE TO INFORMATION REQUEST
(Timelines for the Pediatric Post-marketing Requirements)**

PEDIATRIC POSTMARKETING REQUIREMENTS (PMRS):

Please provide time lines (month/year) for the following anticipated PMRs. Additionally, we request specific dates for the time lines (not "within six months after approval in adults, etc" (depending upon the final action upon this application, the proposed specific time lines may be modified to address any delay in the final action).

Timelines for the anticipated Pediatric Postmarketing Requirements (PMRs):

Pediatric Research Equity Act (PREA):

1) To conduct a clinical trial in pediatric patients aged 2 to < 18 years who have iron deficiency anemia and who are receiving either hemodialysis or peritoneal dialysis. In addition to any other items, the trial will obtain pharmacokinetic (PK), pharmacodynamic (PD) and safety data from at least 50 patients exposed to ferumoxytol. In this trial, patients will be randomized to oral iron (25 patients) or one of two dose ferumoxytol dose regimens (25 patients in each dose cohort). Endpoints will consist of PK, PD, comparisons of hemoglobin changes and safety summaries.

Final clinical protocol submission date: December 2009

Clinical trial completion date: April 2013

Final trial report submission date: October 2013

2) To conduct a clinical trial in pediatric patients aged 2 to < 18 years who have iron deficiency anemia and chronic kidney disease that does not require dialysis. In addition to any other items, the trial will obtain pharmacokinetic (PK), pharmacodynamic (PD) and safety data from at least 50 patients exposed to ferumoxytol. In this trial, patients will be randomized to oral iron (25 patients) or one of two dose ferumoxytol dose regimens (25 patients in each dose cohort). Endpoints will consist of PK, PD, comparisons of hemoglobin changes and safety summaries.

Final clinical protocol submission date: December 2009

Clinical trial completion date: April 2013

Final trial report submission date: October 2013

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, June 08, 2009 2:18 PM
To: 'Mohammed Salem'
Subject: RE: NDA 22-180 Feraheme (ferumoxytol Injection): Revised PI and PREA PMRs Timeline
Attachments: 22180.FDA.6.8.09.doc

Dr. Salem,

Please see attached our edits for the PI. Among other editorial edits, please modify table 3 to only show asteriks for the primary endpoint results from the trials and submit the revision (red lined and clean copy).

Thank you,
Hyon-Zu

From: Mohammed Salem [mailto:msalem@amagpharma.com]
Sent: Wednesday, June 03, 2009 2:52 PM
To: Lee, Hyon-Zu
Subject: NDA 22-180 Feraheme (ferumoxytol Injection): Revised PI and PREA PMRs Timeline

Dear Ms. Lee:

Thank you so much for forwarding the Division's edits to the Draft PI, the Pediatric Research Equity Act (PREA) Post-marketing Requirements (PMRs) and the notes on a [redacted] AMAG on June 2, 2009 following our teleconference. Please find attached the AMAG's revisions and comments to the PI and the AMAG timeline for the PREA PMRs. As agreed at our teleconference and as discussed earlier this morning, we plan to respond separately in the next few days and provide a study design concept (or Synopsis) on the Post-marketing Commitment (PMC) on a [redacted]

b(4)

For ease of review of the PI and to provide clarity, we are submitting the PI document in three (3) different versions as follows:

1. A clean copy (after accepting all FDA and AMAG's edits, revisions & comments) - WORD File
2. A version showing only AMAG's revisions with comments after accepting all FDA edits - WORD File
3. A version showing the FDA edits and comments as well as AMAG's revisions and comments - PDF File

AMAG understands the Agency's perspective regarding the inclusion of: [redacted] for Feraheme in the label and is agreeable to your recommendation to remove them. We are asking that the Agency please reconsider our request regarding the [redacted] as discussed below.

b(4)

The time lines (month/year) for the PREA PMRs are also included in this e-mail.

Please note that we are sending these Draft PI versions and PREA PMRs by e-mail today, and we will submit all these documents formally via the FDA Electronic Submissions Gateway (ESG) system following eCTD publication by end of this week.

[redacted], for Feraheme:

We would appreciate the Agency reconsidering our proposal to include the [redacted]

b(4)

6/8/2009

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✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Hyon Z Lee
6/8/2009 02:34:20 PM
CSO

MEMORANDUM OF TELECONFERENCE

Date: June 2, 2009

Time: 10:30 – 11 AM

Location: White Oak Bldg 22, Rm 2376

Application: NDA 22-180: Feraheme (ferumoxytol) Injection

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products

Rafel Rieves, M.D., Division Director

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology

Min Lu, M.D., M.P.H., Medical Reviewer

Ira Krefting, M.D., Associate Director for Safety

Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

And

External Constituent Attendees and Titles:

AMAG Pharmaceutical, Inc.

Mohammed Salem, Ph.D., R.A.C., V.P. of Regulatory Affairs

Lee Allen, M.D., Ph.D., Chief Medical Officer & Senior V.P. of Clinical Development

Brian Pereira, M.D., President & C.E.O.

Louis Brenner, M.D., Senior V.P.

Robert Brenner, M.D., Senior V.P. of Medical Affairs

Ratna Lingamaneni, Ph.D., R.A.C., Director of Regulatory Affairs

The Division arranged the teleconference with the sponsor to discuss the labeling and items tying into the postmarketing commitment (PMC) for ferumoxytol.

The Division stated that we have the following comments on the PI:

- We have some challenges with the Dosage and Administration section regarding the re-administration of the drug (based on the Clinical Studies section). This potentially ties into the PMC and efficacy. Your proposed text in the Dosage and Administration section states as follows: _____

_____ We are not aware of a study that you submitted that provides data for _____ with ferumoxytol.

b(4)

- Your presentation of the different vial sizes (containing different amount of drug) does not correlate to the recommended dose in the Dosage and Administration section.

The sponsor commented that the different vial sizes (containing different amount of drug) was not intended for administration of lower doses, but to provide flexibility in administering the 510 mg dose (for example, administering two x 255mg or four x 127.5mg) since oncologist are used to give IV iron in smaller doses and might not feel comfortable initially to give the entire 510 mg at one time. Also, if the 20 ml size syringes are not available, the 510 mg dose could be administered using the 10 ml size syringes. And thirdly, since you can only puncture into the vial once, the smaller vial sizes were intended to minimize waste.

The Division noted that ferumoxytol is a new IV iron product that has been studied using a particular dosage regimen and it would be misleading to imply that physicians can apply customary administration to this new drug product based on how they have used other iron products in their practice. Deviations from the studied dosing of the drug product must be supported by additional data. The Division also noted that we are in the process of defending the pending citizen petition and that the product label is being carefully considered by numbers of other people in different Offices in the Agency.

The sponsor commented that they are comfortable with the 510 mg dose given at one time.

- Your edited Magnetic Resonance (MR) Imaging section provides improvement to the previous version.
- We do not have data at the current time to support labeling for the _____ but as you develop further studies and gather data, you could submit an efficacy supplement with the proposed labeling later on. We do not envision an additional PMR regarding the " _____" but rather a PMC.

b(4)

The sponsor commented that they are open to dialogue regarding the study.

The Division stated that we will be sending the edited PI and PMRs to the sponsor today.

ACTION ITEM:

The Division will send the revised PI, PMRs and our comments on the _____ (attached below) today.

b(4)

2 Page(s) Withheld

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Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Administrative-2

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/s/

Hyon Z Lee
6/5/2009 01:20:22 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Tuesday, June 02, 2009 11:24 AM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol
Attachments: notes 6.2.09.doc; PMR.5.29.09.doc; dr22180 FDA 5'28 09.doc

Dr. Salem,

Please see attached our revised labeling and PREA PMRs. Also, find attached our thoughts regarding the

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office; 301-796-2050
Fax; 301-796-9849
Hyon.Lee@fda.hhs.gov

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6/2/2009

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 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Hyon Z Lee
6/2/2009 11:57:33 AM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Wednesday, May 20, 2009 11:12 AM
To: 'Mohammed Salem'
Subject: NDA 22-180 feruomxytol: information request
Follow Up Flag: Follow up
Flag Status: Yellow
Attachments: Requests5-20-09.doc

Dr. Salem,

We are reviewing your submission and have some information request (please see attached). Respond by COB tomorrow (May 21, 2009).

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

Hyon.Lee@fda.hhs.gov

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1 Page(s) Withheld



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 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Hyon Z Lee
5/20/2009 11:45:37 AM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Wednesday, May 20, 2009 11:07 AM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol
Follow Up Flag: Follow up
Flag Status: Orange
Attachments: -22180.5.20.09.PI.doc

Dr. Salem,

Please find attached the PI with our edits.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

Hyon.Lee@fda.hhs.gov

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5/20/2009

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 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Hyon Z Lee
5/20/2009 11:44:00 AM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-180

AMAG Pharmaceuticals, Inc
Attention: Mohammed Salem, Ph.D., RAC
100 Hayden Avenue
Lexington, MA 02421

Dear Dr. Salem:

We acknowledge receipt on April 29, 2009 of your April 29, 2009 resubmission to your new drug application for ferumoxytol injection.

We consider this a complete, class 1 response to our December 22, 2008 action letter. Therefore, the user fee goal date is June 29, 2009.

If you have any questions, call me at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Hyon Z Lee

5/12/2009 11:43:04 AM



NDA 22-180

DISCIPLINE REVIEW LETTER

AMAG Pharmaceuticals, Inc
Attention: Mohammed Salem, Ph.D., RAC
100 Hayden Avenue
Lexington, MA 02421

Dear Dr. Salem:

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ferumoxytol injection.

We also refer to your submissions dated January 7 and February 10, 2009.

The Division of Medication Error and Prevention Analysis (DMEPA) has completed the review of your proposed labeling and has the following recommendations:

A. Container Labels and Carton Labeling (Trade and Professional Sample)

1. The proprietary and established names lack prominence on the container labels and the strength lacks prominence on all labels and labeling. Additionally, the proprietary and established names are presented separately from the strength on some panels of the carton labeling (i.e., proprietary and established names at the top and the strength at the bottom). The proprietary name, established name, and strength are how the product is initially identified so this information should be presented together and prominently displayed on all the labels and labeling. On the container label, if additional space is needed to accomplish this, we recommend deleting information that is not required per 21 CFR 201.10(i). Such examples of information that may be deleted include your prominent logo, product description and usual dosage statement.

Additionally, the statement of drug concentration (30 mg/mL) is equal in font size to the total drug content statement. The total drug content statement should be larger in size than the mg/mL statement of drug concentration. See the following example:

TRADENAME
(Ferumoxytol Injection)
XX mg elemental iron per XX mL
(30 mg/mL)

2. Differentiate the multiple strengths by using contrasting color, boxing, or other means to

b(4)

3. The wording "Single Use Vial" is located next to the statement of drug concentration (30 mg/mL). Relocate the wording "Single Use Vial" to another location on the label. As noted in comment A-1, deleting your logo will provide additional room on the label for this statement to be presented.
4. Since the vials are for single use only, the labels and labeling should also contain a statement to "Discard unused portion". This statement can be combined with the "Single Use Vial" statement to read "Single Use Vial—Discard Unused Portion".
5. The route of administration statement, "IV Use Only", does not have enough prominence on the container labels. Additionally, it contains the abbreviation "IV". Increase the prominence of the route of administration statement. Replace the abbreviation "IV" with the completely spelled word (e.g., "For Intravenous Use Only"). To allow for this, you might consider deleting information that is not required per 21 CFR 201.10(i).

B. Insert Labeling

1. In Section 2 *Dosage and Administration*, the dosing information is not clear. Provide more detailed information on the dosing of the product.
2. In Section 2 *Dosage and Administration*, the instructions for rapid intravenous injection do not state whether the product is to be given diluted or undiluted. State whether the product is to be administered diluted or undiluted. If the product requires dilution, specify those fluids that are compatible with it and give instructions for dilution.
3. In the *Dosage Forms and Strengths* section of Highlights of Prescribing Information and Full Prescribing Information, there is a table that has a column titled ' — ' which lists the actual sizes of the vials in which the product is supplied. Delete this column since calculation errors could occur if the volume stated in the column is misread and mistaken as the fill volume.

b(4)

We are providing these comments to you before we complete our review of the entire application to give you preliminary notice of issues that we have identified. In conformance with the prescription drug user fee reauthorization agreements, these comments do not reflect a final decision on the information reviewed and should not be construed to do so. These comments are preliminary and subject to change as we finalize our review of your application. In addition, we may identify other information that must be provided before we can approve this application.

NDA 22-180
Page 3

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Kyong Kang, Pharm.D.
Chief, Project Management Staff
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Kyong Kang
3/11/2009 03:09:52 PM

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, February 02, 2009 9:48 AM
To: 'Mohammed Salem'
Subject: RE: AMAG Response: NDA 22-180 ferumoxytol: Postmarketing Requirements (PMRs) - Chronic Kidney Disease
Attachments: revised PMR 2.2.09.doc

Dr. Salem,

Please find attached the revised Agency's Postmarketing Requirements for the ferumoxytol NDA application. We have increased the number of subjects for the PREA requirement to _____, subjects _____ **b(4)**

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office; 301-796-2050
Fax; 301-796-9849
Hyon.Lee@fda.hhs.gov

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From: Mohammed Salem [<mailto:msalem@amagpharma.com>]
Sent: Tuesday, December 16, 2008 9:28 AM
To: Lee, Hyon-Zu
Subject: AMAG Response: NDA 22-180 ferumoxytol: Postmarketing Requirements (PMRs) - Chronic Kidney Disease

Dear Ms. Lee:

We have reviewed the Postmarketing Requirements (PMRs) for the ferumoxytol NDA application that included two items under Pediatric Research Equity Act (PREA) requirement : _____ **b(4)**

As requested please find the attached, the responses to the document that provides the timelines on all the proposed PMR studies.

2/2/2009

Postmarketing Requirements (PMRs):

AMAG, please provide time lines (month/year) for the following anticipated PMRs

b(4)

Below we attempted to incorporate your prior dates re: the
(please confirm correctness):

I. Pediatric Research Equity Act (PREA):

1) "To conduct a clinical trial in pediatric patients aged 2 to < 18 years who are receiving either hemodialysis or peritoneal dialysis. In addition to any other items, the trial will obtain pharmacokinetic, pharmacodynamic and safety data from at least 75 subjects. Subjects will be randomized between at least two Ferumoxytol dose regimens.

Clinical protocol submission date: (month/year)

Clinical trial start date: (month/year)

Final trial report submission date: (month/year).

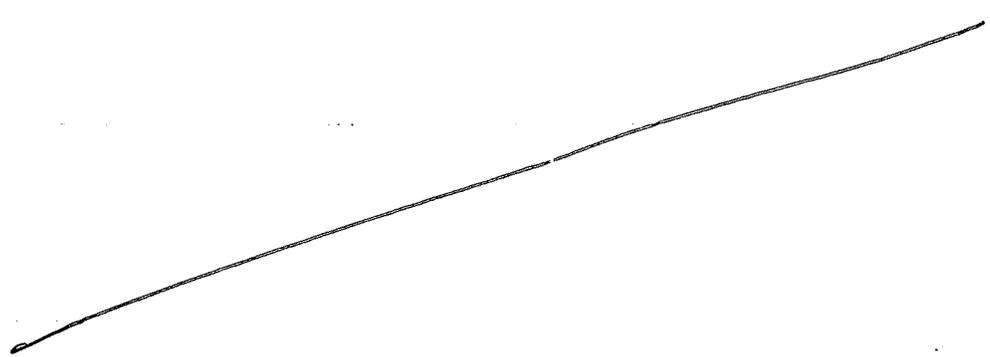
2) To conduct a clinical trial in pediatric patients aged 2 to < 18 years who have a range of chronic kidney disease (stages 1 through 5). In addition to any other items, the trial will obtain pharmacokinetic, pharmacodynamic and safety data from at least 75 subjects. Subjects will be randomized between at least two Ferumoxytol dose regimens.

Clinical protocol submission date: (month/year)

Clinical trial start date: (month/year)

Final trial report submission date: (month/year)."

II. Other PMR:



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/s/

Hyon Z Lee
2/2/2009 10:27:10 AM
CSO

MEMORANDUM OF TELECONFERENCE

Date: December 18, 2008

Time: 9:30 – 10 AM

Location: White Oak Bldg 22, Rm 2201

Application: NDA 22-180: ferumoxytol injection

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products

Rafel Rieves, M.D., Division Director

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology

Min Lu, M.D., M.P.H., Medical Reviewer

Young-Moon Choi, Ph.D., Clinical Pharmacology Reviewer

Sarah Pope, Ph.D., Acting Branch Chief V, Branch V (CMC-Pre-marketing)

Eldon Leutzinger, Ph.D., Chemistry Pool Reviewer

Xiao Chen, Ph.D., Chemistry Reviewer

Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

And

External Constituent Attendees and Titles:

AMAG Pharmaceutical, Inc.

Mohammed Salem, Ph.D., R.A.C., V.P. of Regulatory Affairs

Lee Allen, M.D., Ph.D., Chief Medical Officer & Senior V.P. of Clinical Development

Brian Pereira, M.D., President & C.E.O.

Lou Brenner, M.D., Senior V.P.

Jerome Lewis, Ph.D., Senior V.P. of Scientific Operations

Ratna Lingamaneni, Ph.D., R.A.C., Director of Regulatory Affairs

Scott McMillan, Ph.D., Executive Director, Manufacturing Operations

The Division arranged the teleconference with the sponsor to discuss the pending action of the ferumoxytol NDA resubmission dated October 30, 2008.

The Division noted that we are planning to take an action on December 22, 2008 and the concern remains in the deficiencies in the manufacturing facility. The Division stated that we are planning to include an information request regarding the quantitative aspects of iron dextran modification in the action letter.

The sponsor indicated that there is a medical need for ferumoxytol and that the approval is critical for the company. They asked if it is possible to approve ferumoxytol on the condition of

not launching the drug product until the manufacturing deficiencies are resolved. They stated that they responded to the 483 observations and tried to communicate with the district office and the Office of Compliance (OC) for resolution of the issues, but that they were not successful. They indicated that they prefer to delay the action rather than receiving a not favorable letter.

The Division responded that it is better to close out the review cycle and open up a new subsequent cycle with the resubmission. Also, the deficiencies in the manufacturing facility need to be resolved before the drug product can be approved, and that at the present time, the recommendation is that these deficiencies do not support approval. The Division clarified that the OC does the complete evaluation of the manufacturing sites, sends a final recommendation, and that the review depends on the acceptability or the non-acceptability of OC. The Division stated that we will check internally if there is any mechanism for the sponsor to communicate with OC.

The sponsor asked if the action letter will contain other issues than facility deficiencies, and stated that they want to finalize the labeling during the present cycle if possible.

The Division responded that the labeling needs to be vetted through multiple review disciplines before it can be finalized and that we will close out the labeling during the next review cycle.

The teleconference concluded.

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/s/

Hyon Z Lee
1/12/2009 07:37:58 AM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Friday, December 19, 2008 10:13 AM
To: 'Mohammed Salem'
Subject: RE: AMAG Response: NDA 22-180 ferumoxytol: Postmarketing Requirements (PMRs) - Chronic Kidney Disease
Follow Up Flag: Follow up
Flag Status: Blue

Dr. Salem,

As stated over the telephone yesterday, we will send revised studies required for PREA. Please disregard the prior communications regarding PREA requirements.

Thank you,
Hyon-Zu

From: Mohammed Salem [mailto:msalem@amagpharma.com]
Sent: Tuesday, December 16, 2008 9:28 AM
To: Lee, Hyon-Zu
Subject: AMAG Response: NDA 22-180 ferumoxytol: Postmarketing Requirements (PMRs) - Chronic Kidney Disease

Dear Ms. Lee:

We have reviewed the Postmarketing Requirements (PMRs) for the ferumoxytol NDA application that included two items under Pediatric Research Equity Act (PREA) requirement _____

As requested please find the attached, the responses to the document that provides the timelines on all the proposed PMR studies.

b(4)

We will also plan to provide the attached document with a separate cover letter as a formal electronic submission to the NDA 22-180 via the electronic gateway system.

Please let me know if you have any questions regarding this submission.

Thank you,
Mohammed Salem

12/22/2008



Mohammed Salem, Ph.D., RAC
Vice President, Regulatory Affairs
AMAG Pharmaceuticals, Inc.
100 Hayden Avenue
Lexington, MA 02421

www.amagpharma.com

617.498.3300 **Main**

617.498.3332 **Direct**

617.499.3360 **Fax**

857.998.2798 **Mobile**

From: Lee, Hyon-Zu [mailto:Hyon.Lee@fda.hhs.gov]
Sent: Monday, December 15, 2008 2:25 PM
To: Mohammed Salem
Subject: NDA 22-180 ferumoxytol: Postmarketing Requirements (PMRs)

Dr. Salem,

Please see attached the Agency's Postmarketing Requirements for the ferumoxytol NDA application. There are two items under Pediatric Research Equity Act (PREA) and one other PMR.

Please respond by noon tomorrow.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

Hyon.Lee@fda.hhs.gov

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12/22/2008

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/s/

Hyon Z Lee
12/22/2008 10:15:20 AM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Thursday, December 18, 2008 1:43 PM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol: proposed proprietary name review

Dr. Salem,

DMEPA (Division of Medication Error Prevention and Analysis) has reviewed your proposed proprietary name, Feraheme, and has concluded that it is acceptable. However, the proposed proprietary name **must be re-evaluated 90 days prior to the approval of the NDA**. Also, if **any** of the proposed product characteristics are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

Please let me know if you have any questions.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050
Fax: 301-796-9849
Hyon.Lee@fda.hhs.gov

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12/18/2008

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/s/

Hyon Z Lee
12/18/2008 04:28:07 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Tuesday, December 16, 2008 1:39 PM
To: 'Mohammed Salem'
Subject: RE: NDA 22-180 ferumoxytol: FDA edits on the PI
Follow Up Flag: Follow up
Flag Status: Blue
Attachments: 12-16-08 FDA to AMAG.doc

Dr. Salem,

Please see attached the revised version with minor edits.

We made the following additional revisions:

1. Highlights: Adverse Reactions- deleted the company website.
2. 5.4 under Warnings and Precautions: revised the cross-reference from [see *Pharmacokinetics (12.3)*] to [see *Clinical Pharmacology (12.3)*].
3. 8.1 under Pregnancy subsection: added "caused" in the second sentence, first paragraph.

When submitting the PI, the Highlights should be in two columns followed by the Full Prescribing Information: Contents also in two columns, and the rest of the PI in one column.

Thank you,
Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, December 15, 2008 5:11 PM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol: FDA edits on the PI

Dr. Salem,

Please see attached FDA edits on the PI and respond by COB Dec. 17, 2008.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office; 301-796-2050

Fax; 301-796-9849

Hyon.Lee@fda.hhs.gov

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12/16/2008

14 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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Hyon Z Lee
12/15/2008 06:22:00 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, December 15, 2008 2:25 PM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol: Postmarketing Requirements (PMRs)
Attachments: PMR to AMAG.12.12.08.doc

Dr. Salem,

Please see attached the Agency's Postmarketing Requirements for the ferumoxytol NDA application. There are two items under Pediatric Research Equity Act (PREA) and one other PMR.

Please respond by noon tomorrow.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

Hyon.Lee@fda.hhs.gov

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12/15/2008

Postmarketing Requirements (PMRs):

AMAG, please provide time lines (month/year) for the following anticipated PMRs

┌

b(4)

_____ below we attempted to incorporate your prior dates re: the
please confirm correctness):

I. Pediatric Research Equity Act (PREA):

1) "To conduct a clinical trial in pediatric patients aged 2 to < 18 years who are receiving either hemodialysis or peritoneal dialysis. In addition to any other items, the trial will obtain pharmacokinetic, pharmacodynamic and safety data from at least _____ subjects. Subjects will be randomized between at least two Ferumoxytol dose regimens.

(4)

Clinical protocol submission date: (month/year)

Clinical trial start date: (month/year)

Final trial report submission date: (month/year).

2) To conduct a clinical trial in pediatric patients aged 2 to < 18 years who have a range of chronic kidney disease (stages 1 through 5). In addition to any other items, the trial will obtain pharmacokinetic, pharmacodynamic and safety data from at least _____ subjects. Subjects will be randomized between at least two Ferumoxytol dose regimens.

Clinical protocol submission date: (month/year)

Clinical trial start date: (month/year)

Final trial report submission date: (month/year)."

b(4)

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/s/

Hyon Z Lee
12/15/2008 03:54:07 PM
CSO

MEMORANDUM OF TELECONFERENCE

Date: November 6, 2008

Time: 5 – 5:15 PM

Location: White Oak Bldg 22, Rm 2327

Application: NDA 22-180: ferumoxytol injection

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products

Rafel Rieves, M.D., Division Director

Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

And

External Constituent Attendees and Titles:

AMAG Pharmaceutical, Inc.

Mohammed Salem, Ph.D., R.A.C., V.P. of Regulatory Affairs

Lee Allen, M.D., Ph.D., Chief Medical Officer & Senior V.P. of Clinical Development

Brian Pereira, M.D., President & C.E.O.

The Division arranged the teleconference to discuss the review timeline of the ferumoxytol NDA resubmission dated October 30, 2008.

The Division stated that we discussed the resubmission with the members of the review team including CMC and decided to classify as a Class 2 resubmission because of the need for re-inspection of the clinical sites and the facility site. The team will do our best to act before the PDUFA due date of April 30, 2009 but this will depend on when the inspections will be completed.

The sponsor asked the rationale for the clinical site re-inspection as there are no discrepancies for the case report data.

The Division responded that there is a need to resolve DSI. We need to be vigilant in the data integrity and have received communications from outside the Agency which adds level of vigilance. Also, upon our preliminary review of the submitted labeling, it needs extensive revisions. The Division stated we made the decision of the Class 2 taking into account of these concerns (the label, re-inspections of the establishment and clinical site and also concerns of relationship to iron dextran).

The sponsor indicated that they have provided complete response regarding iron dextran issues and that ferumoxytol does not resemble iron dextran. They stated they are facing financial problems if the resubmission will be classified as Class 2 and that they might have to lay off employees.

The Division commented that the sponsor could consider dispute resolution process.

The sponsor responded that they do not want to take the dispute resolution pathway and stated that they want Class 1.

The Division agreed to reconsider the supplied data and reconsider the type of classification and stated that we will have more internal meetings and get back to the sponsor by November 13 or 14, 2008.

The teleconference concluded.

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/s/

Hyon Z Lee
11/17/2008 12:58:07 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-180

AMAG Pharmaceuticals, Inc.
Attention: Mohammed Salem, Ph.D., R.A.C.
100 Hayden Avenue
Lexington, MA 02421

Dear Dr. Salem:

We acknowledge receipt on October 30, 2008 of your October 30, 2008 resubmission to your new drug application for ferumoxylol injection.

We consider this a complete, class 1 response to our October 17, 2008 action letter. Therefore, the user fee goal date is December 30, 2008.

If you have any questions, call me at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Health Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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/s/

Hyon Z Lee
11/12/2008 04:04:42 PM

MEMORANDUM OF MEETING

MEETING DATE: June 26, 2008
TIME: 12 – 1:30 PM
LOCATION: Conference Room 2376 (White Oak)
APPLICATION: NDA 22-180
DRUG NAME: Ferumoxytol Injection
TYPE OF MEETING: Mid-Cycle Meeting

MEETING CHAIR: Rafel Rieves, M.D.

MEETING RECORDER: Hyon-Zu Lee, Pharm.D.

FDA ATTENDEES:

Office of Oncology Drug Products (OODP)
Richard Pazdur, M.D., Director

Division of Medical Imaging and Hematology Products (DMIHP)
Rafel Rieves, M.D., Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology
Min Lu, M.D., M.P.H., Medical Reviewer
Eldon Leutzinger, Ph.D., Chemistry Pool Reviewer
Xiao Chen, Ph.D., CMC Reviewer
Aloka Chakravarty, Ph.D., Director, Statistics
Jyoti Zalkikar, Ph.D., Statistics Team Leader
Satish Misra, Ph.D., Statistics Reviewer
Young-Moon Choi, Clinical Pharmacology Team Leader
Adebayo Laniyonu, Ph.D., Pharmacology/Toxicology Team Leader
David Bailey, Ph.D., Pharmacology/Toxicology Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager

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/s/

Hyon Z Lee
10/16/2008 02:45:26 PM
CSO

MEMORANDUM OF TELECONFERENCE

Date: October 7, 2008

Time: 2:30 – 3:30 PM

Location: White Oak Bldg 22, Rm 2327

Application: NDA 22-180: ferumoxytol injection

Between

FDA Attendees:

Division of Medical Imaging and Hematology Products

Rafel Rieves, M.D., Division Director

Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader, Hematology

Min Lu, M.D., M.P.H., Medical Reviewer

Young-Moon Choi, Ph.D., Clinical Pharmacology Reviewer

David Bailey, Ph.D., Pharmacology/Toxicology Reviewer

Eldon Leutzinger, Ph.D., Chemistry Pool Reviewer

Xiao Chen, Ph.D., Chemistry Reviewer

Hyon-Zu Lee, Pharm.D., Regulatory Project Manager

And

External Constituent Attendees and Titles:

AMAG Pharmaceutical, Inc.

Mohammed Salem, Ph.D., R.A.C., V.P. of Regulatory Affairs

Lee Allen, M.D., Ph.D., Chief Medical Officer & Senior V.P. of Clinical Development

Brian Pereira, M.D., President & C.E.O.

Lou Brenner, M.D., Senior V.P.

Jerome Lewis, Ph.D., Senior V.P. of Scientific Operations

Rob Brenner, M.D., Senior V.P. of Medical Affairs

Ratna Lingamaneni, Ph.D., R.A.C., Director of Regulatory Affairs

Tim Frigo, Ph.D., Director of Research & Development

The Division set up the teleconference to discuss the chemical moiety of ferumoxytol (if it contains or has any characteristics of iron dextran) and the Division's plan for this NDA cycle.

After the introduction, the Division stated that we anticipate finishing up the reviews to meet the PDUFA due date of October 19, 2008 and that we will not be sending any labeling comments to the sponsor. The action letter will include information requests for data related to risks to serious allergic reactions to iron dextran, justifications for labeling and summary related to potential clinical applicability to iron dextran products.

Then the Agency asked the sponsor for an overall assessment of similarities/differences between ferumoxytol and iron dextran and if the ferumoxytol contains any free dextran within the drug.

The sponsor stated that ferumoxytol contains iron & polyglucose sorbitol carboxymethylether (PSC) and went through the manufacturing and control process for ferumoxytol. They explained that the ferumoxytol contains modified dextran, and does not contain any underivatized dextran as shown by the NMR data. They also discussed results for ELISA (to test the reactivity of PSC to anti-dextran antibodies) and rat paw edema assay (to measure the anaphylactic response to rats). PSC showed minimum reactivity to anti-dextran antibody and very low level of rat paw edema score. The applicant stated that the discussed results were provided in the P2 section of Module 3 and the Process Validation Report PVR-4043-01.

The Division stated that we will not be asking for additional information at this time but that the sponsor is welcome to submit. The action letter will address the similarities/dissimilarities to iron dextran, labeling issues and questions raised with the inspection of the facility.

The teleconference concluded.

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/s/

Hyon Z Lee
10/15/2008 05:16:13 PM
CSO

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/s/

Hyon Z Lee
10/16/2008 02:45:26 PM
CSO

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

CLINICAL INSPECTION SUMMARY

DATE: Oct 14, 2008

TO: Hyon-Zu Lee, Regulatory Project Manager
Min Lu, Medical Officer
Division of Medical Imaging and Hematology Products

FROM: John Lee, Medical Officer
Good Clinical Practice Branch II
Division of Scientific Investigations

THROUGH: Tejashri Purohit-Sheth, MD
Branch Chief, Good Clinical Practice Branch II
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

NDA: NDA 22-180

APPLICANT: AMAG Pharmaceuticals, Inc.

DRUG: Ferumoxytol

NME: No

THERAPEUTIC CLASSIFICATION: Standard review

INDICATIONS: Treatment of iron deficiency anemia in patients with chronic kidney disease

CONSULTATION REQUEST DATE: March 28, 2008

DIVISION ACTION GOAL DATE: October 17, 2008

PDUFA DATE: October 19, 2008

I. BACKGROUND

Nearly 20% of the United States (US) adult population has chronic kidney disease (CKD) and the US prevalence is increasing. This recent prevalence estimate is based on the following definition of CKD: evidence of kidney damage (most often persistent albuminuria) or decreased glomerular filtration rate (GFR) < 60 (mL/min/1.73 m²) for at least 3 months. The National Kidney Foundation (NKF) stratifies CKD into 5 stages: stage 1 = GFR 90 - 120; stage 2 = GFR 60 - 89; stage 3 = GFR 30 - 59; stage 4 = GFR 15 - 29; and stage 5 (or kidney failure) = GFR < 15, with stage 5D = dialysis. Using this stratification, the prevalence by stage in US adults has been recently estimated to be about 6% for stage 1, 5% each for stages 2 and 3, and 0.5% for stages 4 and 5 combined.

Anemia affects the majority of patients with stage 5 CKD and a substantial proportion of patients with earlier stages of CKD. The prevalence of anemia increases with advancing disease, and anemia is well known to be associated with serious cardiovascular complications (left ventricular hypertrophy, congestive heart failure), decreased quality of life, hospitalizations, and increased mortality. Iron deficiency and decreased erythropoiesis is commonly associated with anemia of CKD. The etiology of iron deficiency is multifactorial and includes decreased dietary iron intake or absorption, iron sequestration in inflammation, blood loss, and increased iron utilization, particularly with the use of erythropoiesis stimulating agents (ESA). Iron deficiency may be described as being absolute based on laboratory indicators (serum ferritin < 100 ng/mL, transferrin saturation < 20%) or as being functional based on hemoglobin response to therapy (increased erythropoiesis upon administration of intravenous iron). For patients with CKD, the 2000 NKF guidelines recommend the use of: (1) oral iron to prevent iron deficiency and to maintain iron stores, (2) intravenous iron when oral therapy is insufficient to replete iron stores or in stage 5D CKD patients on hemodialysis, (3) either oral or intravenous iron in stages 1-5 CKD and in stage 5D CKD on peritoneal dialysis. For iron replacement, the typical total dose is 1.0 g per therapeutic course. The most frequently used preparations in the US (sodium ferric gluconate and iron sucrose) are typically given in doses of 100 to 200 mg and require 5 to 10 administrations per therapeutic course.

Ferumoxytol is a magnetically active iron oxide nanoparticle (with a special coating designed to minimize immunogenicity) originally developed as a diagnostic contrast agent for magnetic resonance imaging. As other iron oxides, ferumoxytol is expected to be metabolized via a pathway involving transferrin, ferritin, hemosiderin and hemoglobin. Humans maximally conserve iron; from typical iron stores of 2 to 4 g, some iron may be lost via the gastrointestinal tract or menses (1 mg/day in men, 2 mg/day in menstruating women). Initial studies suggest that intravenous ferumoxytol can reliably and conveniently deliver high doses of iron (up to 500 mg). Inspections in support of this NDA review consisted of audits at 3 clinical sites participating in 3 pivotal studies intended to evaluate the safety and efficacy of ferumoxytol under two clinical settings:

- Protocol 62745-5: *A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in Hemodialysis Patients who are Receiving Supplemental Erythropoietin Therapy.* In this open-label study, approximately 250 subjects (post-amendment) with stage 5D CKD (on hemodialysis and erythropoietin) were randomized 1:1 to two arms, intravenous ferumoxytol versus oral iron. In the test group, ferumoxytol was given as two 510 mg doses, at Day 0 followed by a second dose within 5 days of the first. In the control group, 200 mg of elemental iron was given daily for 3 weeks. The change in hemoglobin was compared at 5 weeks (Day 35).
- Protocols 62745-6 and 62745-7: *A Phase III Study of the Safety and Efficacy of Ferumoxytol (Compared with Oral Iron) as an Iron Replacement Therapy in Chronic Kidney Disease Patients Not on Dialysis.* In each of these two open-label studies of identical design, approximately 300 subjects with CKD stages 1 - 5 were randomized 3:1 to two arms, intravenous ferumoxytol versus oral iron. The treatment regimens and primary endpoint were the same as in the study involving patients with CKD stage 5D on hemodialysis and erythropoietin therapies (Protocol 62745-5).

Three domestic sites were selected for audit due to high enrollment: Drs. Provenzano, Bernardo, and Bland.

II. INSPECTION RESULTS

	Clinical Site	Protocol Site Subjects	Inspection Dates	Classification	
				Field	Final
1	Robert Provenzano, MD St. John Hospital and Medical Center 22201 Moross Road, Suite 150 Detroit, Michigan	Protocol 62745-5 Site 139 26 subjects	August 4 - 8 2008	VAI	VAI
2	Marializa V. Bernardo, MD Southwest Houston Research, LTD 10850 S. Wilcrest Drive, Suite 170-A Houston, Texas	Protocol 62745-6 Site 109 55 subjects	August 18 - 22 2008	NAI	pending
3	Andrew Bland, MD Renal Care Associates 515 NE Glen Oak 108 Peoria, Illinois	Protocol 62745-7 Site 203 41 subjects	October 6 - 10 2008	NAI	pending

NAI = no action indicated (no deviations from regulations); VAI = voluntary action indicated (no significant deviations from regulations); OAI = official action indicated (significant deviations from regulations); NA = not applicable

Classification:

Field = field investigator's initial recommendation in classifying the inspection result

Final = CDER's final classification of the inspection result

1. Robert Provenzano, MD (Site 139): St. John Hospital and Medical Center

22201 Moross Road, Suite 150
Detroit, Michigan 48236

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations.
- Data verification: primary efficacy endpoint data, adverse events, protocol deviations, concomitant medication use, and subject discontinuation
- Subjects: 164 subjects were screened, 29 enrolled in study 62745-5, and 26 completed the study. Complete records were reviewed for all 29 subjects.

b. General observations and commentary:

- Cited Deficiencies (Form FDA 483):
 - Failure to maintain adequate case histories with respect to adverse event data for subject 554. Prior to dose 2 on 7/8/06, the subject was hypotensive (blood pressure 52/28), diaphoretic, difficult to arouse, and reported being light-headed. Dose 2 was postponed until 7/11/06. The adverse event form submitted to the sponsor reported a headache for the date of 7/8/08 and did not list the other symptoms.

- Investigational drug disposition records were inaccurate with respect to use by two subject pairs (622 and 626, 648 and 655). The Drug Accountability Records for the active study agent indicated that 3 vials were issued to subject 622 on each of two days (11/28/06 and 11/30/06), but the source records showed that subject 626 received the test product and not subject 622. Subject 622 received only the oral iron control product. The Drug Accountability Records for the oral iron control product indicated that the control product was issued to subject 648 on 3/5/07, but the source documents showed that the control product was issued to subject 655 on 3/5/07.
 - Other considerations relevant to data integrity:
 - The protocol specifies that erythropoietin dosing must remain constant from Day 0 until study completion but allows dosing changes if the subject's hemoglobin decreases by ≥ 0.5 g/dL and is < 11.0 g/dL. Dose adjustments were often made at hemodialysis, apparently in response to a decrease in hemoglobin ≥ 0.5 g/dL at a hemoglobin < 11.0 g/dL. Although permitted by the protocol, changes in erythropoietin dosing complicate the interpretation of study results, for both efficacy and safety assessments: observed differences in achieved hemoglobin cannot be attributed to an efficacy difference between ferumoxytol and oral iron, and adverse events may be associated with erythropoietin use, including changes in erythropoietin dosing. Even in this randomized study, the potentially different effects of different forms of iron supplementation (intravenous ferumoxytol versus oral iron) on erythropoietin requirements complicate the interpretation of study results despite reliable data collected in accordance with the study protocol.
 - Adverse events, including serious adverse events, were not always consistently reported to the sponsor when the events did not appear to be treatment-related. Two specific examples observed at inspection were line or graft sepsis (subjects 530 and 513) and hypotension during hemodialysis (subjects 644 and 554). The failure to report all adverse events appears to be limited to a few cases and does not appear to significantly affect the reliability of the safety data collected at this site.
 - c. Assessment of data integrity: Data appear reliable. However, inaccurate drug disposition records (see above, second bullet under *Cited Deficiencies*) suggest that the data from four subjects (622, 626, 648, and 655) may not be reliable. DSI recommends removing efficacy and safety data from these four subjects in analyzing study results.
2. Marializa V. Bernardo, MD (Site 109): Southwest Houston Research, LTD
10850 S. Wilcrest Drive, Suite 170-A
Houston, Texas 77099
- a. What was inspected:
 - Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations.
 - Data verification: primary efficacy endpoint data, adverse events, protocol deviations, concomitant medication use, and subject discontinuation
 - Subjects: Complete records were reviewed for 12 subjects completing study 62745-6.
 - b. General observations and commentary: The study appears to have been conducted in accordance with the study protocol and applicable good clinical practice (GCP) regulations. Study conduct and results were well-documented. Observed deficiencies were limited to a few minor deficiencies in obtaining informed consent. A Form FDA 483 (cited deficiencies) was not issued.
 - c. Assessment of data integrity: Data appear reliable.

3. Andrew Bland, MD (Site 203): Renal Care Associates

515 NE Glen Oak 108
Peoria, Illinois 61603

a. What was inspected:

- Scope of inspection: subject eligibility, informed consent, test article accountability and disposition, adherence to protocol and applicable regulations.
- Data verification: primary efficacy endpoint data, adverse events, protocol deviations, concomitant medication use, and subject discontinuation
- Subjects: 41 subjects were randomized into study 62745-7, of whom 37 completed the study. Subject records were reviewed for 10 subjects. Complete subject records were reviewed for 6 subjects.

b. General observations and commentary: The study appears to have been conducted in accordance with the study protocol and applicable good clinical practice (GCP) regulations. Study conduct and results were well-documented. Observed deficiencies were limited to not maintaining adequate records regarding test article disposition and reconciliation; however, the inspection found that the subjects received the appropriate randomized product. A Form FDA 483 (cited deficiencies) was not issued.

c. Assessment of data integrity: Data appear reliable.

III. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

In general, the data generated by the three clinical investigator sites are considered acceptable in support of this application, with the exception of four subjects at Site 139. Inaccurate drug disposition records at Site 139 (see above, second bullet under *Cited Deficiencies*) raises concerns about the reliability of the data from subjects 622, 626, 648, and 655. DSI recommends removing the efficacy and safety data from these four subjects in analyzing study results.

Aside from this concern regarding these four subjects at Site 139, serious deficiencies were not observed at inspection of these clinical sites. Minor deficiencies consisted of occasionally not reporting adverse events if they do not appear to be treatment-related (Site 139), suboptimal records for test article disposition and reconciliation (site 203), and suboptimal informed consent procedures (Site 109). In general, these deficiencies are not expected to affect data integrity.

Provided that the data from subjects 622, 626, 648, and 655 at Site 139 are removed from study analyses, the data generated from these clinical sites are considered acceptable in support of the proposed indication. However, the review division will need to consider the issue raised above (Site 139, regarding changes to erythropoietin dosing during study) in the determination of safety and efficacy of ferumoxytol in support of the proposed indication. While observed for Site 139, this protocol-related concern may be applicable to many other clinical sites.

Note: The final inspection reports for Sites 109 and 203 (Drs. Bernardo and Bland, respectively) are pending; upon receipt and review of the final inspection reports, an addendum to this clinical inspection summary will be provided if additional observations of clinical or regulatory significance are discovered.

{See appended electronic signature page}

John Lee, M.D.
Good Clinical Practice Branch II
Division of Scientific Investigations

CONCURRENCE:

{See appended electronic signature page}

Tejashri Purohit-Sheth, M.D.

Branch Chief

Good Clinical Practice Branch II

Division of Scientific Investigations

Office of Compliance

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/s/

John Lee
10/14/2008 11:38:59 AM
MEDICAL OFFICER

Tejashri Purohit-Sheth
10/14/2008 11:53:03 AM
MEDICAL OFFICER

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Tuesday, September 30, 2008 4:30 PM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol

Dr. Salem,

We are reviewing the clinical section of your submission and have the following information request.

Please provide for each of the clinical efficacy and safety studies the number of patients who were injectable iron-naïve (also by treatment group for controlled studies).

Please submit by COB October 2, 2008.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

Hyon.Lee@fda.hhs.gov

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9/30/2008

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/s/

Hyon Z Lee
9/30/2008 04:35:05 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, September 29, 2008 3:18 PM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol

Dr. Salem,

We are reviewing your submission dated September 22, 2008 regarding labeling and have the following comment:

Although you have included "For IV Use Only." in the single and multivial carton labels, this statement was placed on the top panel of the carton. Please increase the prominence of the font and move this statement into both the front and back of carton label (next to "Rx only").

Please resubmit by COB October 2, 2008.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

Hyon.Lee@fda.hhs.gov

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9/29/2008

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/s/

Hyon Z Lee
9/29/2008 03:34:30 PM
CSO

From: Lee, Hyon-Zu
Sent: Friday, September 19, 2008 4:48 PM
To: 'Mohammed Salem'
Subject: ferumoxytol: Information Request

Dr. Salem,

Please provide clarification on the attached document.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

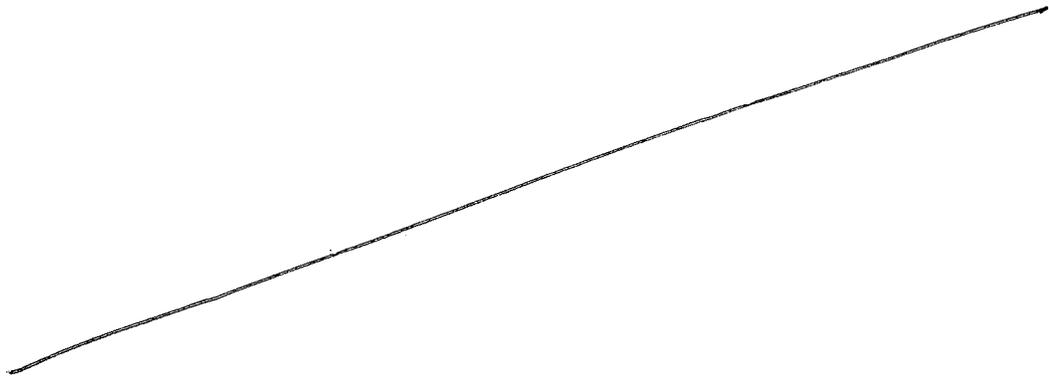
Hyon.Lee@fda.hhs.gov

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9/19/2008

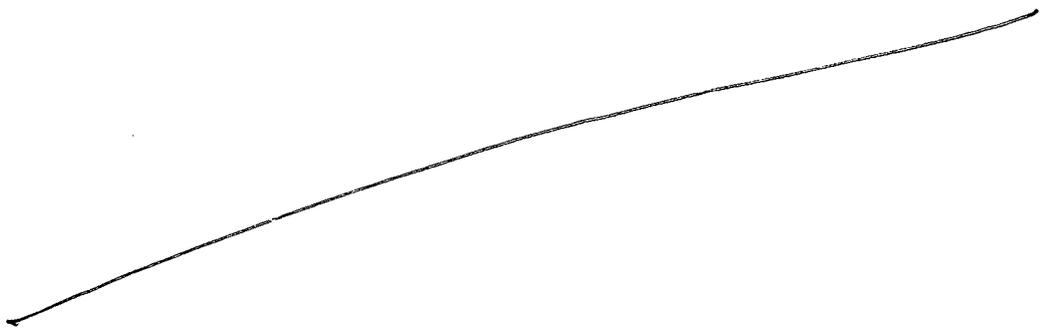
When analyzing the sponsor provided dataset S_EFFIC.xpt (efficacy dataset), some discrepancies (highlighted) were noted in the labeling and analysis for ITT population. Please provide clarification.

Protocol 62,745-5 Post - Summary of Efficacy (ITT Population)

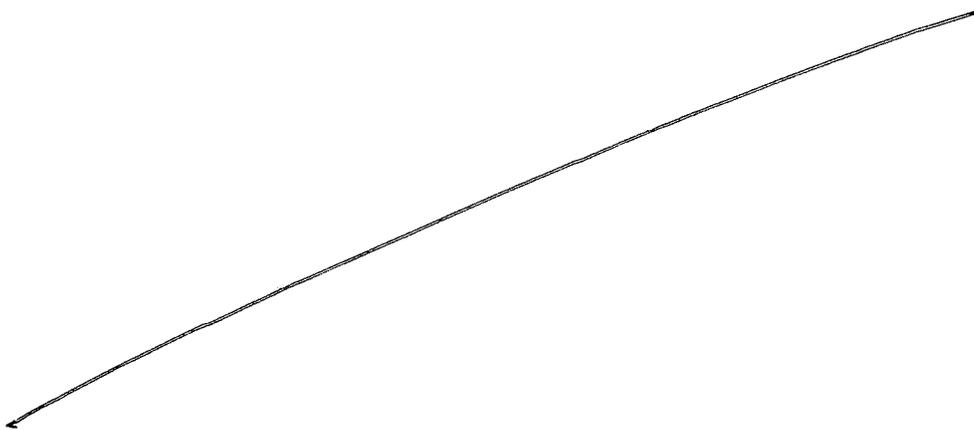


Protocol 62,745-6 - Summary of Efficacy (ITT Population)

b(4)



Protocol 62,745-7 - Summary of Efficacy (ITT Population)



b(4)

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ON ORIGINAL**

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Hyon Z Lee
9/19/2008 05:31:27 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Thursday, September 18, 2008 3:53 PM
To: 'Mohammed Salem'
Subject: ferumoxytol PI: FDA edits
Attachments: 22180 FDA to AMAG 9.18.09.clean..doc

Dr. Salem,

We are providing you our preliminary edits of the ferumoxytol label. Please see attached and let me know when you will respond.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050
Fax: 301-796-9849
Hyon.Lee@fda.hhs.gov

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9/18/2008

13 Page(s) Withheld

 Trade Secret / Confidential (b4)

 Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

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/s/

Hyon Z Lee
9/18/2008 04:30:47 PM
CSO



NDA 22-180

INFORMATION REQUEST LETTER

AMAG Pharmaceuticals, Inc.
Attention: Mohammed Salem, Ph.D., RAC
100 Hayden Avenue
Lexington, MA 02421

Dear Dr. Salem:

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ferumoxytol injection.

We are reviewing the Clinical and Chemistry, Manufacturing and Controls (CMC) sections of your submission and have the following comments and information requests. We request a prompt written response by September 23, 2008 in order to continue our evaluation of your NDA.

Clinical:

1. For Studies 62,745-6, 62,745-7, and Study 62745-5 pre-amendment and post-amendment separately, please provide a table summarizing duration of interval between the two ferumoxytol doses by number of days (1, 2, 3, 4, 5, 6, 7, 8, etc.) giving total numbers of patients within each interval duration (e.g., how many patients had their two doses separated by 1 day? By 2 days?, etc.).
2. Provide the number (%) of patients who had serum ferritin ≥ 800 ng/mL and TSAT $\geq 50\%$ during the post-treatment period in CKD patients who received ferumoxytol 510 mg for 2 doses based on all available database.

CMC:

Drug Substance:

3. _____
4. The proposed specification limit for mean particle size of _____ nm is still too broad. The mean value for particle size for the provided 30 lots is _____

b(4)

5. Provide an updated drug substance specification table.

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/s/

Rafel Rieves
9/18/2008 08:39:50 AM



NDA 22-180

INFORMATION REQUEST LETTER

AMAG Pharmaceuticals, Inc
Attention: Mohammed Salem, Ph.D., RAC
125 CambridgePark Drive, 2nd Floor
Cambridge, MA 02140

Dear Dr. Salem:

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ferumoxytol injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in ten days of receipt of this letter in order to continue our evaluation of your NDA.

Drug Substance:

1. For the proposed drug substance specifications, we have the following comments:

- a. _____

- b. The proposed acceptance criterion for magnetic susceptibility _____
_____ is too broad. Tighten this criterion based on your batch release data.
- c. The proposed acceptance limit for mean particle size (_____ μm) is too broad. Tighten this criterion to better reflect your batch data.
- d. The proposed acceptance limit for Total Carbon Content (_____) is too broad. Tighten the acceptance limit for Total Carbon Content to _____
- e. The proposed specification of $< / >$ ionic iron is too broad compared to your provided batch analysis data (all lots $< / >$ _____ μg). Additionally, you provided no information regarding the safety of your proposed limit. Tighten your proposed acceptance criterion for ionic iron based on your batch data and any applicable safety data.

b(4)

- f. The proposed acceptance criterion ($< \text{--- ppm}$) for --- content is too broad compared to the provided batch analysis data (maximum value --- ppm). Tighten this criterion based on your batch data. **b(4)**
- g. Provide an updated drug substance specification table.

2.

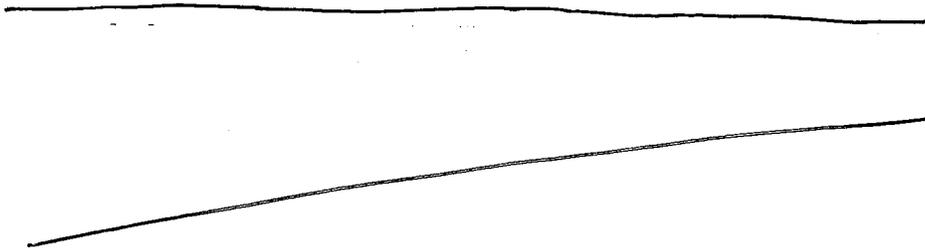
3.

4. Since you agreed to include specifications for particle size --- , modify the post approval stability protocol to include this test. **b(4)**

Drug Product:

5. For the proposed drug substance specifications, we have the following comments:
- a. The proposed acceptance limit for magnetic susceptibility (---) is too broad. Tighten this criterion based on your batch release data.
 - b. The proposed acceptance limit for mean particle size (--- nm) is too broad. Tighten this criterion to better reflect your batch data.
 - c. The proposed specification limit of --- \% ionic iron is too broad compared to the batch analysis data (all lots $< \text{--- \%}$), and no information was provided regarding the safety of the proposed limit. Tighten the specification limit for ionic iron based on your data and any applicable safety data. **b(4)**
 - d. For the 510 mg/17 mL strength, change the acceptance limit for the volume in each container to be, minimally, greater than the target fill volume.
 - e. Provide an updated drug product specification table.
6. Since you agreed to include a specification for particle size --- , modify the post approval stability protocol to include this test.

Labeling:

7. The proposed single vial carton label needs the following revisions:
 - a. Increase the prominence of the "Rx only" on both the front and side panels of the label by using bolding and larger font.
 - b. On the front panel of the carton label, modify the strength statement under the trade and established names to indicate the amount of active in each vial, such as "510 mg elemental iron per 17 mL (30 mg/mL)". Revise the proposed carton labels for all three vial configurations accordingly.
 - c. Delete the logo located above the company's name "AMAG pharmaceuticals".
8. Revise the proposed vial labels for all three configurations to delete the logo located above the company's name "AMAG pharmaceuticals".
9. 
10. Delete the logo located above the company's name "AMAG pharmaceuticals".

b(4)

If you have any questions, call Hyon-Zu Lee, Pharm.D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Sarah C. Pope, Ph.D.
Acting Chief, Branch V (CMC-Pre-marketing)
Division of Pre-market Assessment and Manufacturing Science
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Sarah Pope
8/29/2008 03:30:04 PM
Concur

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Monday, August 25, 2008 11:10 AM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxitol: Pediatric studies information requests

Dr. Salem,

We are reviewing your submission dated August 4, 2008 containing "Pediatric Studies Description" and the following information requests. Please respond by September 3, 2008:

For each proposed pediatric study:

- provide justification for the proposed sample size / _____
- specify measures to assure appropriate representation of patients across the age range being studied,
- specify the statistical hypothesis(es) that will be tested in each study and describe your statistical methods.

b(4)

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050
Fax: 301-796-9849
Hyon.Lee@fda.hhs.gov

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8/25/2008

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Hyon Z Lee
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CSO

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DTP



NDA 22-180

INFORMATION REQUEST LETTER

AMAG Pharmaceuticals, Inc.
Attention: Mohammed Salem, Ph.D., RAC
Vice President, Regulatory Affairs
125 Cambridge Park Drive, 2nd Fl
Cambridge, MA 02140

Dear Dr. Salem:

Please refer to your December 18, 2007 new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for ferumoxytol, injection.

We are reviewing the Chemistry, Manufacturing and Controls section of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

Propose drug substance specifications and provide release data for the following attributes:

1. Molecular weight distribution (weight average molecular weight and number average molecular weight).
2. Particle size distribution (i.e., D_{10} , D_{50} and D_{90} , etc.).
3. Turbidity, Fe^{++} and Fe^{+++} ratio or their absolute contents, and heavy metals, etc.

Many of these tests should also be performed in the drug substance stability testing program, and the data submitted to the FDA.

Furthermore, include these tests in the drug product specifications, as appropriate, and submit release data as well. Perform drug product stability testing for those attributes to determine whether the stability results may change or demonstrate a trend during storage. Alternatively, provide adequate scientific justification for not testing these quality attributes.

NDA 22-180
Page 2

If you have any questions, call Hyon-Zu Lee, Pharm. D., Regulatory Project Manager, at 301-796-2050.

Sincerely,

Ravi S. Harapanhalli, Ph.D.
Chief, Branch V, DPAMS
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

Ravi Harapanhalli
7/24/2008 05:29:53 PM

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Thursday, July 03, 2008 3:37 PM
To: 'Ratna Lingamani'
Cc: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxitol: Risk Management information requests

Ratna,

Please submit the following information (proposed materials not included in the original submission) requested by our Risk Management staff by July 14, 2008:

6. Evaluation of the Need for Risk Minimizing Activities. Please provide the risk minimization tool involving

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050
Fax: 301-796-9849
Hyon.Lee@fda.hhs.gov

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7/3/2008

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/s/

Hyon Z Lee
7/3/2008 03:56:29 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Thursday, June 26, 2008 4:20 PM
To: 'Mohammed Salem'
Subject: FW: NDA 22-180 ferumoxytol: pediatric protocols
Follow Up Flag: Follow up
Flag Status: Yellow

From: Lee, Hyon-Zu
Sent: Thursday, June 26, 2008 4:08 PM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol: pediatric protocols

Dr. Salem,

Please submit a general description of the pediatric protocol(s) for this application including the start date of enrollment, the start date to begin the studies and the date you plan to submit the studies.

Please submit by August 4, 2008.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050
Fax: 301-796-9849
Hyon.Lee@fda.hhs.gov

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6/26/2008

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/s/

Hyon Z Lee
6/26/2008 04:45:38 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Tuesday, June 03, 2008 3:50 PM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol: Information Request

Dr. Salem,

In addition to the information requests asked to you on May 23, 2008, please provide the following:

1. Summary of occurrence of at least one value of ferritin ≥ 800 ng/mL, TSAT $\geq 50\%$ or both in patients who received ferumoxytol first course (510 mg x 2), second course (510 mg x 4) or single dose (510 mg, cross-over study) treatment based on all available safety database.
2. Summary of serum phosphate < 2 mg/dL and < 1 mg/dL (if any) by treatment group (ferumoxytol, oral iron and placebo) by visit based on all available safety database.
3. For cross-over study (62,745-8), summarize serum phosphate < 2 mg/dL by treatment group (ferumoxytol and placebo) for both prior to cross-over and post cross-over periods.

Again, please let me know when you will be able to submit the above information.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050

Fax: 301-796-9849

Hyon.Lee@fda.hhs.gov

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Hyon Z Lee
6/3/2008 04:01:07 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Friday, May 23, 2008 1:33 PM
To: 'Mohammed Salem'
Subject: NDA 22-180 ferumoxytol

Dr. Salem,

We have the following information requests regarding your NDA 22-180:

1. Summary of adverse events leading to study treatment discontinuation (permanent and temporary) by treatment group in all study subjects in the safety database.
2. Summary of adverse events leading to study treatment discontinuation (permanent and temporary) by treatment group in all CKD subjects.

Please let me know when you will be able to provide the above information.

Thanks,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050
Fax: 301-796-9849
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5/23/2008

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Hyon Z Lee
5/23/2008 01:47:00 PM
CSO

DE-5

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Friday, May 02, 2008 9:32 AM
To: 'msalem@amagpharma.com'
Subject: NDA 22-180 ferumoxytol
Follow Up Flag: Follow up
Flag Status: Yellow

Dr. Salem,

We are reviewing your NDA submission, and have the following information requests:

1. Please compare adverse events indicative of potential hypersensitive/allergic reactions among Ferumoxytol, oral iron, and placebo groups based on all available safety database.
2. Please calculate the incidence of hypersensitivity/allergic reactions based on above events among Ferumoxytol, oral iron, and placebo groups based on all available safety database.
3. Provide narratives for patients who had serious hypersensitivity/allergic reactions or anaphylaxis or anaphylactoid reactions (e.g., subject 239-821).

Please let me know when you will be able to submit the responses for the above questions.

Thank you,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office; 301-796-2050
Fax; 301-796-9849
Hyon.Lee@fda.hhs.gov

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5/7/2008

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Hyon Z Lee
5/7/2008 02:03:00 PM
CSO

Lee, Hyon-Zu

From: Lee, Hyon-Zu
Sent: Tuesday, April 01, 2008 10:04 AM
To: 'msalem@amagpharma.com'
Subject: NDA 22-180 ferumoxytol: information requests
Importance: High
Follow Up Flag: Follow up
Flag Status: Blue
Attachments: HighlightsofClinicalPharmacology.doc

Dr. Salem,

We are reviewing the NDA submission, and have the following information requests regarding the QTc study, CSR-62745-9, entitled: "a Phase 1 active- and placebo-controlled study of the electrocardiogram effects and pharmacokinetics of ferumoxytol in healthy men and women".

Please complete the attached ClinPharm table and submit as soon as possible. Additionally, please provide a copy of the most recent Investigator's Brochure for this application.

Please submit or provide the direct link for the SAS codes for primary analysis as they relate to this QTc Study Report.

Thanks,

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

Office: 301-796-2050
Fax: 301-796-9849
Hyon.Lee@fda.hhs.gov

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4/2/2008

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Hyon Z Lee
4/2/2008 01:23:46 PM
CSO



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

NDA 22-180

AMAG Pharmaceuticals, Inc
Attention: Mohammed Salem, Ph.D., RAC
125 CambridgePark Drive, 2nd Floor
Cambridge, MA 02140

Dear Dr. Salem:

Please refer to your new drug application (NDA) dated December 18, 2007, received December 19, 2007, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Ferumoxytol Injection.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is Standard. Therefore, the user fee goal date is October 19, 2008.

During our filing review of your application, we identified the following potential review issues and request additional information as noted:

Clinical:

1. Only one trial of ferumoxytol was conducted in patients undergoing hemodialysis using the proposed dose regimen. Adequacy of the safety information for the proposed dose in this population may be limited and will be a review issue.
2. The safety profiles appear to be different between patients who were enrolled pre-amendment and post-amendment in Study 62,745-5 (for example, most of the deaths in the ferumoxytol patients occurred before the amendment while most of the oral iron deaths occurred afterwards). Please provide explanations for the differences.
3. Provide a summary table of cardiovascular adverse reactions by treatment group by study.
4. Provide a summary table for composite of all deaths and cardiovascular adverse reactions by treatment group by study.
5. Two patients died prior to receipt of any study medication (patient 121-503 in Study 62,745-5 and patient 139-805 in study 62,745-8). Please indicate the treatment group assignment for each of these patients.
6. Clarify the number of subjects who were exposed to Ferumoxytol and the number exposed to control treatment in each study for the 11 clinical studies.

Clinical Pharmacology:

7. It is noted that the PK-PD correlation (i.e., plasma concentration or dose vs. safety or efficacy parameters) has not been reported in the clinical pharmacology section of the submission. Please provide any available data about exposure vs. safety and/or efficacy parameters such as Hgb, serum ferritin, and TSAT.

Labeling (Physician's Labeling Rule Format):

8. Highlights:

- When the labeling is in final draft, the Highlights and Contents must be limited in length to one-half page, 8 point font in a two-column format. [See 21 CFR 201.57(d)(8)].
- The drug name should be followed by dosage form and route of administration. [See 21 CFR 201.57(a)(2)].
- Highlights limitation statement should be bolded and be placed on the line immediately beneath the heading.
- Drug name, dosage form and route of administration statement under the Highlights limitation statement should be bolded.
- The tradename should be in regular font, not in italics throughout the labeling.
- Initial U.S. Approval statement must be placed on the line immediately beneath the name of the product.
- Under Indications and Usage, please include the established pharmacologic class as follows: "(Drug) is a (name of class) indicated for (indications)".
- Under Dosage Forms and Strengths, the _____ should be bulleted or in tabular presentation.
- All headings must be presented in the center of a horizontal line. The horizontal line can be a solid or dashed line.
- The preferred format for revision date presented at the end of Highlights in bold is "Revised: Month Year" or "Revised: Month/Year" (i.e., Revised: June 2003 or Revised: 6/2003).

b(4)

9. Full Prescribing Information: Contents:

- The Agency recommends use of a two-column format for the Table of Contents, and if possible, that it be limited in length to one-half page.
- A horizontal line must be located between the Table of Contents and the Full Prescribing Information.
- Table of Contents section headings must be in bold type and should be in upper-case letters. The Table of Contents subsection headings must be indented and not bolded.

10. Full Prescribing Information (FPI):

- The revision date at the end of Highlights replaces the "revision" or "issued" date at the end of the labeling. The revision date should not appear in both places.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that

may be identified during our review. Issues may be added, deleted, expanded upon, or modified as we review the application.

If you have not already done so, you must submit the content of labeling [21 CFR 314.50(1)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. The content of labeling must be in the Prescribing Information (physician labeling rule) format.

Please respond only to the above requests for additional information. While we anticipate that any response submitted in a timely manner will be reviewed during this review cycle, such review decisions will be made on a case-by-case basis at the time of receipt of the submission.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirements. We acknowledge receipt of your request for a waiver of pediatric studies for this application for pediatric patients 0-2 years of age.

All applications for new active ingredients, new dosage forms, new indications, new routes of administration, and new dosing regimens are required to contain an assessment of the safety and effectiveness of the product in pediatric patients unless this requirement is waived or deferred. We note that you have not fulfilled the requirement. We acknowledge receipt of your request for a deferral of pediatric studies for this application for pediatric patients 2-~~7~~ years of age.

b(4)

If you have any questions, call me at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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Hyon Z Lee
2/28/2008 03:31:47 PM



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

NDA 22-180

NDA ACKNOWLEDGMENT

AMAG Pharmaceuticals, Inc
Attention: Mohammed Salem, Ph.D., RAC
125 CambridgePark Drive, 2nd Floor
Cambridge, MA 02140

Dear Dr. Salem:

We have received your new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for the following:

Name of Drug Product: Ferumoxytol Injection

Date of Application: December 18, 2007

Date of Receipt: December 19, 2007

Our Reference Number: NDA 22-180

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 17, 2008 in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/oc/datacouncil/spl.html>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must be in the Prescribing Information (physician labeling rule) format.

The NDA number provided above be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Medical Imaging and Hematology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

NDA 22-180

Page 2

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/cder/ddms/binders.htm>.

If you have any questions, call me at 301-796-2050.

Sincerely,

{See appended electronic signature page}

Hyon-Zu Lee, Pharm.D.
Regulatory Project Manager
Division of Medical Imaging and Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

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Hyon Z Lee
12/20/2007 04:06:34 PM

MEMORANDUM OF TELECONFERENCE

MEETING DATE: July 20, 2007
TIME: 9:30 AM – 11 PM
LOCATION: Conference Room 1415 (White Oak)
APPLICATION: IND 62,745
DRUG NAME: Ferumoxytol Injection
TYPE OF MEETING: Pre-NDA meeting

MEETING CHAIR: Kathy Robie-Suh, M.D., Ph.D.

MEETING RECORDER: Hyon-Zu Lee, Pharm.D.

FDA ATTENDEES:

Division of Medical Imaging and Hematology Products (DMIHP)

Rafel Rieves, M.D., Acting Division Director
Kathy Robie-Suh, M.D., Ph.D., Medical Team Leader
Min Lu, M.D., M.P.H., Medical Reviewer
David Bailey, Ph.D., Pharmacology/Toxicology Reviewer
Sunday Awe, Ph.D., Pharmacology/Toxicology Reviewer
Eldon Leutzinger, Ph.D., Chemistry Pool Reviewer
Young Moon Choi, Ph.D., Clinical Pharmacology Team Leader
Satish Misra, Ph.D., Statistics Reviewer
Hyon-Zu Lee, Pharm.D., Regulatory Health Project Manager

EXTERNAL CONSTITUENT ATTENDEES:

Advanced Magnetics, Inc.

Brian Pereira, M.D., President, CEO and Chief Medical Officer
Mohammed Salem, Ph.D., Vice President of Regulatory Affairs & QA
Louis Brenner, M.D., Senior Vice President
Annamaria Kausz, M.D., Senior Director of Medical Affairs
Ratna Lingamaneni, Ph.D., Associate Director of Regulatory Affairs
Jovanna Baptista, M.S., Associate Director of Biostatistics and Data Management

Consultants

b(4)

BACKGROUND AND PURPOSE OF THE TELECONFERENCE:

Advanced Magnetics submitted a pre-NDA meeting request on May 15, 2007 to obtain the Agency's concurrence on the development program of ferumoxytol in Chronic Kidney Disease (CKD), to discuss the Phase 1, Phase 2 and Phase 3 clinical data to support the safety and

efficacy, to discuss the rationale for priority review and the requirements under Pediatric Research Equity Act (PREA).

SUMMARY OF THE TELECONFERENCE:

In response to the questions in the June 21, 2007 background package, the following agreements were reached after the discussion. The format provides the firm's questions in italics followed by DMIHP in bolded font and the sponsor's response to FDA's response in regular font.

During the discussion, the sponsor used the various slides below to address FDA's comments.

Clinical

Question 1: Safety exposure

The main focus of this clinical program was to evaluate the safety and efficacy of a ferumoxytol therapeutic course of 1.02 g given as a regimen of 2 x 510 mg in subjects with all stages of CKD. Approximately 1,722 subjects were exposed to ferumoxytol in the clinical program, of whom 1,563 were subjects with all stages of CKD [non dialysis, hemodialysis (HD), peritoneal dialysis (PD) and transplants]. The combined clinical data represent a total of approximately 802 subjects who received a therapeutic course of ferumoxytol as a regimen of 2 x 510 mg, 70 subjects who received a regimen of 4 x 255 mg, and 15 subjects who received a regimen of 8 x 128 mg. Additionally, a total of 714 subjects received a single dose of 510 mg ferumoxytol, and 121 subjects received lower doses (≤ 4 mg/kg, 1 x 250 mg, or 1 x 125 mg) of ferumoxytol. Approximately 68 subjects in Phase III studies who had been treated with a course of ferumoxytol, given as regimens of 2 x 510 mg (N=56) or 4 x 255 mg (N=12), also received a second course of ferumoxytol as a regimen of 2 x 510 mg.

Of the 802 subjects who received a full course of ferumoxytol as a regimen 2 x 510 mg, 58 subjects were healthy volunteers who received two doses of 510 mg ferumoxytol within 24 hours in Study 62,745-9 (Thorough QTc study). The safety database also includes 101 other subjects (healthy volunteers and imaging patients) from Phase I and II studies who received ferumoxytol at ≤ 4 mg/kg.

Overall, the safety data demonstrate that ferumoxytol has been well tolerated in subjects with all stages of CKD compared to oral iron and saline placebo. Details on exposure and safety of ferumoxytol are provided in Section 12.4.4.

Does the Agency agree that the overall safety exposure to ferumoxytol is sufficient to support a market application?

FDA response:

The overall safety exposure to ferumoxytol in your clinical studies appears to be reasonable for submission. However, the sufficiency of the safety data to support approval for marketing is a review issue. Support for the proposed dose regimen in the intended population also will be a subject of the review.

Sponsor agreed.

Question 2: Safety and Efficacy to Support Registration

Advanced Magnetics, Inc. believes that the completed comprehensive Phase III development program in subjects with CKD stages 1-5 and 5D, supported by Phase I and II trials in healthy volunteers and subjects with CKD stages 1-5 and 5D, provides sufficient evidence of the safety and efficacy of ferumoxytol. The proposed indication for ferumoxytol is for the treatment of iron deficiency anemia in patients with CKD. The clinical data is summarized in Sections 12.4.3 and 12.4.4.

Does the Agency agree that the completed clinical studies in subjects with CKD stages 1-5 and 5D provide sufficient safety and efficacy data to support a market application of ferumoxytol for the treatment of iron deficiency anemia in CKD patients?

FDA response:

With regard to the safety database, see response above. Adequacy of the application with regard to safety and efficacy to support marketing approval will be a review issue. It is noted that only one Phase 3 study was conducted in patients with CKD stage 5D and it appears that different dose regimens were used in that study. Your additional studies conducted in patients with CKD stages 1-5 will need to support the desired indication in this population. However, the studies you plan for submission appear acceptable for submission.

The sponsor agreed that this would be a review issue and explained the slides below regarding the subjects exposed to different dosing regimen, responses and adverse event rates.

Question 3: Dose

The safety and efficacy of ferumoxytol as an iron replacement therapy (1.02 g course) has been evaluated with ferumoxytol regimens of 8 x 128 mg, 4 x 255 mg and 2 x 510 mg, with the focus of the pivotal clinical program on the 2 x 510 mg regimen as the most appropriate to consistently replete iron stores, enhance compliance with therapy and thus improve patient care. In addition, 68 subjects in the Phase III studies who continued to meet the original study entry criteria were treated with a second 1.02 g therapeutic course of ferumoxytol as a regimen of 2 x 510 mg ferumoxytol.

A ferumoxytol regimen of 2 x 510 mg resulted in statistically significant increases in hemoglobin and ferritin compared with oral iron. Therapy with ferumoxytol has been well tolerated in subjects with all stages of CKD. Compared to oral iron, a complete course of ferumoxytol (1.02 g) given as a regimen of 2 x 510 mg was well tolerated. A second course of ferumoxytol given as a regimen of 2 x 510 mg (for a total exposure of 2.04 g) in CKD subjects also resulted in improved hemoglobin and was well tolerated. Please refer to Sections 12.4.3 and 12.4.4 for details.

- a) *Does the Agency agree that the completed clinical studies of ferumoxytol as a regimen of two doses of 510 mg substantiate the safety and efficacy of ferumoxytol in CKD patients?*

FDA response:

See responses to questions 1 and 2.

The Agency asked about the number of deaths in the clinical studies; the sponsor responded that there were 30 deaths in the clinical program. They stated that the death rate was 2.7% (8 out of 296) in the control group (oral iron) and 1% (18 out of 1722) in the ferumoxytol group.

The Agency emphasized the importance of mortality comparisons between the active and control products and note that, in general, no imbalance in the death rates should be demonstrated.

The sponsor responded that they would submit a detailed discussion and description of deaths to the NDA.

b) *Does the Agency agree that the studies of repeat courses of ferumoxytol are adequate to be able to show it is safe and effective for the treatment of iron deficiency anemia in CKD patients?*

FDA response:

The safety exposure experience with repeated courses of ferumoxytol appears to be limited. The data provided will be evaluated in the course of the NDA review. A sufficient safety database will be needed to establish the safety of exposure to repeated ferumoxytol treatment cycles.

The sponsor stated that they would include all data in the Integrated Summary of Safety (ISS) and Integrated Summary of Efficacy (ISE), and explained the breakdown of death rate as follows:

- 2 x 510 mg course: 0.8% death rate
- 4 x 255 mg course: 1.7% death rate
- oral iron: 1.07% death rate

Question 4: Clinical Pharmacology

The pharmacokinetic (PK) properties of ferumoxytol have been evaluated both in healthy volunteers (Study 7228-01 and Study 62,745-09) and in subjects with CKD stage 5D (Study 62,745-02). Data from these studies demonstrate that ferumoxytol exhibits dose-dependent, capacity-limited elimination, mostly via uptake into the reticuloendothelial system. The PK profile of ferumoxytol was best described using a two-compartment model with non-linear elimination, and is similar to the profiles described for iron dextran and iron sucrose. The study in subjects with CKD stage 5D demonstrated that ferumoxytol is not dialyzed, which was not unexpected given its large molecular weight. Ferumoxytol appears to be cleared from plasma at least as rapidly in subjects with CKD stage 5D as in healthy volunteers. Please refer to Section 12.4.2 for details.

Does the Agency agree that the overall clinical pharmacology data from studies 7228-01, 62,745-09 and 62,745-02 are adequate to support the registration of ferumoxytol for the treatment of iron deficiency anemia in CKD patients?

FDA response:

We acknowledge that the pharmacokinetic properties of ferumoxytol have been evaluated in healthy volunteers and chronic kidney disease patients. We also acknowledge that you did not establish the relationship of systemic exposure of ferumoxytol with clinical endpoints in Phase 1 and 2 studies, but evaluated two dose levels in Phase 3 studies.

From a Clinical Pharmacology perspective, the adequacy of these studies to support your NDA is contingent upon a thorough review of the submission.

The sponsor stated that 1gm course is a long-standing prevailing practice and that the 128mg, 255mg and 510mg doses gave similar efficacy and safety results in Phase 2 studies, and that the 510mg dose was selected because it was the most convenient dose.

Special Programs

Question 5: Pediatric Deferral

Based on the low incidence and prevalence of CKD in children relative to adults, Advanced Magnetics, Inc. requests a deferral from conducting a pediatric trial with ferumoxytol. Please refer to Section 12.5.1 for details. An outline of the proposed Pediatric Study design is provided in Appendix A for the Agency's review.

- a) *Does the FDA agree that a request for a deferral for conducting a pediatric study is appropriate?*

FDA response:

You may submit a request for deferral of pediatric studies with your justifications in the NDA application. Your pediatric development plan should address all pediatric age ranges.

The sponsor agreed and stated that they were planning to ask for a waiver for the pediatric population less than 2 years of age.

The Agency stated that the all pediatric age range group needed to be addressed including justifications for deviations from PREA expectations.

- b) *Does the Agency agree with the proposed pediatric study design?*

FDA response:

The full protocol for any pediatric study that you plan should be submitted for review. Adequacy of your proposed pediatric study(ies) to satisfy any requirement for pediatric study under PREA will be evaluated after submission of your NDA.

The sponsor stated that they were planning to submit the final proposal for pediatric studies not in the NDA, but at a later date.

Question 6: Priority Review Status for NDA Review

Despite the availability of approved IV iron therapies, their low utilization in patients with CKD stages 1-5 suggests that there continues to be an unmet need for efficient and safe alternative therapies for the treatment of iron deficiency anemia in CKD. Advanced Magnetics, Inc. believes that ferumoxytol, with its ease and practicality of direct injection and its favorable safety profile, will facilitate optimal therapy of iron deficiency anemia in CKD.

Appropriate iron replacement therapy may also permit achievement of target hemoglobin with a reduction in ESA use. In a post-hoc analysis, pooled data from two identically-designed Phase III randomized trials revealed that in subjects with CKD stages 1 -5 not receiving ESA, subjects receiving ferumoxytol were two-fold more likely to achieve target hemoglobin than subjects receiving oral iron. These data suggest that ferumoxytol may delay, limit, or obviate the need for ESA treatment in patients with CKD stages 1 -5 with iron deficiency anemia. These are potentially important benefits given recent concerns about the safety of using high doses of ESA in CKD patients.

As detailed in Section 12.5.2, ferumoxytol satisfies several criteria for priority review status.

Does the Agency agree that the ferumoxytol NDA is appropriate for consideration for Priority Review?

FDA response:

The review status will be determined after NDA submission. You may submit your request with justifications in the NDA submission. As you note there are approved safe and effective intravenous iron preparations available, so support for priority review of ferumoxytol would need to be particularly persuasive.

The sponsor explained the slide 22 below, and stated they would provide justifications in the NDA.

Nonclinical

Question 7: Nonclinical Program

The nonclinical pharmacology, pharmacodynamics, safety pharmacology, pharmacokinetics, and toxicology of ferumoxytol have been evaluated using various in vitro systems and animal models. In vivo and in vitro systems have been utilized to assess toxicologic effects, including single and repeat dose toxicity, genotoxicity, reproductive toxicity, and specialized studies of local irritation, hemolysis and potential for inducing immediate hypersensitivity reactions. Details of these study designs and the results are provided in Section 12.3.

Does the Agency agree that the overall nonclinical program is adequate to support the review and approval of the ferumoxytol NDA?

FDA response:

It appears that the information provided in the study reports submitted and the unreported studies included by title only are adequate to support submission of the NDA.

However, with the number of reports "In Preparation" as indicated in the pre-NDA meeting package, it is premature to indicate whether the information is adequate to support approval of the NDA. Upon review of final reports, it may be determined that other studies or additional data are needed to address issues that may arise during in depth review of reported and unreported nonclinical studies as well as issues that may arise from review of clinical trials or from evaluation by other disciplines to support approval.

The sponsor agreed and stated that they would submit all reports in the NDA.

The Agency stated that the sponsor should submit full final study reports, and the sponsor agreed.

NDA Format

Question 8: Clinical Data Submission

Advanced Magnetics, Inc. intends to submit the NDA for ferumoxytol in eCTD format. The electronic submission will be published by _____ in accordance with current ICH and FDA eCTD Specifications.

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Case report tabulations will be provided as SAS Datasets for the clinical studies conducted in support of the indication. Each dataset will be provided as a SAS Transport (XPORT) file in accordance with the 1999 FDA guidances, "Providing Regulatory Submissions in Electronic Format - General Considerations," and "Providing Regulatory Submissions in Electronic Format - NDAs" and current FDA study data specifications. Data definition files describing the format and content of each dataset as well as annotated Case Report Forms for each study will be provided.

Individual annotated electrocardiogram (ECG) waveform data obtained in Study 62749-9 (Thorough QTc study) will be uploaded to the Mortara ECG Data Warehouse and will be available for FDA review at the time of the NDA submission. The annotated ECG waveform data files for the study were created by _____ in accordance with the HL 7 normative standard. More details on the format of the NDA are discussed in Section 13.

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Does the Agency agree with the Sponsor's approach for the clinical data submission in the NDA?

FDA response:

Refer to all pertinent guidance for electronic Common Technical Document (eCTD) including: www.fda.gov/cder/regulatory/ersr/.

The sponsor stated that they are planning to submit the NDA in the fourth quarter of this year in eCTD format and that it would be a fully electronic submission.

Also, provide the derived efficacy datasets for each study. This will include one record per patient, study ID, unique patient ID, demographic characteristics (age, sex, race, center), treatment arms, treatment compliance, dose regimen, covariates, CKD status, the day of

evaluation, responders (yes/no), Hgb values, and other efficacy parameters including ferritin levels. Additional displays of data may be requested during review as needed.

The sponsor agreed and stated that they would also include geographical regions as one of the variable in the derived efficacy datasets.

CMC Comments:

We have noted that there are no questions for CMC in the meeting package for the coming Pre-NDA meeting to be held on July 20, 2007. We also note that the last meeting with the Agency for CMC was on November 4, 2005 and are wondering if there are any updates to your CMC development plan. In the event that there have been updates or changes to your development plan for CMC that the Agency is not aware of from previous meetings and that will become part of the forthcoming NDA, we recommend that you request a separate meeting to discuss it with the Agency.

The sponsor indicated that there were minor CMC changes in the commercial configurations after the briefing package was submitted in 2005. They stated that the changes in raw materials, vendors and vials were provided in the annual report this year and in the CMC amendment (serial number 95), but that there were no changes in the formulations and methods, that they were not planning to have a separate CMC pre-NDA meeting and that all information would be submitted in the NDA.

Additional FDA comments:

In your NDA submission please also provide the following:

- **Integrated summary of safety that should include all deaths, other SAEs, discontinuations, hypersensitivity/allergic reactions, as well as all AEs and clinical laboratory, vital signs, ECGs, and other safety evaluations.**
- **Above safety analysis by study population and dose regimen.**
- **Summary and analysis of possible iron overload (ferritin >800 ng/mL or TSAT>50%) in your clinical studies.**
- **Your prospectively written statistical analysis plan (SAP) for your Phase 3 studies in your NDA submission.**
- **Efficacy analysis in intent-to-treat population for each Phase 3 study.**
- **In the event that the Day 35 data were missing, your analyses imputed the baseline value for value on Day 35. Please provide analyses considering other imputation methods and provide sensitivity analyses. These sensitivity analyses should be part of your SAP for your Phase 3 studies.**
- **Full datasets from all clinical studies**

- **Narratives for all patients who experienced serious adverse events, withdrew due to adverse events or died.**
- **Case report forms for all patients who withdrew from the study prematurely regardless of reason for withdrawal and for all deaths**
- **A table that shows the studies, centers, investigators and number of subjects enrolled to assist in determination for DSI inspection decisions.**

The Agency added that the sponsor should pay close attention to guidance and language to include in the Physician Labeling Rule (PLR).

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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/s/

Hyon Z Lee

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MEMORANDUM OF MEETING MINUTES

Meeting Date: October 9, 2003

Time: 3:30-5:00 PM

Location: Parklawn Building, 3rd Floor, Conference Room B

Application: IND 62,745

Type of Meeting: End of Phase II

Meeting Chair: Kathy Robie Suh, M.D., Ph.D.

Meeting Recorder: Tanya Clayton, B.S.

FDA Attendees, Titles, and Office/Division:

Division of Gastrointestinal and Coagulation Drug Products

Robert Justice, M.D., M.Sc.	Division Director
Joyce Korvick, M.D., M.P.H.	Deputy Division Director
Kathy Robie Suh, M.D., Ph.D.	Medical Team Leader, Hematology
Liang Zhou, Ph.D.	Team Chemistry Leader
Suliman AL-Fayoumi, Ph.D.	Biopharm Reviewer
Tanya Clayton, B.S.	Regulatory Project Manager

External Constituent Attendees and Titles:

Advanced Magnetix, Inc.

Mark Roessel	Vice President, Regulatory Affairs
Paula Jacobs, Ph.D.	Vice President, Development
Deborah Strahs	Clinical Trials Coordinator
Lisa Gordon	Development

Background:

On August 5, 2003, the sponsors requested a End of Phase II meeting for the purpose of reviewing with the Division the safety and efficacy data obtained for ferumoxytol from the two Phase II studies in chronic kidney disease and hemodialysis patients. The sponsor also wanted to get the Agency's input on the design of Phase III clinical trials and any necessary Phase IV clinical studies.

A subsequent September 10, 2003 background package was submitted, which contained 6 questions.

Following introductions, the Sponsor provided a brief overview of the safety and efficacy results of the Phase II clinical trials.

Discussion Points: (bullet format):

1. Does the Division have specific recommendations on the primary efficacy endpoint for an intravenous iron therapy?
 - **Change in hemoglobin from baseline is acceptable as the primary efficacy endpoint.**
 - **The protocol should specify a clinically significant increase in hemoglobin that will be used to classify a patient as a success or failure. Proportions of patients successfully treated in each treatment groups should be compared as an efficacy analysis.**
 - **Stable baseline hemoglobin must be well-documented (more than two measurements).**
 - **Please clarify duration of dosing.**
 - **The firm indicated that dosing is intended to occur over 2 weeks.**
 - **Please clarify time at which efficacy endpoints will be assessed for the primary efficacy analysis.**
 - **The firm will specify this in the protocol and provide a statistical plan.**

2. Does the division have comments on the use of oral iron as a control group?
 - **The proposed use of oral iron as a control group is acceptable.**
 - **The study protocols should provide for assessing compliance with oral iron therapy.**
 - **Each clinical study should be sized to demonstrate superiority of either of the ferumoxytol dose regimens separately over oral iron with regard to the change in hemoglobin.**

3. Does the Division have comments or recommendations to the sponsor for establishing a meaningful safety profile for ferumoxytol?
 - **The proposed clinical development plan appears to provide data on about 300 patients who have been exposed to repeated doses of ferumoxytol. The database should include about 1500 patients/subjects exposed to ferumoxytol and 300-600 patients in each clinical setting (i.e, renal failure patients on hemodialysis and chronic renal failure patients not on hemodialysis and incorporate some evaluation of longer term safety and safety on re-exposure. Refer to "ICH-E1A: Guideline for Industry. The Extent of Population Exposure to Assess Clinical Safety: For Drugs Intended for Long-term Treatment of Non-Life Threatening Conditions."**
 - **The firm will provide a proposal to address this concern.**
 - **Patients should be followed for at least 1 month after the last dose.**

4. Does the Division have recommendations for presenting safety data from medical imaging clinical trials?
 - **It is appropriate to present all safety data accumulated with ferumoxytol for all patients who have been exposed to the drug.**
 - **The proposed subanalyses are acceptable. In addition, separate subanalyses of renal failure patients on hemodialysis and those not on hemodialysis should be performed.**

5. If the safety of a 510 mg of iron dose of ferumoxytol can be established, and the efficacy of lower doses of ferumoxytol is established, can the product be labeled so that doses up to 510 mg of iron may be administered?

- Adequate information from clinical studies will be needed to support the dosing recommendation, including rate of drug administration, duration of treatment and dosing frequency.
- Since repeated dosing likely will be used in clinical practice, it should be studied in your trials.

6. Can pediatric use be studied as a Phase IV commitment?

- Currently, the Pediatric Rule is not being enforced.

Additional comments:

Clinical

- You have proposed a single study to support approval of ferumoxytol for — indication (treatment of iron deficiency anemia in renal failure patients) ✓

b(4)

You should refer to “**Guidance for Industry: Providing Clinical Evidence of Effectiveness for Human Drugs and Biological Products**, May 1998.”

- You should submit full protocols for the Phase 3 studies to the Division for review.

Pharmacology/Toxicology

- Please initiate the following non-clinical studies:
 1. 13-week intravenous toxicity studies in rodent and non-rodent species,

2. Reproductive toxicity studies including Segment I intravenous fertility and reproductive performance study in rats and Segment II intravenous teratology studies in rats and rabbits.
- These studies should be completed prior to initiation of Phase 3 clinical studies.

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Kathy Robie-Suh
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