CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103951Orig1s5173

CHEMISTRY REVIEW(S)

MEMORANDUM

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

SUBJECT:	Review of the supplement STN 103951-5173, supporting a conversion of the current label to the Physician's Labeling Rule (PLR) format
FROM:	Ingrid Markovic, Ph.D., CMC Reviewer, DTP/OBP/OPS/CDER 6/15/11
TO:	103951-5173 file
THROUGH:	Barry Cherney, Ph.D., Deputy Director, DTP/OBP/OPS/CDER 6-15-11
SPONSOR:	Amgen
PRODUCTS:	Aranesp® (*darbepoetin alfa*)
REVIEWED:	June 2, 2011
REVISED:	June 9, 2011

Recommendation

Proposed revisions to the label, which acknowledge removal of Human Serum Albumin (HSA) formulation, and an autoinjector presentation, from the Aranesp license are acceptable from a Chemistry Manufacturing and Controls perspective. These changes are not expected to have an impact on the quality and safety of Aranesp formulated in Polysorbate 80 or the other two approved presentations (i.e., vials and prefilled syringes).

1. Changes to the PLR label

The Sponsor provided notification to the agency that Aranesp license will no longer include the autoinjector presentation ((b) (4) or the HSA formulation (b) (4) therefore, the revisions in the label will reflect currently marketed product, which seems a prudent decision. The above listed changes are acknowledged by the CMC team and are considered acceptable from our perspective. This is because the quality of the remaining formulation of Aranesp (i.e., Polysorbate 80) or the other two approved presentations (i.e., vials and prefilled syringes) has an acceptable safety and efficacy profile which does not appear to differ from the presentations that are being discontinued. Furthermore, withdrawal of the HSA

formulation reduces the theoretic risk associated with transmission of human pathogens and is consistent with risk reduction strategies used for control of adventitious viruses. While the HSA free formulation has a greater risk associated with modifications to the active drug substance, this risk has been adequately assessed and controlled on stability. The PLR label is being updated by the clinical group to reflect such revisions to the Aranesp license.

2. Categorical exclusion from environmental assessment

Approval of this supplement will not alter significantly the concentration or distribution of the Epogen or Aranesp substance or their degradation products in the environment according to the FDA "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications," July 1998, CMC 6, Revision 1. The Sponsor complies with the categorical exclusion criteria listed in 21 CFR 25.31(c), and no extraordinary circumstances exist. Therefore, approval of categorical exclusion from environmental assessment is granted.

Patel, Mona

From: Ramanadham, Mahesh
ent: Friday, May 27, 2011 4:12 PM
o: Patel, Mona; CDER-TB-EER; Pohlhaus, Timothy
Cc: Jones, Karen; Keegan, Patricia
Subject: RE: Urgent Re-Request: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL STN 103951/5173)

Attachments: 103951-5173 TB-EER response.doc

Dear Mona,

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for STN 103951/5173. Please see the attached form for individual site compliance statuses. Although the compliance status of AML Puerto Rico is initially OAI, NGDMT does not feel that the nature of the deficiencies at this firm affect the approvability of the supplement. There are no pending or ongoing compliance actions that prevent approval of this supplement.

103951-5173
B-EER response.do.

Sincerely,

ahesh Ramanadham, PharmD/M.B.A.
LT., USPHS
Regulatory Compliance Officer
CDER, Office of Compliance
Division of Manufacturing and Product Quality,
Manufacturing Assessment and Pre-Approval Compliance Branch
(301)796-3272

From: Patel, Mona
Sent: Friday, May 27, 2011 10:14 AM
To: CDER-TB-EER; Pohlhaus, Timothy
Cc: Jones, Karen; Keegan, Patricia
Subject: Urgent Re-Request: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL STN 103951/5173)
Importance: High

Hello,

Please perform another compliance check as the last one performed is 4.22.11.

It is imperative I have this completed ASAP. If you have any questions, please do not hesitate to call me.

Mona

From: CDER-TB-EER
Sent: Friday, April 22, 2011 11:30 AM
To: Patel, Mona; Pohlhaus, Timothy
: CDER-TB-EER
Subject: RE: Complete Response Resubmission: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL STN 103951/5173)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the attached form below to find the current compliance status of each site. There are no pending or ongoing compliance actions that would prevent approval of STN 103951/5173 at this time.
<< File: STN 103951s5173 final.doc >>
Sincerely,

Marisa Stock
Consumer Safety Officer
FDA/CDER/OC/DMPQ
(301) 796-4753

From: Patel, Mona
Sent: Monday, April 18, 2011 11:55 AM
To: Pohlhaus, Timothy
Cc: CDER-TB-EER
Subject: Complete Response Resubmission: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL STN 103951/5173)

I am requesting an EER request for the Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

The action due date is May 23, 2011.

The last one done for this supplement was on March 29, 2010. If you need me to submit another EER request, please let me know.

Mona

From: Pohlhaus, Timothy
Sent: Monday, March 29, 2010 1:22 PM
To: Patel, Mona
Cc: CDER-TB-EER; Pohlhaus, Timothy
Subject: RE: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL STN 103951/5173)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for Amgen, Inc.'s STN 103951/5173. Please see the attached response for the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of STN 103951/5173 at this time.

<< File: 103951-5173 TB-EER response.doc >>

Timothy J. Pohlhaus, Ph.D.
Staff Fellow
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 3218
Silver Spring, MD 20993
Phone - (301) 796-5224

Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

Instructions:
The review team should email this form to the email account "CDER-TB-EER" to submit:

1) an initial TB-EER within 10 business days of the application filing date
2) a final TB-EER 15-30 days prior to the action date

Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: April 27, 2010

Applicant Name: Amgen, Incorporated
STN(s): 103951/5173
Product(s): Aranesp (darbepoetin alfa)
Short summary of application: Efficacy Supplement (PLR conversion)

FACILITY INFORMATION

Firm Name: Amgen, Inc.
Address: One Amgen Center Drive, Thousand Oaks, CA 91320
FEI: 2026154
Short summary of manufacturing activities performed: Drug Substance Bulk Manufacturing, Drug Substance and Drug Product Release Testing, Drug Substance and Drug Product Stability Testing

On March 23, 2010, Lisa Shamon-Taylor of Amgen (via correspondence with Mona Patel) confirmed that this site is (b) (4) This site was inspected April 7-11, 2008 by LOS-DO and classified NAI. The (b) (4), and CTL profiles were covered and are considered acceptable.

Firm Name: Amgen, Inc.

---

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Address: 4000 Nelson Road, Longmont, CO 80503
FEI:3002892484
Short summary of manufacturing activities performed: Drug Substance Bulk Manufacturing, Drug Substance Release Testing, Drug Substance and Drug Product Stability Testing

Inspected by DEN-DO August 23 - September 3, 2010 and classified VAI. This was a biennial GMP surveillance inspection. The (b) (4) profile was updated and considered acceptable.

Firm Name: Amgen Manufacturing, Limited
Address: P.O. Box 4060, Road 31 km 24.6, Juncos, PR 00777-4060
FEI: 1000110364
Short summary of manufacturing activities performed: Drug Substance Bulk Manufacturing, Drug Product Manufacturing, Drug Substance and Drug Product Release Testing

Inspected by SJN-DO from 4/18/11-4/29/11 and initially classified OAI. This was a GMP inspection that found deficiencies in the (b) (4). However NGDMT does not believe the GMP deficiencies at this facility affect the nature of this supplement. NGDMT finds this site acceptable for the purposes of this supplement.

Firm Name: Amgen Europe B.V.
Address: Minervum 7061, 4817 ZK, Breda, Netherlands
FEI: 3005889661
Short summary of manufacturing activities performed: Assembly of SureClick autoinjector

This registered site has not been inspected and would not be considered for inspection due to the scope of its responsibilities. An inspection is not required for approval of this supplement.

Patel, Mona

From: Patel, Mona
Sent: Friday, May 27, 2011 10:14 AM
To: CDER-TB-EER; Pohlhaus, Timothy
Cc: Jones, Karen; Keegan, Patricia
Subject: Urgent Re-Request: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL STN 103951/5173)

Importance: High

Attachments: STN 103951s5173 final.doc; 103951-5173 TB-EER response.doc

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STN 103951s5173 final.doc (39 ...

Sincerely,

Marisa Stock
Consumer Safety Officer
FDA/CDER/OC/DMPQ
(301) 796-4753

From: Patel, Mona
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I am requesting an EER request for the Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

The action due date is May 23, 2011.

The last one done for this supplement was on March 29, 2010. If you need me to submit another EER request, please let me know.

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The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for Amgen, Inc.'s STN 103951/5173. Please see the attached response for the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of STN 103951/5173 at this time.

103951-5173
B-EER response.do.

Timothy J. Pohlhaus, Ph.D.
Staff Fellow
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 3218
Silver Spring, MD 20993
Phone - (301) 796-5224

Patel, Mona

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103951-5173
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APPLICATION INFORMATION

PDUFA Action Date: April 27, 2010

Applicant Name: Amgen, Incorporated
STN(s): 103951/5173
Product(s): Aranesp (darbepoetin alfa)
Short summary of application: Efficacy Supplement (PLR conversion)

FACILITY INFORMATION

Firm Name: Amgen, Inc.
Address: One Amgen Center Drive, Thousand Oaks, CA 91320
FEI: 2026154
Short summary of manufacturing activities performed: Drug Substance Bulk Manufacturing, Drug Substance and Drug Product Release Testing, Drug Substance and Drug Product Stability Testing

On March 23, 2010, Lisa Shamon-Taylor of Amgen (via correspondence with Mona Patel) confirmed that this site is (b) (4) This site was inspected April 7-11, 2008 by LOS-DO and classified NAI. The (b) (4) and CTL profiles were covered and are considered acceptable.

---

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Firm Name: Amgen, Inc.
Address: 4000 Nelson Road, Longmont, CO 80503
FEI:3002892484
Short summary of manufacturing activities performed: Drug Substance Bulk Manufacturing, Drug Substance Release Testing, Drug Substance and Drug Product Stability Testing

Inspected August 30 – September 3, 2010 and classified VAI. The (b) (4) profile was covered during this routine biotech cGMP inspection and is acceptable.

Firm Name: Amgen Manufacturing, Limited
Address: P.O. Box 4060, Road 31 km 24.6, Juncos, PR 00777-4060
FEI: 1000110364
Short summary of manufacturing activities performed: Drug Substance Bulk Manufacturing, Drug Product Manufacturing, Drug Substance and Drug Product Release Testing

Inspected July 27 – September 11, 2009 and classified VAI. The (b) (4) profiles were covered during this routine biotech cGMP inspection and are acceptable.

(b) (4)

Firm Name: Amgen Europe B.V.
Address: Minervum 7061, 4817 ZK, Breda, Netherlands
FEI: 3005889661
Short summary of manufacturing activities performed: Assembly of SureClick autoinjector

This registered site has not been inspected and would not be considered for inspection due to the scope of its responsibilities. An inspection is not required for approval of this supplement.

Patel, Mona

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Cc: CDER-TB-EER
Subject: Complete Response Resubmission: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL STN 103951/5173)

Attachments: 103951-5173 TB-EER response.doc

I am requesting an EER request for the Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

The action due date is May 23, 2011.

The last one done for this supplement was on March 29, 2010. If you need me to submit another EER request, please let me know.

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From: Pohlhaus, Timothy
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To: Patel, Mona
Cc: CDER-TB-EER; Pohlhaus, Timothy
Subject: RE: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL STN 103951/5173)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for Amgen, Inc.'s STN 103951/5173. Please see the attached response for the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of STN 103951/5173 at this time.

103951-5173
B-EER response.do.

Timothy J. Pohlhaus, Ph.D.
Staff Fellow
Food and Drug Administration
CDER/OC/DMPQ
10903 New Hampshire Avenue
Building 51, Room 3218
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Note: All manufacturing[1] locations named in the pending submission, whether contract facilities or facilities owned by the applicant, should be listed on this form. For bundled supplements, one TB-EER to include all STNs should be submitted.

APPLICATION INFORMATION

PDUFA Action Date: April 27, 2010

Applicant Name: Amgen, Incorporated
STN(s): 103951/5173
Product(s): Aranesp (darbepoetin alfa)
Short summary of application: Efficacy Supplement (PLR conversion)

FACILITY INFORMATION

Firm Name: Amgen, Inc.
Address: One Amgen Center Drive, Thousand Oaks, CA 91320
FEI: 2026154
Short summary of manufacturing activities performed: Drug Substance Bulk Manufacturing, Drug Substance and Drug Product Release Testing, Drug Substance and Drug Product Stability Testing

On March 23, 2010, Lisa Shamon-Taylor of Amgen (via correspondence with Mona Patel) confirmed that this site is (b) (4) This site was inspected April 7-11, 2008 by LOS-DO and classified NAI. The (b) (4) and CTL profiles were covered and are considered acceptable.

Firm Name: Amgen, Inc.

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[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Address: 4000 Nelson Road, Longmont, CO 80503
FEI:3002892484
Short summary of manufacturing activities performed: Drug Substance Bulk Manufacturing, Drug Substance Release Testing, Drug Substance and Drug Product Stability Testing

An inspection was conducted at Amgen, Longmont, CO on January 31, 2008 for preapproval coverage of the firm's laboratory operations. The inspection was classified NAI. Although the firm's GMP inspection coverage is outdated, for purposes of this supplement, we will consider the profile acceptable and will work with the DEN-DO to expedite a surveillance inspection.

Firm Name: Amgen Manufacturing, Limited
Address: P.O. Box 4060, Road 31 km 24.6, Juncos, PR 00777-4060
FEI: 1000110364
Short summary of manufacturing activities performed: Drug Substance Bulk Manufacturing, Drug Product Manufacturing, Drug Substance and Drug Product Release Testing

Inspected June 27 – September 11, 2009 by SJN-DO and classified VAI. The (b) (4) profiles were covered and are considered acceptable.

Firm Name: Amgen Europe B.V.
Address: Minervum 7061, 4817 ZK, Breda, Netherlands
FEI: 3005889661
Short summary of manufacturing activities performed: Assembly of SureClick autoinjector

This registered site has not been inspected and would not be considered for inspection due to the scope of its responsibilities. An inspection is not required for approval of this supplement.

Patel, Mona

From: Patel, Mona
Sent: Thursday, March 18, 2010 12:53 PM
To: CDER-TB-EER
Subject: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL STN 103951/5173)

Attachments: Aranesp BLA 103951.5173 (3.18.2010).doc; Aranesp BLA 103951.5173 356h attachment.pdf

Hi,

I am requesting an EER requests for the Complete Response Resubmissions for PLR Supplements (Efficacy): Aranesp (BL 103951/5173).

The action due date for this supplement is April 27, 2010.


Aranesp BLA .03951.5173 (3.18..


Aranesp BLA 03951.5173 356h a.

Mona Patel, PharmD | Lt, USPHS | Regulatory Project Manager | Division of Biologic Oncology Products, Office of Oncology Drug Products, CDER, FDA | White Oak Complex, Bldg. 22, Room 2328 | 10903 New Hampshire Avenue | Silver Spring, MD 20993
☎301.796.4236 (phone) • 301.796.9849 (fax) | mona.patel@fda.hhs.gov (email)


consider the environment before printing this e-mail

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APPLICATION INFORMATION

PDUFA Action Date: April 27, 2010

Applicant Name: Amgen, Incorporated
STN(s): 103951/5173
Product(s): Aranesp (darbepoetin alfa)
Short summary of application: Efficacy Supplement (PLR conversion)

FACILITY INFORMATION

See Attachment

[1]The regulations at 21 C.F.R. § 207.3(a)(8) defines "manufacturing or processing" as "the manufacture, preparation, propagation, compounding, or processing of a drug or drugs as used in section 510 of the act [21 U.S.C. § 360] and is the making by chemical, physical, biological, or other procedures of any articles that meet the definition of drugs in section 201(g) of the act. The term includes manipulation, sampling, testing, or control procedures applied to the final product or to any part of the process. The term also includes repackaging or otherwise changing the container, wrapper, or labeling of any drug package to further the distribution of the drug from the original place of manufacture to the person who makes final delivery or sale to the ultimate consumer."

Attachment to Form 356h
Establishment Information for Aranesp® (darbepoetin alfa)

Product & Facility	Contact Person	Registration Number (CFN) / Labeler Code	Manufacturing Steps / Type of Testing
Amgen Inc. One Amgen Center Drive Thousand Oaks, CA 91320	Madhavan Balachandran SVP, Thousand Oaks Operations (805) 447-3872	2026154 / 055513	Drug Substance Bulk Manufacturing: • (b) (4) • • Drug Substance and Drug Product Release Testing Drug Substance and Drug Product Stability Testing
Amgen Inc. 4000 Nelson Road Longmont, CO 80503 *(Longmont facility)*	David Bengston VP, Colorado Operations (303) 401-1850	1724627 / 055513	Drug Substance Bulk Manufacturing: • (b) (4) • • Drug Substance Release Testing Drug Substance and Drug Product Stability Testing
Amgen Manufacturing, Limited P.O. Box 4060 Road 31 km 24.6 Juncos, PR 00777-4060	Emilio Rivera VP, Puerto Rico Operations 787-916-2090	2650228 / 059703	Drug Substance Bulk Manufacturing: • (b) (4) • • Drug Product Manufacturing: • (b) (4) • • Drug Substance and Drug Product Release Testing
Amgen Europe B.V. Minervum 7061 4817 ZK, Breda, Netherlands	Hubert Koevoets, Managing Director Telephone: +31 076-573.2021	3005889661/024646	Assembly of the SureClick™ autoinjector

MEMORANDUM

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

SUBJECT:	Review of supplements STN 103234-5166 and 103951-5173 supporting a conversion of current labeling to the Physician's Labeling Rule (PLR) format
FROM:	Ingrid Markovic, Ph.D., CMC Reviewer, DTP/OBP/OPS/CDER 10/13/08
TO:	103234-5166 and 103951-5173 file
THROUGH:	Barry Cherney, Ph.D., Deputy Director, DTP/OBP/OPS/CDER
SPONSOR:	Amgen Barry Cherney 10-17-09
PRODUCTS:	Epogen® (*epoetin alfa*) and Aranesp® (*darbepoetin alfa*)
ACTION DATE:	October 24, 2008

Recommendation

The proposed changes supporting a conversion of the current labeling to the Physician's Labeling Rule (PLR) format are acceptable from a Chemistry Manufacturing and Controls perspective. However, the PI dos not indicate that Epogen should be protected from light. The PI should be revised to reflect Epogen's sensitivity to light.

1. Categorical exclusion from environmental assessment

Approval of this supplement will not alter significantly the concentration or distribution of the Epogen or Aranesp substance or their degradation products in the environment according to the FDA "Guidance for Industry: Environmental Assessment of Human Drug and Biologics Applications," July 1998, CMC 6, Revision 1. The Sponsor complies with the categorical exclusion criteria listed in 21 CFR 25.31(c), and no extraordinary circumstances exist. Therefore, approval of categorical exclusion from environmental assessment is granted.

2. Suggestions for the PLR label

It is recommended that the wording "protect from light" is added to epogen's Package Insert. Although these two products have comparable sensitivity to light, such statement is present in the Aranesp label but it is missing from the Epogen's.

Excerpt from the package insert:

(b) (4)

(b) (4)

This point was communicated to Neal Storm from Amgen during a teleconference on October 16, 2008. He stated that he will follow up with the CMC group regarding issues with Epogen's stability in light. No commitments were made.