DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

DISTRICT ADDRESS AND PHONE NUMBER	DATE(S) OF INSPECTION
One Montvale Avenue Stoneham, MA 02180 (781) 596-7700 Fax:(781) 596-7896 Industry Information: www.fda.gov/oc/industry	09/18/2008 - 10/14/2008* FEI NUMBER 1220373

NAME AND TITLE OF INDIVIDUAL TO WHOM REPORT ISSUED

TO: Brian J.G. Pereira, M.D., President and Chief Executive Officer

FIRM NAME	STREET ADDRESS
AMAG Pharmaceuticals Inc	61 Mooney Street
CITY, STATE, ZIP CODE, COUNTRY	TYPE ESTABLISHMENT INSPECTED
Cambridge, MA 02138-1038	Manufacturer

This document lists observations made by the FDA representative(s) during the inspection of your facility. They are inspectional observations, and do not represent a final Agency determination regarding your compliance. If you have an objection regarding an observation, or have implemented, or plan to implement, corrective action in response to an observation, you may discuss the objection or action with the FDA representative(s) during the inspection or submit this information to FDA at the address above. If you have any questions, please contact FDA at the phone number and address above.

DURING AN INSPECTION OF YOUR FIRM WE OBSERVED:

OBSERVATION 1

Written records are not always made of investigations into unexplained discrepancies.

The following examples demonstrate inadequate investigational procedures and their examples:

A. Complaints

The procedure Drug Product Complaints, SOP 801.02 does not require the firm to request alleged defective product for further investigation. Additionally, there is no requirement to perform a production record review to further investigate the source of the complaint.

1. A complaint for surface adhesion inside the vial was initiated January 30, 2006 for Feridex I.V. This investigation is inadequate in that it does not address why the firm did not request the readily available product returns. The method of [redacted] stability samples stored on their [redacted] versus those stored [redacted] was inadequate; no additional analytical testing was performed on complainant vials, retains, or stability samples.

Exemption 4

2. There is no adequate justification for why the firm has not performed an investigation into why a uniform coating of Feridex I.V. adheres to the vial where it was stored.

3. There is no adequate justification for why the firm has not performed an investigation into the repeated adhesion of Ferumoxytol I.V. to identical locations and patterns inside the vial, irregardless of swirling the aqueous colloid. This phenomenon does not occur for all vials; some vials exhibit uniform distribution post swirling.

B. Raw Materials

There is no procedure that specifies following the rejection of raw materials, that an investigation shall be performed.

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1. An investigation for [redacted] (code [redacted], lot [redacted] was found to have 'gross contamination with polyethylene pieces.' This lot was used in the manufacture of at [redacted] lots of Ferumoxytol drug substance. The contamination was discovered during production. The investigation was inadequate for the following:

   a. Manufacturing observed polyethylene bag pieces while manufacturing Ferumoxytol drug substance on May 19, 2008, June 9, 2008, and June 23, 2008.

      i. There is no adequate justification for not involving quality until June 27, 2008, over a month after the initial observation by engineering.

      ii. There is no procedure that requires production supervisors to remain in the production area while maintenance occurs during production operations. There is no adequate justification for why this procedure does not exist.

   Exempt 4

   b. The procedure for visual inspection for incoming raw materials, QC of Raw Materials, QSOP 002, version October 18, 2007 and the [redacted] are inadequate; they only require Quality Control personnel to verify the color of the raw material. There are no instructions for execution of the visual inspection.

   c. The investigation was inadequate in that it did not evaluate increasing the incoming sample size, based on the component variability after discovering polyethylene bag pieces during production.

   d. The supplier of the [redacted] has never been audited.

C. Out of Specification Investigation

The Out of Specification Test Result Investigation Procedure, QSOP 018, version March 28, 2000 allows for:

- Following a laboratory investigation without an assignable cause, two retests are executed. If the two retests pass, the average of the original OOS result and two retests is reported.

- Following a laboratory investigation without an assignable cause, the original analyst obtains two failing results, and two additional analysts obtain passing results. The average of the two passing results is reported. There is no scientific justification for invalidating the original analyst's result; it is assumed that the original analyst is improperly trained.

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1. An out of specification result was obtained for Iron Content assay for Ferumoxytol I.V., lot [redacted]. Three analysts executed this assay: the original analyst failed the assay upon retest, two different analysts tested the same samples and they passed. The investigation did not determine the root cause of the out of specification result, training was assumed to be the root cause.

OBSERVATION 2

Laboratory controls do not include the establishment of scientifically sound and appropriate sampling plans and test procedures designed to assure that drug product containers and closures conform to appropriate standards of identity, strength, quality and purity.

Container closure and Feridex I.V. compatibility studies have not been adequately performed to demonstrate the container closure will not affect the quality and safety of the drug product.

Container closure and Ferumoxtyol I.V. compatibility studies have not been performed to demonstrate the container closure will not affect the quality and safety of the drug product.

OBSERVATION 3

Control procedures are not established which monitor the output and validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product.

A. The following examples demonstrate lack of process validation:

Exemption 4

1. There is no process validation for the siliconization of the [redacted] stoppers used for Feridex I.V. container closure. Additionally, the procedure Siliconization of [redacted], version [redacted] allows for a variable number of stoppers to be siliconized.

2. There is no scientific justification for lack of validation for the creation of the +/- [redacted]% range of speed for the mixer in the [redacted] liter reactor used to manufacture [redacted] batches of Ferumoxytol drug substance.

OBSERVATION 4

Individuals responsible for supervising the manufacture and processing of a drug product lack the training to perform their assigned functions in such a manner as to assure the drug product has the safety, identity, strength, quality and purity that it purports or is represented to possess.

Personnel are inadequately trained to effectively perform their duties:

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A. During the manufacture of Ferumoxytol drug substance lot [redacted] the [redacted] mixer ceased to function during production. While the engineer was fixing the mixer, he noticed pieces of floating plastic in the drug substance. Production management was not present when the engineer discovered the polyethylene bag pieces. Therefore, production continued to blend the [redacted] without knowing the plastic pieces were in the blender.

- Production supervisors are not trained to remain in the manufacturing area while engineers interrupt manufacturing operations.
- There is no procedure which requires production supervisors to remain in the production area to oversee engineering activities during maintenance interruptions.
- There is no procedure or training to require engineers to report potential product adulteration to production supervisors or other management officials, therefore the engineer did not report the floating plastic pieces in the drug substance to management.

B. The Senior Manager of Production authorized and executed a planned deviation from the validated cleaning procedure for the [redacted] liter reactor on September 9, 2008. The Production Manager and Vice President of Quality Control approved this planned deviation on September 12, 2008, after execution. The planned deviation was opened on September 10, 2008, after deviating from the validated cleaning procedure.

Exemption 4

C. The Senior Vice President of Operations, Vice President of Quality, and Vice President of Regulatory Affairs approved the specification change for relative humidity from [redacted]% to [redacted]% for the Clean Room, #107 where filling of Ferumoxytol I.V. and Feridex I.V. occurs. There was no scientific justification to support this change from the validated Clean Room environment.

OBSERVATION 5

Established test procedures are not followed and documented at the time of performance.

Analysts in the Quality Control department are not documenting the pH for the [redacted] sample mixture for drug product release testing for Feridex I.V. and Ferumoxytol I.V. This is required as part of procedure Bacterial Endotoxin, QCP 9010, version August 29, 2007.

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OBSERVATION 6

Written procedures are not established for the cleaning and maintenance of equipment, including utensils, used in the manufacture, processing, packing or holding of a drug product.

A. The cleaning validation for product-contact equipment for Ferumoxytol I.V. and/ or Feridex I.V. and their respective drug substances are inadequate for the following reasons:

1. Process changes were made to the routine cleaning process for the [redacted] liter reactor used in the manufacture of the drug substance for Ferumoxytol I.V. These changes have not been validated:
   a. The volume of [redacted] was decreased approximately [redacted] fold
   b. Previously the pressure for the [redacted] was not controlled, now it is controlled
   c. A [redacted] micron filter was added to the outlet valve on the bottom of the reactor used for circulation
   d. The water for injection rinses were increased from [redacted] to [redacted] minutes and the volume of water for injection decreased for rinses [redacted] and [redacted] from approximatley [redacted] liters to approximately [redacted] liters.

2. The procedure Equipment Cleaning, MSOP 3020 for routine cleaning of Ferumoxytol I.V. and Feridex I.V. manufacturing equipment allows the use of cleaning with water or [redacted] The cleaning validation does not state whether [redacted] or water was used. The firm is unable to demonstrate that worst-case cleaning validation was executed.

3. There is no justification for only executing one cleaning validation run for each piece of Feridex I.V. manufacturing equipment used for drug product and drug substance.

4. There is no endotoxin testing performed.

5. Acceptance criteria for cleaned manufacturing equipment for bioburden of [redacted] cfu/ [redacted] cm^2 is unjustified.

6. [redacted] plates used in microbial level determination during cleaning validation were not qualified for use.

7. The sole use of [redacted] plates [redacted] cm^2 each, for microbiological monitoring of manufacturing equipment is inadequate. There is no justification for only sampling two locations for each piece of equipment.

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OBSERVATION 7

Deviations from written production and process control procedures are not justified.

The procedure Documentation of Process Deviations, MSOP 3016, version May 18, 2007 and QC and Production Document System, QSOP 007, version October 5, 2000 do not require justification for acceptance of deviations from approving officials, execution of a risk assessment to evaluate potential product quality impact, or provisions for closure of a deviation. For example:

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Planned deviation 2008-141, created September 10, 2008, allowed production personnel to deviate from the validated cleaning procedure for the [redacted] liter reactor, Cleaning of the Reactor for Code 5128, MCP 4039 by allowing [redacted] to sit in the reactor for approximately [redacted] hours. There was no documented justification for why the Production Manager and the Vice President of Quality Control approved this planned deviation. A risk assessment was not performed to evaluate effects on the integrity of the [redacted] liter reactor and the potential risk for the manufacture of the subsequent batch of Ferumoxytol drug substance.

OBSERVATION 8

There are no written procedures for production and process controls designed to assure that the drug products have the identity, strength, quality, and purity they purport or are represented to possess.

The procedure Documentation of Process Deviations, MSOP 3016, version May 18, 2007 does not contain a procedure for change control or its assessment. This procedure was effective thorough July 23, 2008. The following examples demonstrate a lack of an adequate change control system:

A. Production made a permanent change to the [redacted] liter reactor mixing speed for Ferumoxytol drug substance from the set point of [redacted], to include a range of [redacted] +/- [redacted]%. The change control does not document the evaluation for whether this change would affect product quality.

Exemption 4

B. Engineering modified wiring connections on the same cooling relay which services the Clean Room complex. This change caused the relative humidity in the Clean Room complex to exceed the established specification of [redacted]% relative humidity. Therefore, Production and Quality Control approved the relative humidity specification change to [redacted]%. A change control was not executed to scientifically evaluate how this specification change would affect operations and quality of the Clean Room complex used to fill Ferumoxytol I.V. and Feridex I.V.

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C. Two planned deviations allowed a [redacted]% reduction in batch size for the manufacture of Feridex I.V. lots [redacted] and [redacted] A change control was not initiated to determine the potential impact of this change and whether validation was necessary. Exemption 4

OBSERVATION 9

An adequate number of batches of each drug product are not tested to determine an appropriate expiration date.

Specifically, there is no justification for placing only one lot (08080402) of Ferumoxytol I.V. on stability following a process change. Previously, the [redacted] was first mixed with p[redacted] and was subsequently filtered with a [redacted]um filter. The process change made to Ferumoxytol drug substance now requires separate [redacted] for injection through [redacted]um filter. Exemption 4

OBSERVATION 10

Reports of analysis from component suppliers are accepted in lieu of testing each component for conformity with all appropriate written specifications, without establishing the reliability of the supplier's analyses through appropriate validation of the supplier's test results at appropriate intervals.

Specifically, per procedure Vendor Qualification System, QSOP 020, version October 25, 2000, states "Vendor qualification is established thorough audits, testing and certificates of analysis," however, several suppliers of critical raw materials and components have never been audited. For example:

- the contract testing laboratory for USP raw materials used in production
- the contract laboratory that conducted validation of endotoxin testing for drug substance and drug product for Feridex I.V. and Ferumoxytol I.V.
- the raw material supplier of [redacted]
- the supplier o[redacted] used in Feridex drug substance
- the supplier of [redacted] gas used in Ferumoxytol drug substance and drug product filling
- the filter supplier for the [redacted] process for Ferumoxytol drug substance purification, and all [redacted] process filters for Feridex I.V. and Ferumoxytol I.V.

Exemption 4

OBSERVATION 11

Each lot of components is not withheld from use until the lot has been sampled, tested, examined, and released by the quality control unit.

Specifically, the procedure Micro Media Release for QC Use, QCP 9055, for the past fourteen (14) years does not require

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[redacted] plates to be inoculated for challenge with a known concentration of microbes. This [redacted] is used in the cleaning validation, routine environmental monitoring during filling, personnel monitoring.

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09/18/2008(Thu), 09/19/2008(Fri), 09/22/2008(Mon), 09/23/2008(Tue), 09/24/2008(Wed), 09/25/2008(Thu), 09/26/2008(Fri), 09/30/2008(Tue), 10/01/2008(Wed), 10/02/2008(Thu), 10/08/2008(Wed), 10/09/2008(Thu), 10/14/2008(Tue)

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