

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

22-180

CHEMISTRY REVIEW(S)

Memorandum

To: NDA 22-180
CC: Eldon E Leutzinger
Through: Sarah Pope, Ph.D.
From: Xiao-Hong Chen, Ph.D.
Date: 6/17/2009
Re: NDA resubmission dated 29-APR-2009 and amendments dated 30-MAR-2009 and 16-JUN-2009

The initial NDA 22-180 was submitted on 18-DEC-2007. CMC reviews #1 (dated 11-AUG-2008) and #2 (dated 8-OCT-2008) were completed with all CMC review issues resolved except for an overall withhold recommendation from the Office of Compliance (OC). A Complete Response (CR) letter was issued on 17-OCT-2008, based on the withhold recommendation and outstanding clinical deficiencies. AMAG, the applicant of the NDA, submitted their responses to the 483 observations to the FDA district office, also in the amendment dated 30-OCT-2008 (AZ). The responses were reviewed by the Office of Compliance, and the Office of Compliance made another "withhold" recommendation on 17-NOV-2008. The FDA issued a second CR letter dated on 22-DEC-2008. Following that, AMAG submitted its responses to the FDA district office to address the 483 observations, and AMAG submitted a resubmission dated 29-APR-2009. Based on the FDA district office's evaluation of AMAG's responses, the Office of Compliance made an "acceptable" recommendation for this NDA (06-MAY-2009).

The Division of Medication Error Prevention and Analysis (DMEPA) completed a labeling review for Ferumoxytol Injection (NDA 22-180) dated 03-MAR-2009 in which they made recommendations regarding the proposed container labels, carton labeling, and package insert labeling. In a submission dated 30-MAR-2009, the applicant submitted revised labels and labeling addressing DMEPA's requested changes. In this submission, AMAG addressed most container/carton comments satisfactorily. However, AMAG also changed the container and carton labels to include a circular blue and green logo next to the established name. In a review (dated 12-JUN-2009) conducted by Felicia Duffy (DMEPA) for this labeling amendment, she had the following comments to be conveyed to the applicant.

"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

June 17, 2009

strength so that the most prominent information on the container label and carton labeling is the proprietary name, established name, and product strength.”

These comments were conveyed to AMAG on 15-JUN-2009. AMAG responded to the above comments on 16-JUN-2009. AMAG has accepted the FDA comments in its response dated 16-JUN-2009. AMAG agreed to decrease the size of the circular blue and green logo, so that it is much less prominent (refer to the revised Container Label and Carton Labeling in the submission dated 16-JUN-2009). The revised labeling was found acceptable by DMEPA. Please refer to Kellie Taylor's review dated 16-JUN-2009.

There are no outstanding CMC issues for this NDA, and this NDA is now recommended for approval from the CMC perspective.

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Xiao Hong Chen
6/17/2009 02:44:48 PM
CHEMIST

Sarah Pope
6/17/2009 02:56:52 PM
CHEMIST

Memorandum

To: NDA 22-180
CC: Eldon E Leutzinger
Through: Sarah Pope, Ph.D.
From: Xiao-Hong Chen, Ph.D.
Date: 12/18/2008
Re: NDA resubmission dated 30-OCT-2008

The initial NDA 22-180 was submitted on 18-DEC-2007. CMC review #1 (dated 11-AUG-2008) and #2 (dated 8-OCT-2008) were completed with all CMC review issues resolved except the withholding recommendation from the Office of Compliance (OC) for the pre-approval inspection of the establishment. A Complete Response (CR) letter resulted from the clinical deficiencies and 483 observations of the pre-approval inspections was issued on October 17, 2008. AMAG, the applicant of the NDA, sent a resubmission dated 30-OCT-2008 (AZ) in response to the CR letter. In the response to the clinical deficiency (Q1a) regarding the anaphylactic reaction occurred during the clinical studies, AMAG provided some CMC information on the pharmaceutical development strategy.

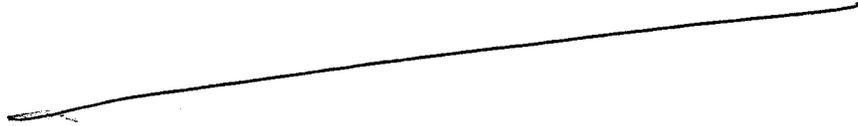
The provided CMC information is not new, and they are from the CMC information submitted in the original NDA and the amendments. Therefore, no review is necessary for the provided CMC information. A response to the resent Citizen Petition (FDA-2008-P-0524) (CP) from a CMC standpoint was drafted and will be forwarded to Elizabeth Sadove, regulatory counsel. Please refer to the CMC response to CP dated 12-DEC-2008.

An EES request was entered on November 6, 2008, and the OC issued a "withhold" recommendation on November 17, 2008. NDA 22-180 cannot be approved from the CMC perspective without an overall "Acceptable" recommendation from the OC.

In an internal team meeting to discuss the pending issues of the application on December 15, 2008, it was concluded that the following information will be requested in order to determine the chemical structural differences between PSC and dextran:

b(4)

December 18, 2008



b(4)

**APPEARS THIS WAY
ON ORIGINAL**

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/s/

Eldon Leutzinger
12/18/2008 11:33:41 AM
CHEMIST
For Xiao H. Chen

Sarah Pope
12/18/2008 11:40:27 AM
CHEMIST

Memorandum

To: NDA 22-180
CC: Eldon Leutzinger, Ph.D.; Xiao-Hong Chen, Ph.D.; Rik Lostritto, Ph.D.
From: Sarah C. Pope, Ph.D.
Date: 10/17/2008
Re: Final CMC recommendation for NDA 22-180

NDA 22-180 (Ferumoxytol Injection) was initially submitted on 18-DEC-2007 and was granted a standard review by the Agency. Chemistry Review #1 (dated 29-AUG-2008) identified several Chemistry, Manufacturing and Controls (CMC) deficiencies which were subsequently communicated to the Applicant and resolved. Resolution of these CMC deficiencies is captured in Chemistry Review #2 (dated 09-OCT-2008) with the exception of a final recommendation from the Office of Compliance.

This memo serves to update that determination. The Office of Compliance issued an overall withhold recommendation for this application on 16-OCT-2008. Accordingly, from a CMC perspective, approval of NDA 22-180 cannot be recommended until any related deficiencies are resolved.

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/s/

Sarah Pope
10/17/2008 07:33:49 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-180

Ferumoxytol Injection

AMAG Pharmaceuticals, Inc.

Xiao-Hong Chen, Ph.D.

**Office of New Drug Quality Assessment
Division of Premarketing Assessment and Manufacturing
Science (Branch V)**

CMC Review of NDA 22-180

**For the Division of Medical Imaging and Hematology
Products (HFD-160)**



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Chemistry Review Data Sheet

1. NDA 22-180
2. REVIEW #2
3. REVIEW DATE: 8-OCT-2008
4. REVIEWERS: Xiao-Hong Chen, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 62,745	13-JUN-2001

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	18-DEC-2007
Amendment 0013 (BC)	7-AUG-2008
Amendment 0016 (BC)	5-SEP-2008
Amendment 0017 (BL)	22-SEP-2008
Amendment 0018 (BZ)	23-SEP-2008
Amendment 0020 (BL)	1-OCT-2008

7. NAME & ADDRESS OF APPLICANT:

Name: AMAG Pharmaceuticals, Inc.
Address: 125 Cambridge Park Drive
Cambridge, MA 02140



CHEMISTRY REVIEW



Chemistry Review Data Sheet

Representative: Mhammed A. Salem, Ph.D., RAC

Telephone: 617-498-3300

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ferumoxytol
Code Name/# (ONDQA only): 5128 (for drug substance); 7228 (for drug product)
c) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 2
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Iron replacement therapy in hemodialysis patients

11. DOSAGE FORM: Sterile solution

12. STRENGTH/POTENCY: 510 mg/17 mL; 255 mg/8.5 mL; 127.5 mg/4.25 mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product



Chemistry Review Data Sheet

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Polyglucose sorbitol carboxymethylether (PCS) superparamagnetic iron oxide

Or

Carboxymethyl poly(glucose)-sorbitol ether superparamagnetic iron oxide

Or

Or

~~_____~~

The general formula for the iron oxide in polyglucose sorbitol carboxymethylether (PSC)-covered superparamagnetic iron oxide is:

The average chemical formula for the iron oxide in polyglucose sorbitol carboxymethylether-covered superparamagnetic iron oxide is:



b(4)

b(4)



CHEMISTRY REVIEW



Chemistry Review Data Sheet

The general formula for the polysaccharide polyglucose sorbitol carboxymethylether (Code 4043) that covers the iron oxide is:

b(4)

The molecular weight of PSC is $C_{400.32}H_{638.16}O_{339.32}Na_{14.16}$

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
10095	III			3	Adequate.	Reviewed by Libaniel Rodriguez and Mark Sassman on 02/24/2003 and 08/17/2006, respectively.	
	III			3	Adequate.	Reviewed by Radhika Rajagopalan on 03/24/1997.	

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:



CHEMISTRY REVIEW



Chemistry Review Data Sheet

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/REVIEWER	COMMENTS
EES	Site inspections	10-MAR-2008	Pending	Pending
Pharm/Tox	N/A			
Biopharm	N/A			
ODS/DMEPA	Risk Management Plan	19-SEP-2008	Acceptable	Acceptable with recommendations
DDMAC	Labeling consult	12-SEP-2008	Complete	Comments conveyed to AMAG.
Methods Validation	N/A		May be submitted if the NDA is approved.	Method validation request may be submitted to the field lab for verification post approval if deemed necessary.
EA	N/A		Acceptable	Applicant cites 21 CFR 25.31(b) as applicable.
Microbiology	Sterility assurance	12-SEP-2008	Acceptable	



The Chemistry Review for NDA 22-180

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application maybe approved from the chemistry, manufacturing, and controls (CMC) standpoint, provided that the Office of Compliance issues an overall "acceptable" recommendation for the application.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A.

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance is a non-stoichiometric magnetite, commonly called polyglucose sorbitol carboxymethylether (PSC)-covered superparamagnetic iron oxide. The chemical composition of ferumoxytol drug substance is as follows: approximately carbohydrate and iron oxide by weight. The superparamagnetic iron oxide crystals have the and are about nm in size. The PSC is associated with the iron oxide . The overall colloidal particle size is 17-31 nm in diameter (Dynamic Light Scattering, volume-weighted), and it is approximately 750 kDa when measured by size exclusion chromatography.

b(4)

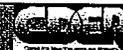
The drug substance is manufactured by the Applicant. It is

b(4)

The drug substance is quite stable when stored under long term (2-8°C) and accelerated conditions. The proposed month retest date is supported by the stability data, and is found to be acceptable.



CHEMISTRY REVIEW



Executive Summary Section

Drug Product

Ferumoxytol is an aqueous colloid of superparamagnetic iron oxide covered with PSC, formulated with mannitol, USP, to attain osmolality of 300 milliosmoles. It will be marketed in three strengths and is filled into three vial configurations: _____

b(4)

_____ Each single-use vial (30 mg elemental iron/mL) contains 510 mg, 255 mg, and 127.5 mg in 17 mL, 8.5 mL and 4.25 mL volumes, respectively.

_____ The control and stability of the drug product is quite similar to that of the drug substance. The drug product has demonstrated good stability over 24 months at the recommended storage conditions: 20° to 25°C (68° to 77°F) with excursions allowed between 15° and 30°C (59° and 86°F). The proposed 24 month expiry is granted.

b(4)

B. Description of How the Drug Product is Intended to be Used

The ferumoxytol drug product is supplied as a colloid liquid that contains 30 mg/mL (element iron) of ferumoxytol in three vial configurations. Each vial contains 127.5 mg, 255 mg and 510 mg of ferumoxytol. The drug is administered by intravenous bolus injection. No prior dilution or constitution is needed prior to administration.

b(4)

The recommended dose is 510 mg as rapid IV administration at a rate of up to 1 mL/sec.

C. Basis for Approvability or Not-Approval Recommendation

An overall recommendation from the Office of Compliance has not yet been issued for this application. However, all Chemistry, Manufacturing and Controls review issues have been resolved. Therefore, this application is recommended for approval from a CMC standpoint, pending an acceptable recommendation from the Office of Compliance.

III. Administrative

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

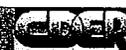
Reviewer Name/Date: Xiao Hong Chen, Ph.D.

Acting Branch Chief Name/Date: Sarah C. Pope, Ph.D.

C. CC Block



CHEMISTRY REVIEW



Executive Summary Section

Hyon-Zu Lee/OODP/DMIHP/Regulatory PM
Elton Leutzinger/ONDQA/PAL

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ON ORIGINAL**

25 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Withheld Track Number: Chemistry-1

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/s/

Xiao Hong Chen
10/8/2008 04:21:16 PM
CHEMIST

Sarah Pope
10/9/2008 05:57:43 PM
CHEMIST

CHEMISTRY REVIEW

NDA 22-180

Ferumoxytol Injection

AMAG Pharmaceuticals, Inc.

Xiao-Hong Chen, Ph.D.

**Office of New Drug Quality Assessment
Division of Premarketing Assessment and Manufacturing
Science (Branch V)**

CMC Review of NDA 22-180

**For the Division of Medical Imaging and Hematology
Products (HFD-160)**



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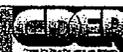
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CHEMISTRY REVIEW



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Chemistry Review Data Sheet

1. NDA 22-180
2. REVIEW #1
3. REVIEW DATE: 11-AUG-2008
4. REVIEWERS: Xiao-Hong Chen, Ph.D.

5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
IND 62,745	13-JUN-2001

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original	18-DEC-2007
Amendment 001	7-AUG-2008

7. NAME & ADDRESS OF APPLICANT:

Name: AMAG Pharmaceuticals, Inc.
Address: 125 Cambridge Park Drive
Cambridge, MA 02140
Representative: Mhammed A. Salem, Ph.D., RAC
Telephone: 617-498-3300



CHEMISTRY REVIEW



Chemistry Review Data Sheet

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: N/A
b) Non-Proprietary Name (USAN): Ferumoxytol
Code Name/# (ONDQA only): 5128 (for drug substance); 7228 (for drug product)
c) Chem. Type/Submission Priority (ONDQA only):
- Chem. Type: 2
 - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: Iron replacement therapy in
hemodialysis patients

11. DOSAGE FORM: Sterile solution

12. STRENGTH/POTENCY: 510 mg/17 mL; 255 mg/8.5 mL; 127.5 mg/4.25 mL

13. ROUTE OF ADMINISTRATION: Intravenous

14. Rx/OTC DISPENSED: Rx OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product



16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Polyglucose sorbitol carboxymethylether (PCS) superparamagnetic iron oxide

Or

Carboxymethyl poly(glucose)-sorbitol ether superparamagnetic iron oxide

Or

b(4)

The general formula for the iron oxide in polyglucose sorbitol carboxymethylether (PSC)-covered superparamagnetic iron oxide is:

b(4)

The average chemical formula for the iron oxide in polyglucose sorbitol carboxymethylether-covered superparamagnetic iron oxide is:



Chemistry Review Data Sheet

The general formula for the polysaccharide polyglucose sorbitol carboxymethylether (Code 4043) that covers the iron oxide is:

_____ **b(4)**

The molecular weight of PSC is $C_{400.32}H_{638.16}O_{339.32}Na_{14.16}$

17. RELATED/SUPPORTING DOCUMENTS:

A. Supporting DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS ³
_____	III	_____	_____	3	Adequate.	Reviewed by Libaniel Rodriguez and Mark Sassman on 02/24/2003 and 08/17/2006, respectively.	
_____	III	_____	_____	3	Adequate.	Reviewed by Radhika Rajagopalan on 03/24/1997.	

b(4)

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

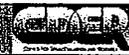
³ Include reference to location in most recent CMC review

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS



CHEMISTRY REVIEW



Chemistry Review Data Sheet

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS	SUBJECT	DATE FORWARDED	STATUS/REVIEWER	COMMENTS
EES	Site inspections	10-MAR-2008	Pending	Pending
Pharm/Tox	N/A			
Biopharm	N/A			
ODS/DMEP	Labeling consult		Pending	Pending
Methods Validation	N/A		May be submitted if the NDA is approved.	
EA	N/A		Acceptable	Applicant cites 21 CFR 25.31(b) as applicable.
Microbiology	Sterility assurance		Pending	Pending



The Chemistry Review for NDA 22-180

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The application is approvable from a chemistry, manufacturing, and controls (CMC) standpoint, provided that the CMC deficiencies listed at the end of the review are resolved, the Office of Compliance issues an overall "acceptable" recommendation for the application, and acceptable container/carton labeling is submitted. Note that the consult for container/carton labeling (to the Division of Medication Errors and Prevention) is still pending.

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

N/A.

II. Summary of Chemistry Assessment

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The drug substance is a non-stoichiometric magnetite, commonly called polyglucose sorbitol carboxymethylether (PSC)-covered superparamagnetic iron oxide. The chemical composition of ferumoxytol drug substance is as follows: approximately $\frac{1}{5}$ carbohydrate and $\frac{4}{5}$ iron oxide by weight. The superparamagnetic iron oxide crystals have the $\frac{1}{5}$ and are about $\frac{1}{5}$ μm in size. The PSC is associated with the iron oxide $\frac{1}{5}$. The overall colloidal particle size is 17-31 nm in diameter (Dynamic Light Scattering, volume-weighted), and it is approximately 750 kDa when measured by size exclusion chromatography.

b(4)

The drug substance is manufactured by the Applicant. It is

b(4)



CHEMISTRY REVIEW



Executive Summary Section

The drug substance is quite stable when stored under long term (2-8°C) and accelerated conditions. The proposed ← month retest date is supported by the stability data, and is found to be acceptable.

b(4)

Drug Product

Ferumoxytol is an aqueous colloid of superparamagnetic iron oxide covered with PSC, formulated with mannitol, USP, to attain osmolality of 300 milliosmoles. It will be marketed in three strengths and is filled into three vial configurations: _____
_____. Each single-use vial (30 mg elemental iron/mL) contains 510 mg, 255 mg, and 127.5 mg in 17 mL, 8.5 mL and 4.25 mL volumes, respectively.

b(4)

_____ The control and stability of the drug product is quite similar to that of the drug substance. The drug product has demonstrated good stability over 24 months at the recommended storage conditions: 20° to 25°C (68° to 77°F) with excursions allowed between 15° and 30°C (59° and 86°F). The proposed 24 month expiry is granted.

B. Description of How the Drug Product is Intended to be Used

The ferumoxytol drug product is supplied as a colloid liquid that contains 30 mg/mL (element iron) of ferumoxytol in three vial configurations. Each vial contains 127.5 mg, 255 mg and 510 mg of ferumoxytol. The drug is administered by intravenous bolus injection. No prior dilution or constitution is needed prior to administration.

The recommended dose is 510 mg as rapid IV administration at a rate of up to 1 mL/sec.

C. Basis for Approvability or Not-Approval Recommendation

N/A

III. Administrative

A. Reviewer's Signature

See appended electronic signature page.

B. Endorsement Block

Reviewer Name/Date: Xiao Hong Chen, Ph.D.
Acting Branch Chief Name/Date: Sarah Pope, Ph.D.



C. CC Block

Hyon-Zu Lee/OODP/DMIHP/Regulatory PM
Elton Leutzinger/ONDQA/PAL

90 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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

/s/

Xiao Hong Chen
8/29/2008 02:53:11 PM
CHEMIST

Sarah Pope
8/29/2008 03:32:10 PM
CHEMIST
Concur

Report.txt
61 MOONEY ST
CAMBRIDGE, MA 021381038

DMF No:

AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER

Profile	:	CSN	OAI Status:	NONE
Last Milestone:		OC RECOMMENDATION		
Milestone Date:		05-MAY-09		
Decision	:	ACCEPTABLE		
Reason	:	DISTRICT RECOMMENDATION		
Profile	:	SVT	OAI Status:	NONE
Last Milestone:		OC RECOMMENDATION		
Milestone Date:		05-MAY-09		
Decision	:	ACCEPTABLE		
Reason	:	DISTRICT RECOMMENDATION		

♀

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

Application:	NDA 22180/000	Action Goal:	
Stamp:	19-DEC-2007	District Goal:	20-AUG-2008
Regulatory Due:	29-JUN-2009	Brand Name:	FERUMOXYTOL
INJECTION			
Applicant:	AMAG PHARMS INC	Estab. Name:	
	100 HAYDEN AVE	Generic Name:	FERUMOXYTOL
	LEXINGTON, MA 02421		
Priority:	2S	Dosage Form:	(INJECTION)
Org Code:	160	Strength:	510 MG, 255 MG,
127.5 M			

Application Comment: AMAG PHARMACEUTICALS, INC, 61 MOONEY ST., CAMBRIDGE, MA
02138 IS RESPONSIBLE FOR DS AND DP MANUFACTURING AND CONTROL
TESTING.
EVALUATION BASED I AM RESUBMITTING ALL MANUFACTURING SITES FOR EES
OUTSTANDING 483 ON AMAG'S STATEMENT THAT THEY HAD REPONDED TO ALL
OF THEIR OBSERVATIONS TO THE DISTRICT OFFICE IN THE COVER LETTER
CHEN () NDA RESUBMSSION DATED 30-OCT-2008. (on 06-NOV-2008 by X.
301-796-1337)

FDA Contacts:	H. LEE	301-796-2050	, Project
Manager			
Chemist	X. CHEN	301-796-1337	, Review
Leader	ID = 124115		, Team

Report.txt

Overall Recommendation: ACCEPTABLE on 06-MAY-2009 by C. CRUZ
(HFD-323)301-796-3254

FERGUSON(HFD-322)301-796-3247 WITHHOLD on 17-NOV-2008 by S.

(HFD-323)301-796-3254 WITHHOLD on 16-OCT-2008 by C. CRUZ

Establishment: CFN 1220373 FEI 1220373
AMAG PHARMACEUTICALS INC
61 MOONEY ST
CAMBRIDGE, MA 021381038

DMF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER

Profile: CSN OAI Status: NONE

Emilestone Name Creator	Date	Type	Insp. Date	Decision & Reason
----------------------------	------	------	------------	-------------------

SUBMITTED TO OC CHENX	10-MAR-2008			
SUBMITTED TO DO FERGUSONS	10-MAR-2008	GMP		
ASSIGNED INSPECTION T RPENTA	14-APR-2008	PS		
INSPECTION SCHEDULED RPENTA	09-SEP-2008		29-SEP-2008	
INSPECTION PERFORMED RPENTA	14-OCT-2008		14-OCT-2008	

EI REVEALED THE FOLLOWING OBSERVATIONS: THE FIRM HAS NOT PERFORMED AN INVESTIGATION INTO

Report.txt

THE REASON FOR ADHESION OF FINISHED PPRODUCT TO IDENTICAL PATTERNS AND LOCATIONS INSIDE

SOME OF THE VIALS AFTER _____ ; CONTAINER/CLOSURE STUDIES ON THIS NEW PRODUCT ARE NOT

b(4)

PERFORMED TO DEMONSTRATE THE QUALITY AND SAFETY OF THE DRUG; THE FIRM HAS A TREND WHERE

THEY ARE NOT FOLLOWING UP WITH INVESTIGATIONS ON OOS AND AVERAGING RESULTS, DRUG PRODUCT

COMPLAINTS, AND REJECTED RAW MATERIALS; NO REASONING OR VALIDATION OF THE PERFORMANCE OF

A PROCESS CHANGE OF _____ PERSONNEL INADEQUATELY

b(4)

TRAINED; CLEANING VALIDATION OF PRODUCT CONTACT EQUIPT FOR API AND FINISHED PRODUCT

♀ 13-MAY-2009
2 of 4

FDA CDER EES

Page

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

INADEQUATE; OTHER CGMPs REGARDING QUALITY CONTROL, JUSTIFICATION FOR PLANNED DEVIATIONS,

INADEQUATE STABILITY STUDIES, AND NO AUDITING OF SEVERAL SUPPLIERS OF CRITICAL RAW MATERIALS.

INSPECTION PERFORMED 14-OCT-2008
MHAGGERT

14-OCT-2008

483678 483678 483678 483677 483677 The current inspection noted the following non-exhaustive summary of deficiencies: failure to adequately investigate a complaint for

Feridex I.V.; inadequate investigation into varying appearance for Feridex I.V. and

Ferumoxytol I.V.; inadequate investigation and corrective action for adulterated Ferumoxytol drug substance (lot was not released); the out of specification

procedure

allows for acceptance of passing retests without scientific justification and allows for

reporting the average of failed and passing results without scientific justification or

root cause determination; inadequate investigation into an out of specification result

(lot was released for research purposes); compatibility studies for container closures

were not adequately performed/ were not performed for Feridex I.V. and Ferumoxytol I.V.;

two examples demonstrated lack of process validation; four examples demonstrated employees are not properly trained or do not possess the appropriate knowledge for the

technician/ senior management positions; the pH for the _____ is

b(4)

not documented; cleaning validation is inadequate for Feridex I.V. and Ferumoxytol I.V.;

the deviation procedure does not require justification for acceptance of deviations or

the execution of a risk assessment, demonstrated in a planned deviation; the system for

change control through May 2007 was inadequate, demonstrated with three examples; several

critical vendors have never been audited; _____ have not been growth promoted

b(4)

for the past fourteen years.

DO RECOMMENDATION 15-OCT-2008
RPENTA

WITHHOLD

VALIDATION

EQUIPMENT CLEANING

EI FOUND THE FOLLOWING DEFICIENCIES; THE FIRM HAS NOT PERFORMED AN INVESTIGATION INTO THE

ADHESION OF FINISHED PRODUCT TO IDENTICAL LOCATION AND PATTERNS INSIDE SOME OF THE VIALS

WHEN _____ CONTAINER CLOSURE SAFETY STUDIES ARE NOT PERFORMED TO DEMONSTRATE QUALITY

b(4)

AND SAFETY; TRENDS WHERE FIRM IS NOT FOLLOWING UP ON INVESTIGATIONS IN OOS RESULTS, DRUG

PRODUCT COMPLAINTS AND RAW MATERIAL REJECTIONS; FIRM HAS NO REASONING OR VALIDATION OF

b(4)

Report.txt

THE PERFORMANCE OF THE CHANGE IN RANGE OF SPEED IN _____ CLEANING VALIDATION FOR

PRODUCT CONTACT EQUIPT FOR API AND FINISHED PRODUCT IS INADEQUATE; NO JUSTIFICATION OF

PLANNED DEVIATIONS, INADEQUATE (1) STABILITY STUDIES AND NO AUDITING OF SEVERAL SUPPLIERS

OF CRITICAL RAW MATERIALS.

OC RECOMMENDATION 16-OCT-2008 WITHHOLD
CRUZC

DISTRICT RECOMMENDATION

BASED ON THE FD-483, CDER/OC RECOMMENDS WITHHOLD DUE TO THE FOLLOWING GMP DEFICIENCIES IN

THE: QUALITY SYSTEMS [IE: INADEQUATE INVESTIGATION, INADEQUATE TRAINING; NO JUSTIFICATION

OF PLANNED DEVIATIONS; NO SUPPLIERS AUDITING FOR CRITICAL MATERIALS; INADEQUATE STABILITY

STUDIES], AND; PRODUCTION SYSTEMS [IE: INADEQUATE CLEANING VALIDATION]. DISTRICT COMPLIANCE BRANCH IS REVIEWING FINDINGS FOR POSSIBLE REGULATORY ACTION.

CDER/OC DEFERS TO THE REVIEW DIVISION THE FOLLOWING ISSUE: CONTAINER/ CLOSURE STUDIES

WERE NOT PERFORMED TO DEMONSTRATE QUALITY AND SAFETY.

SUBMITTED TO OC 06-NOV-2008
CHENX

SUBMITTED TO DO 06-NOV-2008 10D
FERGUSONS

DO RECOMMENDATION 17-NOV-2008 WITHHOLD
RPENTA

VALIDATION EQUIPMENT CLEANING

♀ 13-MAY-2009
3 of 4

FDA CDER EES

Page

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Report.txt

EI 14-OCT-2008 RESPONSES OF 11/3 & 10/2008 RECEIVED AND UNDER REVIEW. WARNING LETTER
INADEQUATE LAB CONTROLS
RECOMMENDED FOR COMERCIAL PRODUCT.
LTR
PEND REG ACTION - WARNING

OC RECOMMENDATION 17-NOV-2008
FERGUSONS

STABILITY PROGRAM
TRAINING
WITHHOLD

SUBMITTED TO DO 28-APR-2009 10D
CRUZC

DISTRICT RECOMMENDATION

DO RECOMMENDATION 30-APR-2009
DEMERSON

ACCEPTABLE

BASED ON FILE REVIEW

THE LAST GMP INSPECTION RESULTED IN A WL RECOMMENDATION WHICH WAS TURNED DOWN BY CDER AND

THE FIRM CAME IN FOR A REGULATORY MEETING ON 3/11/09. COMPLIANCE CHANGED CLASSIFICATION

TO VAI ON 4/28/09 AS FIRM HAS STOPPED PRODUCTION OF ALL COMMERCIAL DRUG PRODUCTS. WE ARE NOT PLANNING TO RE-INSPECT AT THIS TIME.

OC RECOMMENDATION 05-MAY-2009
FERGUSONS

ACCEPTABLE

DISTRICT RECOMMENDATION

Profile: SVT OAI Status: NONE

EMilestone Name Date Type Insp. Date Decision & Reason
Creator

SUBMITTED TO OC 10-MAR-2008
CHENX
SUBMITTED TO DO 10-MAR-2008 PS
FERGUSONS

INSPECTION SCHEDULED 19-SEP-2008 29-SEP-2008

RPENTA

INSPECTION PERFORMED 14-OCT-2008
RPENTA

14-OCT-2008

EI FOUND THE FOLLOWING DEFICIENCIES WHICH WILL ARE EXPANDED IN CNS SUBMISSION.
NOT

PERFORMED INVESTIGATION INTO REASON OF ADHESION ON INSIDE SWALLS OF VIALS WHEN

CONTAINER CLOSURE STUDIES NOT PERFORMED; TREND WHERE NOT FOLLOWING UP
INVESTIGATIONS ON

OOS, DRUG COMPLAINTS, RAW MATERIAL REJECTIONS; NO REASONING OR VALIDATION OF THE
PERFORMANCE ON A PROCESS CHANGE IN RANGE OF SPEED IN ; PERSONEL
INADEQUATELY

b(4)

TRAINED; CLEANING VALIDATION ON PRODUCT CONTACT EQUIPT OF API AND FINISHED PRODUCT
IS

INADEQUATE; NO JUSTIFICATION ON PLANEND DEVIATIONS; INADEQUATE STABILITY STUDIES
AND

OTHERS.

DO RECOMMENDATION 15-OCT-2008
RPENTA

WITHHOLD

VALIDATION

EQUIPMENT CLEANING

EI REVEALED THE FOLLOWING DEFICIENCIES: FIRM HAS NOT PERFORMED INVESTIGATION INTO
REASON

FOR ADHESION OF FINISHED PRODUCT TO IDENTICAL LOCATIONS AND PATTERNS INSIDE SOME
OF THE

VIALS AFTER CONTAINER/CLOSURE STUDIES NOT PERFORMED TO DEMONSTRATE
QUALITY AND

b(4)

SEFETY; FIRM HAS A TREND WHERE THEY ARE NOT FOLLOWING UP ON INVESTIGATIONS FOR
OOS, DRUG

PEODUCT COMPLAINTS, AND REJECTED RAW MATERIALS; NO REASONING OR VALIDATION OF THE
PERFORMANCE OF A CHANGE IN RANGE OF SPEED IN THE , INADEQUATE TRAINING;
CLEANING

VALIDATION FOR PRODUCT CONTACT EQUIPT FOR API AND FINISHED PRODUCT INADEQUATE; NO
JUSTIFICATION ON PLANNED DEVIATIONS; INADEQUATE (1) STABILITY STUDIES; AND NO
AUDITING OF

SEVERAL SUPPLIERS OF CRITICAL RAW MATERIALS.

OC RECOMMENDATION 16-OCT-2008
CRUZC

WITHHOLD

DISTRICT RECOMMENDATION

BASED ON THE FD-483, CDER/OC RECOMMENDS WITHHOLD DUE TO THE FOLLOWING GMP DEFICIENCIES IN

13-MAY-2009
4 of 4

FDA CDER EES

Page

ESTABLISHMENT EVALUATION REQUEST
DETAIL REPORT

THE: QUALITY SYSTEMS [IE: INADEQUATE INVESTIGATION, INADEQUATE TRAINING; NO JUSTIFICATION OF PLANNED DEVIATIONS; NO SUPPLIERS AUDITING FOR CRITICAL MATERIALS; INADEQUATE STABILITY STUDIES], AND; PRODUCTION SYSTEMS [IE: INADEQUATE CLEANING VALIDATION]. CDER/OC DEFERS TO

THE REVIEW DIVISION THE FOLLOWING ISSUE: CONTAINER/ CLOSURE STUDIES WERE NOT PERFORMED TO

DEMONSTRATE QUALITY AND SAFETY.

SUBMITTED TO OC 06-NOV-2008
CHENX

SUBMITTED TO DO 06-NOV-2008 10D
FERGUSONS

DO RECOMMENDATION 17-NOV-2008
RPENTA

WITHHOLD

VALIDATION

EQUIPMENT CLEANING

EI 14-OCT-2008 RESPONSES OF 11/3 & 10/2008 RECEIVED AND UNDER REVIEW. WARNING LETTER

RECOMMENDED FOR COMMERCIAL PRODUCT.

ORGANIZATION/PERSONNEL

LTR

PEND REG ACTION - WARNING

STABILITY PROGRAM

TRAINING

OC RECOMMENDATION FERGUSONS	17-NOV-2008	Report.txt	WITHHOLD
			DISTRICT RECOMMENDATION
SUBMITTED TO DO CRUZZ	28-APR-2009	10D	
DO RECOMMENDATION DEMERSON	30-APR-2009		ACCEPTABLE

ADEQUATE FIRM RESPONSE

THE LAST GMP INSPECTION RESULTED IN A WL RECOMMENDATION WHICH WAS TURNED DOWN BY CDER AND

THE FIRM CAME IN FOR A REGULATORY MEETING ON 3/11/09. COMPLIANCE CHANGED CLASSIFICATION

TO VAI ON 4/28/09 AS FIRM HAS STOPPED PRODUCTION OF ALL COMMERCIAL DRUG PRODUCTS. WE ARE NOT PLANNING TO RE-INSPECT AT THIS TIME.

OC RECOMMENDATION FERGUSONS	05-MAY-2009		ACCEPTABLE
--------------------------------	-------------	--	------------

DISTRICT RECOMMENDATION

♀

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

Application: NDA 22180/000 Action Goal:
Stamp: 19-DEC-2007 District Goal: 20-AUG-2008
Regulatory Due: 30-DEC-2008 Brand Name: FERUMOXYTOL INJECTION
Applicant: AMAG PHARMS INC Estab. Name:
125 CAMBRIDGE PARK DR 6TH FL Generic Name: FERUMOXYTOL
CAMBRIDGE, MA 02140
Priority: 2S Dosage Form: (INJECTION)
Org Code: 160 Strength: 510 MG, 255 MG, 127.5 M

Application Comment: AMAG PHARMACEUTICALS, INC, 61 MOONEY ST., CAMBRIDGE, MA 02138 IS RESPONSIBLE FOR DS AND DP MANUFACTURING AND CONTROL TESTING. I AM RESUBMITTING ALL MANUFACTURING SITES FOR EES EVALUATION BASED ON AMAG'S STATEMENT THAT THEY HAD RESPONDED TO ALL OUTSTANDING 483 OBSERVATIONS TO THE DISTRICT OFFICE IN THE COVER LETTER OF THEIR NDA RESUBMISSION DATED 30-OCT-2008. (on 06-NOV-2008 by X. CHEN. () 301-796-1337).

FDA Contacts: H. LEE 301-796-2050 , Project Manager
X. CHEN 301-796-1337 , Review Chemist
ID = 124115 , Team Leader

Overall Recommendation: WITHHOLD on 17-NOV-2008 by S. FERGUSON (HFD-322) 301-796-3247
WITHHOLD on 16-OCT-2008 by C. CRUZ (HFD-323) 301-796-3254

Establishment: CFN 1220373 FEI 1220373
AMAG PHARMACEUTICALS INC
61 MOONEY ST
CAMBRIDGE, MA 021381038

MF No: AADA:

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER

Profile:

CSN

OAI Status: POTENTIAL OAI

Milestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-MAR-2008				CHENX
SUBMITTED TO DO	10-MAR-2008	GMP			FERGUSONS
ASSIGNED INSPECTION T	14-APR-2008	PS			RPENTA
INSPECTION SCHEDULED	09-SEP-2008		29-SEP-2008		RPENTA
INSPECTION PERFORMED	14-OCT-2008		14-OCT-2008		RPENTA

EI REVEALED THE FOLLOWING OBSERVATIONS: THE FIRM HAS NOT PERFORMED AN INVESTIGATION INTO THE REASON FOR ADHESION OF FINISHED PPRODUCT TO IDENTICAL PATTERNS AND LOCATIONS INSIDE SOME OF THE VIALS AFTER _____; CONTAINER/CLOSURE STUDIES ON THIS NEW PRODUCT ARE NOT PERFORMED TO DEMONSTRATE THE QUALITY AND SAFETY OF THE DRUG; THE FIRM HAS A TREND WHERE THEY ARE NOT FOLLOWING UP WITH INVESTIGATIONS ON OOS AND AVERAGING RESULTS, DRUG PRODUCT COMPLAINTS, AND REJECTED RAW MATERIALS; NO REASONING OR VALIDATION OF THE PERFORMANCE OF A PROCESS CHANGE OF _____ PERSONNEL INADEQUATELY TRAINED; CLEANING VALIDATION OF PRODUCT CONTACT EQUIPT FOR API AND FINISHED PRODUCT INADEQUATE; OTHER CGMPs REGARDING QUALITY CONTROL, JUSTIFICATION FOR PLANNED DEVIATIONS,

b(4)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

INADEQUATE STABILITY STUDIES, AND NO AUDITING OF SEVERAL SUPPLIERS OF CRITICAL RAW MATERIALS.

INSPECTION PERFORMED 14-OCT-2008

14-OCT-2008

MHAGGERT

483678 483678 483678 483677 483677 The current inspection noted the following non-exhaustive summary of deficiencies: failure to adequately investigate a complaint for Feridex I.V.; inadequate investigation into varying appearance for Feridex I.V. and Ferumoxytol I.V.; inadequate investigation and corrective action for adulterated Ferumoxytol drug substance (lot was not released); the out of specification procedure allows for acceptance of passing retests without scientific justification and allows for reporting the average of failed and passing results without scientific justification or root cause determination; inadequate investigation into an out of specification result (lot was released for research purposes); compatibility studies for container closures were not adequately performed/ were not performed for Feridex I.V. and Ferumoxytol I.V.; two examples demonstrated lack of process validation; four examples demonstrated employees are not properly trained or do not possess the appropriate knowledge for the technician/ senior management positions; the pH for the _____ is not documented; cleaning validation is inadequate for Feridex I.V. and Ferumoxytol I.V.; the deviation procedure does not require justification for acceptance of deviations or the execution of a risk assessment, demonstrated in a planned deviation; the system for change control through May 2007 was inadequate, demonstrated with three examples; several critical vendors have never been audited; _____ have not been growth promoted for the past fourteen years.

b(4)

DO RECOMMENDATION

15-OCT-2008

WITHHOLD

RPENTA

EQUIPMENT CLEANING VALIDATION

EI FOUND THE FOLLOWING DEFICIENCIES; THE FIRM HAS NOT PERFORMED AN INVESTIGATION INTO THE ADHESION OF FINISHED PRODUCT TO IDENTICAL LOCATION AND PATTERNS INSIDE SOME OF THE VIALS WHEN _____ CONTAINER CLOSURE SAFETY STUDIES ARE NOT PERFORMED TO DEMONSTRATE QUALITY AND SAFETY; TRENDS WHERE FIRM IS NOT FOLLOWING UP ON INVESTIGATIONS IN OOS RESULTS, DRUG PRODUCT COMPLAINTS AND RAW MATERIAL REJECTIONS; FIRM HAS NO REASONING OR VALIDATION OF

b(4)

b(4)

THE PERFORMANCE OF THE CHANGE IN RANGE OF SPEED IN _____; CLEANING VALIDATION FOR
PRODUCT CONTACT EQUIPT FOR API AND FINISHED PRODUCT IS INADEQUATE; NO JUSTIFICATION OF
PLANNED DEVIATIONS, INADEQUATE (1) STABILITY STUDIES AND NO AUDITING OF SEVERAL SUPPLIERS
OF CRITICAL RAW MATERIALS.

OC RECOMMENDATION 16-OCT-2008 WITHHOLD CRUZC

DISTRICT RECOMMENDATION

BASED ON THE FD-483, CDER/OC RECOMMENDS WITHHOLD DUE TO THE FOLLOWING GMP DEFICIENCIES IN
THE: QUALITY SYSTEMS [IE: INADEQUATE INVESTIGATION, INADEQUATE TRAINING; NO JUSTIFICATION
OF PLANNED DEVIATIONS; NO SUPPLIERS AUDITING FOR CRITICAL MATERIALS; INADEQUATE STABILITY
STUDIES], AND; PRODUCTION SYSTEMS [IE: INADEQUATE CLEANING VALIDATION]. DISTRICT
COMPLIANCE BRANCH IS REVIEWING FINDINGS FOR POSSIBLE REGULATORY ACTION.

CDER/OC DEFERS TO THE REVIEW DIVISION THE FOLLOWING ISSUE; CONTAINER/ CLOSURE STUDIES
WERE NOT PERFORMED TO DEMONSTRATE QUALITY AND SAFETY.

SUBMITTED TO OC 06-NOV-2008 CHENX

SUBMITTED TO DO 06-NOV-2008 10D FERGUSONS

DO RECOMMENDATION 17-NOV-2008 WITHHOLD RPENTA

EQUIPMENT CLEANING VALIDATION

EI 14-OCT-2008 RESPONSES OF 11/3 & 10/2008 RECEIVED AND UNDER REVIEW. WARNING LETTER

**APPEARS THIS WAY
ON ORIGINAL**

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

RECOMMENDED FOR COMERCIAL PRODUCT.

ORGANIZATION/PERSONNEL
PEND REG ACTION - WARNING LTR
STABILITY PROGRAM
TRAINING
WITHHOLD
DISTRICT RECOMMENDATION

OC RECOMMENDATION 17-NOV-2008

FERGUSONS

Profile: SVT OAI Status: POTENTIAL OAI

EMilestone Name	Date	Type	Insp. Date	Decision & Reason	Creator
SUBMITTED TO OC	10-MAR-2008				CHENX
SUBMITTED TO DO	10-MAR-2008	PS			FERGUSONS
INSPECTION SCHEDULED	19-SEP-2008		29-SEP-2008		RPENTA
INSPECTION PERFORMED	14-OCT-2008		14-OCT-2008		RPENTA

EI FOUND THE FOLLOWING DEFICIENCIES WHICH WILL ARE EXPANDED IN CNS SUBMISSION. NOT PERFORMED INVESTIGATION INTO REASON OF ADHESION ON INSIDE SWALLS OF VIALS WHEN CONTAINER CLOSURE STUDIES NOT PERFORMED; TREND WHERE NOT FOLLOWING UP INVESTIGATIONS ON OOS, DRUG COMPLAINTS, RAW MATERIAL REJECTIONS; NO REASONING OR VALIDATION OF THE PERFORMANCE ON A PROCESS CHANGE IN RANGE OF SPEED IN PERSONEL INADEQUATELY TRAINED; CLEANING VALIDATION ON PRODUCT CONTACT EQUIPT OF API AND FINISHED PRODUCT IS INADEQUATE; NO JUSTIFICATION ON PLANEND DEVIATIONS; INADEQUATE STABILITY STUDIES AND OTHERS.

b(4)

DO RECOMMENDATION 15-OCT-2008 WITHHOLD RPENTA
EQUIPMENT CLEANING VALIDATION

I REVEALED THE FOLLOWING DEFICIENCIES: FIRM HAS NOT PERFORMED INVESTIGATION INTO REASON FOR ADHESION OF FINISHED PRODUCT TO IDENTICAL LOCATIONS AND PATTERNS INSIDE SOME OF THE VIALS AFTER CONTAINER/CLOSURE STUDIES NOT PERFORMED TO DEMONSTRATE QUALITY AND SEFETY; FIRM HAS A TREND WHERE THEY ARE NOT FOLLOWING UP ON INVESTIGATIONS FOR OOS, DRUG

b(4)

ESTABLISHMENT EVALUATION REQUEST

DETAIL REPORT

INADEQUATE LAB CONTROLS

EI 14-OCT-2008 RESPONSES OF 11/3 & 10/2008 RECEIVED AND UNDER REVIEW. WARNING LETTER
RECOMMENDED FOR COMMERCIAL PRODUCT.

PEND REG ACTION - WARNING LTR

STABILITY PROGRAM

TRAINING

OC RECOMMENDATION 17-NOV-2008

WITHHOLD. FERGUSONS

DISTRICT RECOMMENDATION

**APPEARS THIS WAY
ON ORIGINAL**

Report.txt

Responsibilities: DRUG SUBSTANCE MANUFACTURER
FINISHED DOSAGE MANUFACTURER

Profile : CSN OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-OCT-08
Decision : WITHHOLD
Reason : DISTRICT RECOMMENDATION
Profile : SVT OAI Status: NONE
Last Milestone: OC RECOMMENDATION
Milestone Date: 16-OCT-08
Decision : WITHHOLD
Reason : DISTRICT RECOMMENDATION

♀

Initial Quality Assessment (IQA)
Branch V

Pre-Marketing Assessment and Manufacturing Science Division III
Office of New Drug Quality Assessment

OND Division: Division of Medical Imaging & Hematology Products

NDA: 22-180

Applicant: AMAG Pharmaceuticals, Inc., 125 Cambridge Park Drive, Cambridge, MA
02140

Stamp Date: 12/29/2007

PDUFA Date: 12/29/2008

Trademark: Not yet established

Established Name: INN (ferumoxytol); USAN (ferumoxytol)

Dosage Form: sterile solution (30 mg elemental iron / mL), single dose in vial sizes
(510 mg / 17 mL, 17 mL vial; 255 mg / 8.5 mL, 8.5 mL vial; 127.5 mg / 4.25 mL, 4.25 mL
vial)

Route of Administration: IV

Indication: treatment of iron deficiency anemia in patients with Chronic Kidney Disease
(CKD).

Pharmaceutical Assessment Lead: Eldon E. Leutzinger, Ph.D.

YES NO

ONDQA Fileability:

Comments for 74-Day Letter

(not at this time; pending review)

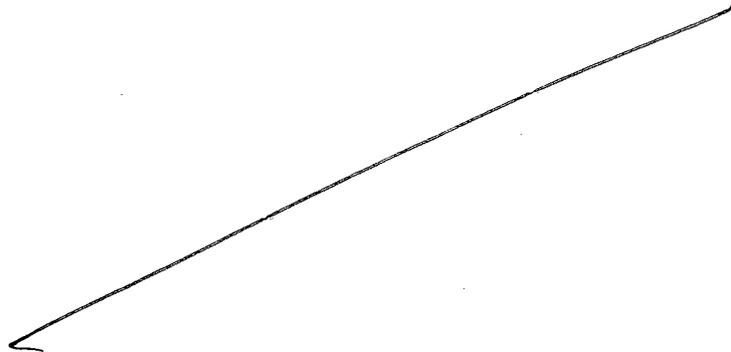
Summary and Critical Issues:

A. Summary

Ferumoxytol Injection is a sterile solution, each mL of which contains ferumoxytol (iron & polyglucose sorbitol carboxymethylether, PSC, comprised of 30 mg iron and 44 mg PSC), mannitol (44 mg) in WFI. Iron is in the form of iron oxide (category of Ultrasmall Superparamagnetic Iron Oxide, USPIO), a nanoparticle of non-stoichiometric magnetite that has the general formula of Fe_3O_4 . It is a single compound with 2.5 iron valences present in the crystal. In the IND development, and during Phase II, ferumoxytol was evaluated as an iron replacement in subjects with CKD, and for feasibility as an MRI contrast agent. For the NDA, ferumoxytol is indicated for treatment of iron deficiency anemia.

Characterization of ferumoxytol drug substance is presented in Section 3.2.S.3. In this section, a Table 3 (page 9) lists the content of iron for 3 batches with mean and standard deviation. From the data in this table, the applicant calculates the approximate molecular formula to be $\text{FeO}_{1.49}$ with the following magnetite crystal structure. See the next page.

Figure 1: Magnetite Crystal Structure



b(4)

The crystals have the _____ These crystals are “coated” with polyglucose sorbitol carboxymethylether at a layer thickness of _____ mm. In the aqueous media of the drug product, the drug substance (iron oxide + carbohydrate coating) exists as a colloid and has colloidal particle size of 17 – 31 nm in diameter (known from volume-weighted Dynamic Light Scattering). The applicant shows a depiction of the drug substance that is shown below, as reproduced from the NDA.

3 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

integrity of the drug substance entity is a theoretical issue regards taking the drug product through the manufacturing process. Secondly, there are potentially changes that could occur in either the internal structure of the iron oxide crystal or the carbohydrate as a result of the manufacturing operations or during storage, either physical or chemical. These issues, although theoretical, need to be considered during the review of the application and whether there are any potential affects on the pharmaceutical properties of the drug product.

C. Comments for 74-Day Letter

None at this time.

Fileability Summary

	PARAMETER	YES	NO	COMMENTS
1.	Is the CMC section sufficiently complete to permit substantive review to begin?	X		
2.	Is the CMC section indexed, paginated and organized in a manner to allow substantive review to begin?	X		
3.	Is the CMC section legible so that substantive review can begin?	X		
4.	Are all of the facilities (manufacturing, packaging, testing, sterilization, etc.) appropriately delineated with full addresses?	X		
5.	Is a statement provided that all the facilities are ready for cGMP / PAI inspection?	X		
6.	Has the applicant developed an environmental impact assessment or claimed categorical exclusion under the applicable regulations?	X		
7.	Does the section contain controls for drug substance?	X		
8.	Does the section contain controls for drug product?	X		
9.	Has the stability data and analysis been provided to support the proposed expiry?	X		
10.	Has all the information requested during the IND phase, and the pre-NDA meetings been included?	X		
11.	Has the applicant submitted draft labeling consistent with 201.56 and 201.57, current divisional labeling policies, and the design of the development package?	X		
12.	Has an investigational formulations section been provided?	X		
13.	Has the applicant provided a method validation package?		X	Not a separate package as such, but a collection of MV reports – reports appear complete.
14.	Is a separate microbiological section included?		X	Included as part of the Process Validation. Microbiology Attributes (sterilization process) is under Section 3.2.P.2.3.6.1.

Drug Master Files Referenced					
DMF Number	Holder	Item Referenced	LOA Included		Comments
			Yes	No	
			X		
			X		
			X		

b(4)

Facilities to be inspected		
Facility	Address	Responsibility
AMAG Pharmaceuticals, Inc	61 Mooney St. Cambridge, MA 02138	Manufacture of drug substance and drug product, quality control and release

Consults To Be Initiated	
Item	Consult To
Microbiological Attributes (Section 3.2.P.2.3.6.1 and other sections as appropriate)	Microbiology Staff

Pharmaceutical Assessment Lead:
Branch Chief:

Eldon E. Leutzinger, Ph.D.
Ravi Harapanhalli, Ph.D.

Date: 01/17/2008
Date:

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

/s/

Eldon Leutzinger
1/18/2008 10:45:06 AM
CHEMIST

Ravi Harapanhalli
1/18/2008 04:07:02 PM
CHEMIST