CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

103951Orig1s5173

ADMINISTRATIVE and CORRESPONDENCE DOCUMENTS

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

BLA # :103951 **Supplement Type (e.g. SE5):** Efficacy **Supplement Number:** 5173

Stamp Date: December 27, 2007 **PDUFA Goal Date:** October 28, 2008

HFD-107 **Trade and generic names/dosage form:** darbepoetin alfa (Aranesp))/multiple

Applicant: Amgen, Inc. **Therapeutic Class:** Cancer Ancillary

Does this application provide for new active ingredient(s), new indication(s), new dosage form, new dosing regimen, or new route of administration? *

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

** SE5, SE6, and SE7 submissions may also trigger PREA. If there are questions, please contact the Rosemary Addy or Grace Carmouze.*

Indication(s) ***previously approved*** **(please complete this section for supplements only):**_____

Each indication covered by current application under review must have pediatric studies: ***Completed, Deferred, and/or Waived.***

Number of indications for this application(s):_____

Indication #1: _____

Is this an orphan indication?

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

Is there a full waiver for this indication (check one)?

- ☐ **Yes: Please proceed to Section A.**
- ☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. Enter into RMS-BLA Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Waived.

tion B: Partially Waived Studies

Age/weight range being partially waived (fill in applicable criteria below):

Min_____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____
Reason(s) for partial waiver:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**
- ❑ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Partially Waived

Section C: Deferred Studies

Age/weight range being deferred (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ❑ **Products in this class for this indication have been studied/labeled for pediatric population**
- ❑ **Disease/condition does not exist in children**
- ❑ **Too few children with disease to study**
- ❑ **There are safety concerns**
- ❑ **Adult studies ready for approval**
- ❑ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Studies Deferred

Section D: Completed Studies

Age/weight range of completed studies (fill in applicable criteria below):

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered RMS-BLA. Enter into CBER Communication as: Memo/Other (OT) - Summary Text: Pediatric Page; and update the special characteristics code in RMS/BLA with Ped Data Submitted and Complete.

This page was completed by:

Monica Hughes, 4/29/08
Lead Regulatory Health Project Manager

cc: BLA 103234/5166
Rosemary Addy or Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT ROSEMARY ADDY OR GRACE CARMOUZE

(revised for TBP licensing products 9-15-2006)

1. Debarment Certification

Amgen 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 application.

Paul Eisenberg, MD, MPH
Vice President, Global Regulatory Affairs & Safety

10/5/07
Date

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

To:	File
From:	Grace Carmouze, Safety RPM Division of Biologic Oncology Products
Through:	Patricia Keegan, MD, Director Division of Biologic Oncology Products
Date:	June 15, 2011
Regarding:	Teleconference to discuss FDA comments to Amgen's June 8, 2011 proposed REMS modifications (sent via e-mail) related to BL STN 103234/5266 & 5166 & BL STN 103951/5258 & 5173

FDA Attendees:

Patricia Keegan, MD, Regulatory Health Project Manager, DBOP
Jeff Summers, MD, Deputy Director for Safety, DBOP
Karen Jones, CPMS, DBOP
Grace Carmouze, Safety RPM, DBOP
Kaushikkumar Shastri, MD, Clinical Reviewer, DBOP
Ebla Ali Ibrahim Regulatory Health Project Manager, DHP
Amarilys Vega, Reviewer, OSE/DRISK
Suzanne Berkman Robottom, PharmD, Team Leader, OSE/DRISK
Nancy Clark Dickinson, PharmD, Regulatory Project Manager, ORP
Katlin McKelvie Backfield, JD, OCC

Amgen:

Edward Burd, PhD – Director, Global Regulatory Affairs
Annie Dang, JD – Manager, Global Regulatory Affairs
Lisa DiMolfetto, PhD – Director, Global Regulatory Affairs
Janet Franklin, MD, MPH – Clinical Research Medical Director, Global Development
Rekha Garg, MD, MS – Executive Director, Global Safety
Danica Katz, MA – Director, Global Safety
Ravi Magavi, MS – Senior Manager, Global Regulatory Affairs
Sundeep Sethi, MD, MBA – Executive Director, Scientific Affairs
Lisa Shamon-Taylor, PhD – Director, Global Regulatory Affairs
Elizabeth Williams, MS, RAC – Manager, Global Regulatory Affairs
Sunita Zalani, PhD – Executive Director, Global Regulatory Affairs

J&J:

Brian Maloney, RPh, MS – Director, Regulatory Affairs
Brenda Sarokhan, MPH – Sr. Director, Medical Education Science Communication

Background

On October 14, 2010, Amgen submitted the first REMS Assessment report for the ESA REMS approved on February 16, 2010 and a Prior Approval Supplement (PAS) proposing modifications to the ESA APPRISE Oncology Program Hospital Designee Enrollment Form and ESA APPRISE Oncology Program website.

On March 22, 2011, proposed REMS modifications were also included in the Amgen resubmissions to the FDA April 27, 2010 Complete Response actions under STNs 103234.5166 & 103951.5173.

In response to FDA's June 2, 2011 request, Amgen sent final PLR labeling (USPI, MG, and PIU) and REMS materials via e-mail to FDA on June 8, 2011. On June 15, 2011, an internal meeting was held between OND, OSE, ORP, and OCC to determine if any final comments/edits needed to be conveyed to Amgen. An action item from the internal meeting was to set-up a teleconference with Amgen to convey FDA's comments and reach agreement.

Teleconference Minutes

On June 15, 2011, FDA held a teleconference to discuss FDA's proposed changes to the ESAs concise REMS document and the Patient Acknowledgement Form flashcard Amgen sent to FDA via e-mail on June 8, 2011. These proposed changes were sent to Amgen prior to the teleconference (see attachment). After some discussion, Amgen agreed to all of FDA's proposed changes. In addition, Amgen agreed to submit formal amendments to the PLR supplements (STNs 103234.5166 & 103951.5173) containing final draft PLR labeling and REMS materials with all agreed-upon changes. The documents submitted will only be "clean" versions (i.e., non-strikethrough). Amgen will also submit letters of cross-reference as amendments to the REMS modification supplements (STNs 103234.5266 & 103951.5258) and to the TREAT supplements STNs (managed by FDA's Division of Hematology Products) by Friday, June 17, 2011.

Call Concluded.

Patel, Mona

From: Jones, Karen
Sent: Wednesday, June 15, 2011 12:13 PM
To: 'Williams, Elizabeth'
Cc: Carmouze, Grace; Patel, Mona; Dang, Annie; Magavi, Ravi
Subject: RE: Request for Telecon
Importance: High
Attachments: Concise REMS template edits 15-JUN-11.doc; kdj-20110615121054.pdf

Hello Elizabeth,

Thank you for agreeing to participate in the telecon and for the call-in information you provided.
Attached are the documents with proposed changes in strike-out which we will discuss during the telecon.

Please confirm receipt.

Thank you.

Karen

From: Williams, Elizabeth [mailto:ewilliam@amgen.com]
Sent: Wednesday, June 15, 2011 11:46 AM
To: Jones, Karen
Cc: Carmouze, Grace; Patel, Mona; Dang, Annie; Magavi, Ravi
Subject: RE: Request for Telecon

Hi Karen,

We are available. Dial-in information is below.

Teleconference information:
Call-in toll-free number: (b) (4)
Call-in number: (b) (4)
Conference Code: (b) (4)

Thanks.

Elizabeth

From: Jones, Karen [mailto:Karen.Jones@fda.hhs.gov]
Sent: Wednesday, June 15, 2011 7:29 AM
To: Williams, Elizabeth
Cc: Carmouze, Grace; Patel, Mona; Dang, Annie; Magavi, Ravi
Subject: Request for Telecon
Importance: High

Hello Elizabeth,

FDA is requesting a telecon today, June 15, 2011, at 12:30 EDT (9:30 am your time) to discuss FDA proposed changes to the REMS. We are requesting that you block off one hour for the call. Please reply as soon as possible to let us know if you can accommodate our request.

Thank you.
Karen

Karen D. Jones
CPMS
OODP/DBOP
301-796-1377

From: Williams, Elizabeth [mailto:ewilliam@amgen.com]
Sent: Friday, June 10, 2011 4:27 PM
To: Carmouze, Grace
Cc: Dang, Annie; Jones, Karen; Magavi, Ravi; Ali Ibrahim, Ebla; Patel, Mona
Subject: RE: Timeline of Submission For Final labeling (ESAs)

11 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Patel, Mona

From: Summers, Jeff
Sent: Monday, June 06, 2011 8:38 AM
To: 'lshamont@amgen.com'
Cc: Patel, Mona; Carmouze, Grace
Subject: FW: ESA REMS
Attachments: HCP Enrollement form revised 6_6_2011.doc

Suggested edits—if you did not already catch this

Jeff

(b) (4)

From: Summers, Jeff
Sent: Sunday, June 05, 2011 5:26 PM
To: 'lshamont@amgen.com'
Cc: Patel, Mona; Carmouze, Grace
Subject: ESA REMS

Lisa
The enrollment forms have the following language that is not consistent with the revised concise REMS.
Jeff

4 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Patel, Mona

From: Summers, Jeff
Sent: Sunday, June 05, 2011 5:26 PM
To: 'Ishamont@amgen.com'
Cc: Patel, Mona; Carmouze, Grace
Subject: ESA REMS

Lisa
The enrollment forms have the following language that is not consistent with the revised concise REMS.
Jeff

(b) (4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

To:	File
From:	Mona Patel, Pharm.D., Regulatory Health Project Manager Division of Biologic Oncology Products
Through:	Patricia Keegan M.D., Director of Division of Biologic Oncology Products
Date:	June 2, 2011
Regarding:	Follow-up teleconference to discuss Amgen's Response to FDA recommendations for proposed REMS modifications related to BL STN 103234/5266 & 5166 & BL STN 103951/5258 & 5173 communicated during the June 1, 2011 teleconference.

FDA Attendees:
Mona Patel, Regulatory Health Project Manager, DBOP
Jeff Summers, Deputy Director of Safety, DBOP
Grace Carmouze, Safety RPM, DBOP
Kaushik Shastri, Clinical Reviewer, DBOP

Amgen:
Annie Dang, JD – Manager, Global Regulatory Affairs
Rekha Garg, MD, MS – Executive Director, Global Safety
Sundeep Sethi, MD, MBA – Executive Director, Scientific Affairs
Elizabeth Williams, MS, RAC – Manager, Global Regulatory Affairs

J&J:
Brian Maloney, RPh, MS – Director, Regulatory Affairs

Teleconference Minutes

On October 14, 2010, Amgen submitted a First Assessment Report to the REMS approved on February 16, 2010 and a Prior Approval Supplement (PAS) describing proposed modifications to the ESA APPRISE Oncology Program Hospital Designee Enrollment Form and ESA APPRISE Oncology Program website.

Proposed REMS modifications were also included in the Complete Response resubmissions to the April 27, 2010 action under STNs 103234.5166 & 103951.5173 on March 22, 2011.

On May 31, 2011, FDA held a teleconference with Amgen to discuss Amgen's responses contained in the May 19, 2011 submission under STN 103234.5166 & STN 103951.5173 for the proposed REMS modifications. FDA conveyed recommendations to Amgen for the proposed REMS modifications. Amgen requested a follow-up teleconference be scheduled to reach agreement on the REMS materials after Amgen had the opportunity to review FDA's recommendations. FDA scheduled a subsequent teleconference for June 1,

2011. Outstanding issues needed to be resolved and another teleconference was scheduled for June 2, 2011 at the request of both parties.

FDA informed Amgen that the legal name change from Centocor Ortho Biotech Products to Janssen Products for materials affecting Procrit will have to be submitted in a separate submission contrary to FDA's communication on May 18, 2011 allowing the legal name change to be submitted as an amendment to PLR. FDA stated that action on STN 103234.5166 & 103951.5173 could potentially occur before the Amgen/Centocor's stipulated public release date of the legal name change. Amgen understood and agreed to submit a separate REMS modification supplement when all REMS materials affected (i.e., MG, Concise REMS document, REMS training modules, Patient Acknowledgement Forms, and Website) by the legal name change were finalized. FDA requested Amgen to submit the draft new Dear Healthcare Provider (DHCP) letters for ongoing communication to HCPs and Hospitals for review. Amgen agreed to submit them to FDA for review by June, 6, 2011. Amgen confirmed that they would submit by June 8, 2011, via email, the revised REMS materials and labeling. FDA requested a formal submission of REMS materials and labeling to occur by June 10, 2011 to which Amgen said yes.

Call Concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

To:	File
From:	Mona Patel, Pharm.D., Regulatory Health Project Manager Division of Biologic Oncology Products
Through:	Jeff Summers M.D., Deputy Director of Safety
Date:	June 1, 2011
Regarding:	Teleconference to discuss Amgen's Response to FDA recommendations for proposed REMS modifications related to BL STN 103234/5266 & 5166 & BL STN 103951/5258 & 5173

FDA Attendees:
Mona Patel, Regulatory Health Project Manager, DBOP
Jeff Summers, Deputy Director of Safety, DBOP
Grace Carmouze, Safety RPM, DBOP
Kaushik Shastri, Clinical Reviewer, DBOP
Amarilys Vega, Reviewer, DRISK
Claudia Karwoski, Division Director, DRISK

Amgen:
Helen Collins, MD – Clinical Research Medical Director, NAML, Global Development
Annie Dang, JD – Manager, Global Regulatory Affairs
Rekha Garg, MD, MS – Executive Director, Global Safety
Sanja Gauthier, MD – Medical Director, Global Safety
Bob Harris, PhD – Director, Global Regulatory Affairs
Danica Katz, MA – Director, Global Safety
Sundeep Sethi, MD, MBA – Executive Director, Scientific Affairs
Lisa Shamon-Taylor, PhD – Director, Global Regulatory Affairs
Jose Vega, MD – Vice President, Global Safety
Elizabeth Williams, MS, RAC – Manager, Global Regulatory Affairs
Sunita Zalani, PhD – Executive Director, Global Regulatory Affairs

J&J:
Mary Guilfoyle – Sr. Director, Compound Development Team Leader
Brian Maloney, RPh, MS – Director, Regulatory Affairs
Brenda Sarokhan, MPH – Sr. Director, Medical Education Science Communication

Teleconference Minutes

On October 14, 2010, Amgen submitted a First Assessment Report to the REMS approved on February 16, 2010 and a Prior Approval Supplement (PAS) describing proposed modifications to the ESA APPRISE Oncology Program Hospital Designee Enrollment Form and ESA APPRISE Oncology Program website.

Proposed REMS modifications were also included in the Complete Response resubmissions to the April 27, 2010 action under STNs 103234.5166 & 103951.5173 on March 22, 2011.

On May 31, 2011, FDA held a teleconference with Amgen to discuss Amgen's responses contained in the May 19, 2011 submission under STN 103234.5166 & STN 103951.5173 for the proposed REMS modifications. Amgen requested a follow-up teleconference be scheduled to reach agreement on the REMS materials after Amgen had the opportunity to review FDA's recommendations conveyed during the May 31, 2011 teleconference. FDA scheduled a subsequent teleconference for June 1, 2011. Amgen sent their response to FDA's May 31, 2011 recommendations to the REMS concise template prior to the June 1, 2011 teleconference. Amgen's response is attached.

Amgen discussed the proposed revisions with FDA. FDA accepted most of Amgen's proposed revisions. FDA requested Amgen insert a transition statement to introduce the list of certification requirements (page 4, C.1.2 and page 8, C.2.2). Amgen agreed to do so.

FDA did not agree with the proposed text on page 14 under D.1.a. (b) (4) and requested Amgen also modify similar language in the 'Guidelines for Patient Acknowledgement Form Integration within Healthcare Systems and Clinics' flashcard. Amgen agreed to do so.

FDA recommended modifying the REMS Supporting document, page 12, section 3.3.1.5, (Healthcare Delivery System Impact and Patient Access, item #2 Requirement for all HCPs and Hospitals to use the ESA APPRISE Oncology Program Patient Acknowledgement Form without modification as a paper-based form), by deleting the first two paragraphs and summarizing the actions already taken to address the problems encountered with the Acknowledgement Form. Amgen agreed to do so.

Amgen also agreed to modify the pop up window under the 'Training & Enrollment' tab containing the following text 'To ensure that you are directed to the appropriate ESA APPRISE Oncology Program Training and Enrollment Module, please select the option that best describes you' by deleting the text under the START button.

FDA requested Amgen provide a timeline of when all of the components of the REMS materials and the carton/container label for Procrit incorporating the legal name change from Centocor Ortho Biotech Products to Janssen Products could be formally submitted to FDA. Amgen discussed providing the REMS materials and the carton/container label for Procrit to FDA via electronic communication by June 10, 2011 with a formal submission to occur no later than June 14, 2011. FDA requested Amgen to email the REMS materials and carton/container label by June 8, 2011. Amgen said they would discuss further internally and would provide a response to FDA on the timeline. Amgen reminded FDA that the legal name change could not be made public until June 22, 2011. FDA requested that Amgen not incorporate name change as an amendment to STNs 103234.5166 & 103951.5173, but rather as a separate supplement. Amgen stated that

they had already begun to make the changes to the ESA materials per FDA's response on May 18, 2011 communicating that the legal name change could be submitted as an amendment to PLR supplements. FDA said they would discuss again further internally and would provide a definitive response regarding the legal name change by June 2, 2011.

Call Concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

To:	File
From:	Mona Patel, Pharm.D., Regulatory Health Project Manager Division of Biologic Oncology Products
Through:	Patricia Keegan M.D., Director of Division of Biologic Oncology Products
Date:	May 31, 2011
Regarding:	Teleconference to discuss FDA recommendations for proposed REMS modifications related to BL STN 103234/5266 & 5166 & BL STN 103951/5258 & 5173

FDA Attendees:
Mona Patel, Regulatory Health Project Manager, DBOP
Jeff Summers, Deputy Director of Safety, DBOP
Patricia Keegan, Division Director, DBOP
Kaushik Shastri, Clinical Reviewer, DBOP
Karen Jones, Chief of Project Management Staff, DBOP
Amarilys Vega, Reviewer, DRISK

Amgen:
Annie Dang, JD – Manager, Global Regulatory Affairs
Janet Franklin, MD, MPH – Clinical Research Medical Director, Global Development
Rekha Garg, MD, MS – Executive Director, Global Safety
Sanja Gauthier, MD – Medical Director, Global Safety
Danica Katz, MA – Director, Global Safety
Sundeep Sethi, MD, MBA – Executive Director, Scientific Affairs
Lisa Shamon-Taylor, PhD – Director, Global Regulatory Affairs
Jose Vega, MD – Vice President, Global Safety
Elizabeth Williams, MS, RAC – Manager, Global Regulatory Affairs
Sunita Zalani, PhD – Executive Director, Global Regulatory Affairs

J&J:
Mary Guilfoyle – Sr. Director, Compound Development Team Leader
Brian Maloney, RPh, MS – Director, Regulatory Affairs
Brenda Sarokhan, MPH – Sr. Director, Medical Education Science Communication

Teleconference Minutes

On October 14, 2010, Amgen submitted a Prior Approval Supplement (PAS) containing the First Assessment Report to the REMS approved on February 16, 2010 and describing proposed modifications to the ESA APPRISE Oncology Program Hospital Designee Enrollment Form and ESA APPRISE Oncology Program website.

In addition, on March 22, 2011, Amgen submitted proposed REMS modifications to reflect modifications to the physician package insert, with that proposed labeling in the Complete Response resubmissions under STNs 103234.5166 & 103951.5173.

FDA requested a teleconference with Amgen to discuss FDA's recommendations for changes to the proposed REMS modifications under all supplements referenced above. Draft FDA recommendations were communicated to Amgen via electronic means on May 31, 2011 prior to the teleconference. The draft recommendations along with FDA's responses to comments posed by Amgen in the May 19, 2011 submission are attached.

FDA discussed Amgen's responses contained in the May 19, 2011 submission under STN 103234.5166 & STN 103951.5173. For response #1, FDA agreed that a tabular format was acceptable and provided advice on improving the table for "space economy" purposes. Amgen committed to propose an alternative. FDA agreed with Amgen's response to comments 1-4 and 5(a b). For 5c, FDA clarified FDA's proposal to modify the pop up window under the 'Training & Enrollment tab containing the following text 'To ensure that you are directed to the appropriate ESA APPRISE Oncology Program Training and Enrollment Module, please select the option that best describes you' by deleting the text under the START button and adding the following third option: I am a non-prescribing HCP (Training Only). Amgen committed to proposing an alternative that would not affect functionality of the website. FDA also agreed with Amgen's responses to comments 6 and 7b. FDA withdrew Comment 7a.

FDA briefly reviewed proposed changes to the REMS concise document provided to Amgen prior to meeting. Amgen provided assurances these changes would be considered for incorporation in the revised concise REMS and reflected in the REMS materials, but they would need time to review all of the changes FDA was proposing to the ESA REMS concise document, and would be ready to discuss the next day. FDA agreed to schedule another teleconference for June 1, 2011 to reach agreement on the REMS documents.

FDA also concurred with Amgen's proposed revision communicated to FDA via email on May 27, 2011 to revise the Instruction for Use for Aranesp and Epogen (see attachment).

Call concluded.

Patel, Mona

From: Patel, Mona

Sent: Tuesday, May 31, 2011 1:49 PM

To: 'Dang, Annie'; Williams, Elizabeth

Subject: REMS Docs for Today's TCON: STNs 103234.5166 & 103951.5173

Attachments: Concise REMS edits 5.31.11 to Amgen.doc; FDA Responses to Amgens responses 5.31.11.doc

Annie and Elizabeth,

Please find attached a track changes document for the Concise REMS and a very brief response to your responses to the most recent FDA REMS comments that may help facilitate discussions at the teleconference.

Thanks

Mona

Response to comment 1

We agree with your proposed changes. We would recommend the following conceptual change to your proposed table.

Healthcare Providers	**Hospital Designees**
Complete Training	Complete Training
Enroll in the ESA APPRISE Oncology Program	Enroll in the ESA APPRISE Oncology Program
Inform · *Provide the Medication Guide to patient* · *Conduct the risk:benefit discussion with the patient and document this has occurred by completing and signing the Patient Acknowledgment Form*	Implement · *Hospital Designee establishes and oversees measures designed to ensure ESA prescribers adhere to the ESA APPRISE Oncology Program requirements in the hospital setting*

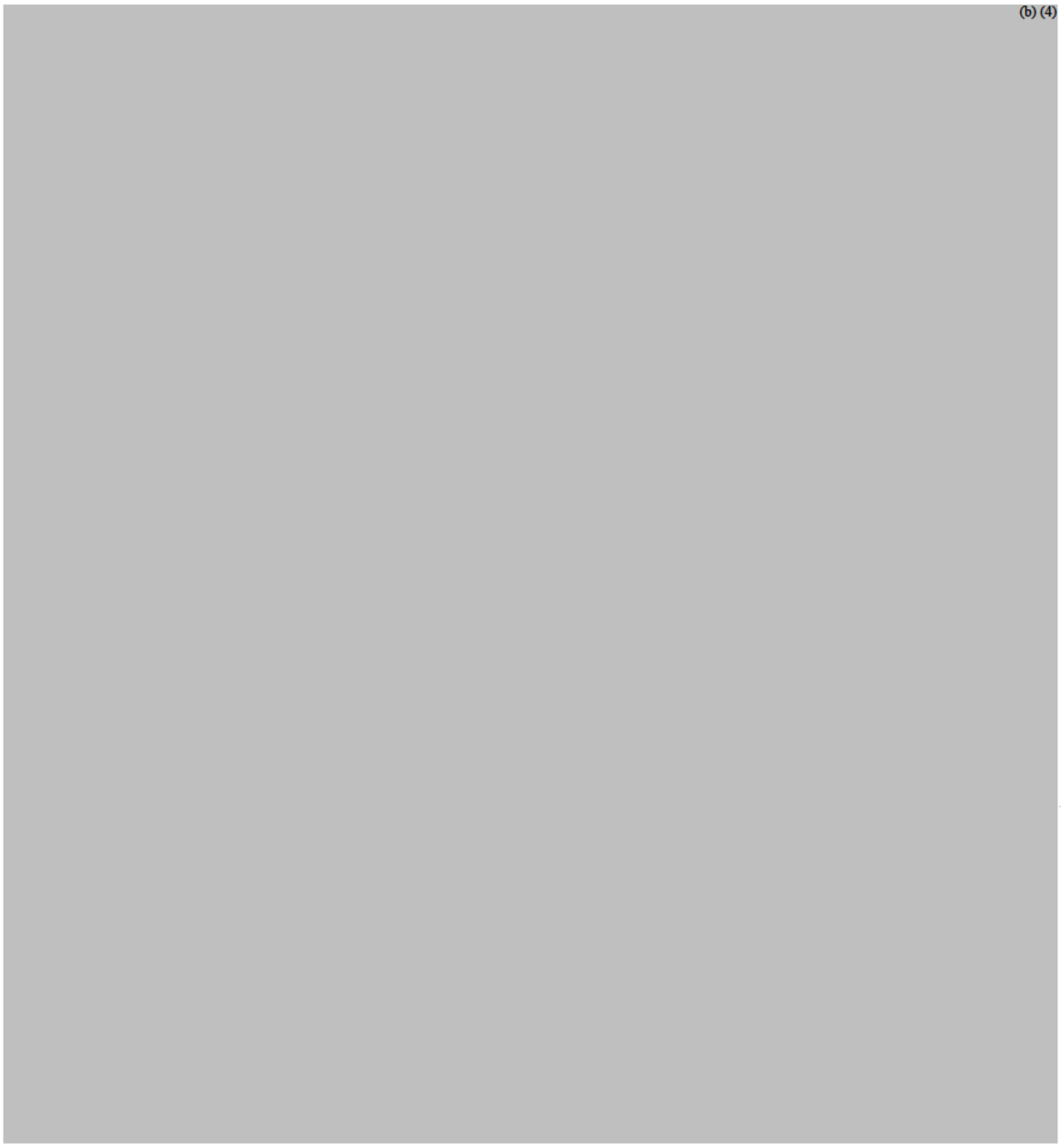
Response to comment 2
Agree

Response to comment 3
Agree

Response to Comment 4
Agree

Response to Comment 5
Agree "a" and "b"

We have the following suggestion for 5 "c" please modify the following screen shot in accordance with the textual suggestion below.



Response to Comment 6
Agree

Response to Comment 7
FDA is withdrawing comment 7a

Response to additional discussion points
Item 1 Agree
Item 2 Agree
Item 3 Agree

Other changes made to the REMS Materials to align with the USAPI
Agree that the enrolment grace period is no longer relevant.

16 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 31, 2011

From: Mona Patel, Pharm.D., Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: STN BL 103234/5166 (5266) and 103951/5173 (5258): Internal meeting to discuss Amgen's Proposed REMS modifications as recent as May 20, 2011 submission and to reach final agreement on REMs materials.

FDA Attendees:
Mona Patel-DBOP
Grace Carmouze-DBOP
Kaushik Shastri-DBOP
Jeff Summers-DBOP
Patricia Keegan-DBOP
Karen Jones-DBOP
Amarilys Vega-OSE
Kristen Miller-ORP
Janice Weiner-ORP
Suzanne Barone-OC
Carole Broadnax-DDMAC

The purpose of this internal team meeting was to discuss Amgen's proposed REMS modifications as recent as May 20, 2011 submission and to reach final agreement on REMs materials.

Discussion: The team reviewed the various documents submitted by Amgen, discussed proposed changes, and agreed to work to send Amgen our proposed draft revisions ASAP.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 26, 2011

From: Mona Patel, Pharm.D., Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: STN BL 103234/5166 and 103951/ 5173: Internal meeting with/DHP to discuss PLR supplements under Epogen and Aranesp.

FDA Attendees:
Mona Patel-DBOP
Grace Carmouze-DBOP
Jeff Summers-DBOP
Ann Farrell-DHP
Saleh Ayache-DHP
Ebla Ali Ibrahim-DHP

The purpose of this internal team meeting was to discuss with DHP outstanding issues with PLR supplements under Epogen and Aranesp and to determine path forward.

Discussion: The team reviewed the outstanding issues with the PLR supplements under Epogen and Aranesp and discussed path forward.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: May 26, 2011

From: Mona Patel, Pharm.D., Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: STN BL 103234/5166 (5266) and 103951/5173 (5258): Internal meeting to discuss ESA Proposed REMS Modifications sent to us as recent as May 20, 2011 under STN 103234.5166 and STN 103951.5173 and cross-referenced to October 14, 2010 submission under STN 103234.5266 & 103951.5258 and to discuss PLR labeling

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FDA Attendees:
Mona Patel-DBOP
Grace Carmouze-DBOP
Kaushik Shastri-DBOP
Jeff Summers-DBOP
Patricia Keegan-DBOP
Karen Jones-DBOP

The purpose of this internal team meeting was to discuss ESA Proposed REMS Modifications sent to us as recent as May 20, 2011 under STN 103234.5166 and STN 103951.5173 and cross-referenced to October 14, 2010 submission under STN 103234.5266 & 103951.5258 and to discuss PLR labeling.

Discussion: The team reviewed the various documents submitted by Amgen, discussed proposed changes, and agreed on next course of action.

Patel, Mona

From: Patel, Mona
Sent: Thursday, May 19, 2011 11:38 AM
To: 'Dang, Annie'; Williams, Elizabeth
Subject: Header for REMS concise doc (Epogen Aranesp)

Attachments: REMS Attachments A and B for Industry.doc

Elizabeth and Annie,

The header for the REMS concise doc needs to be changed. The header is now to appear on the top left-hand corner of the first page of the REMS document and will list the initial REMS approval date (mm/yyyy) on the first line, and the most recent REMS modification date (mm/yyyy) on the second line.

I am attaching a blank template for reference

Mona

REMS Attachments A and B for I...

Grace N. Carmouze
Safety Regulatory Project Manager
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food & Drug Administration

Telephone: 301-796-4223

Initial REMS Approval: XX/XXXX
Most Recent Modification: XX/XXXX

APPENDIX A: REMS TEMPLATE

If you are not proposing to include one of the listed elements, include a statement that the element is not necessary.

Application number TRADE NAME (DRUG NAME)

Class of Product as per label

Applicant name

Address

Contact Information

RISK EVALUATION AND MITIGATION STRATEGY (REMS)

I. GOAL(S):

List the goals and objectives of the REMS.

II. REMS ELEMENTS:

A. Medication Guide or PPI

If a Medication Guide is included in the proposed REMS, include the following:

A Medication Guide will be dispensed with each [drug name] prescription. [Describe in detail how you will comply with 21 CFR 208.24.]

B. Communication Plan

If a Communication Plan is included in the proposed REMS, include the following:

[Applicant] will implement a communication plan to healthcare providers to support implementation of this REMS.

List elements of communication plan. Include a description of the intended audience, including the types and specialties of healthcare providers to which the materials will be directed. Include a schedule for when and how materials will be distributed. Append the printed material and web shots to the REMS Document.

C. Elements To Assure Safe Use

If one or more Elements to Ensure Safe Use are included in the proposed REMS, include the following:

List elements to assure safe use of Section 505-1(f)(3)(A-F) included in this REMS. Elements to assure safe use may, to mitigate a specific serious risk listed in the labeling, require that:

A. Healthcare providers who prescribe [drug name] have particular training or experience, or are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

B. Pharmacies, practitioners, or healthcare settings that dispense [drug name] are specially certified. Append any enrollment forms and relevant attestations/certifications to the REMS;

C. [Drug name] may be dispensed to patients only in certain healthcare settings (e.g., hospitals);

D. [Drug name] may be dispensed to patients with documentation of safe-use conditions;

E. Each patient using [drug name] is subject to certain monitoring. Append specified procedures to the REMS; or

F. Each patient using [drug name] be enrolled in a registry. Append any enrollment forms and other related materials to the REMS Document.

D. Implementation System

If an Implementation System is included in the proposed REMS, include the following:

Describe the implementation system to monitor and evaluate implementation for, and work to improve implementation of, Elements to Assure Safe Use (B), (C), and (D), listed above.

E. Timetable for Submission of Assessments

For products approved under an NDA or BLA, specify the timetable for submission of assessments of the REMS. The timetable for submission of assessments shall be no less frequent than by 18 months, 3 years, and in the 7th year after the REMS is initially approved. You should specify the reporting interval (dates) that each assessment will cover and the planned date of submission to the FDA of the assessment. To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. For example, the reporting interval covered by an assessment that is to be submitted by July 31st should conclude no earlier than June 1st.

Include the following paragraph in your REMS:

COMPANY will submit REMS Assessments to the FDA <<Insert schedule of assessments: at a minimum, by 18 months, by 3 years and in the 7th year from the date of approval of the REMS.>> To facilitate inclusion of as much information as possible while allowing reasonable time to prepare the submission, the reporting interval covered by each assessment should conclude no earlier than 60 days before the submission date for that assessment. COMPANY will submit each assessment so that it will be received by the FDA on or before the due date.

APPENDIX B: SUPPORTING DOCUMENT

This REMS Supporting Document should include the following listed sections 1 through 6. If you are not proposing to include one of the listed elements, the REMS Supporting Document should simply state that the element is not necessary. Include in section 4 the reason you believe each of the potential elements you are proposing to include in the REMS is necessary to ensure that the benefits of the drug outweigh the risks.

1. Table of Contents
2. Background
3. Goals
4. Supporting Information on Proposed REMS Elements
    a. Additional Potential Elements
        i. Medication Guide
        ii. Patient Package Insert
        iii. Communication Plan
    b. Elements to Assure Safe Use, including a statement of how the elements to assure safe use will mitigate the observed safety risk
    c. Implementation System
    d. Timetable for Submission of Assessments of the REMS (for products approved under and NDA or BLA)
5. REMS Assessment Plan (for products approved under a NDA or BLA)
6. Other Relevant Information

Patel, Mona

From: Patel, Mona
Sent: Wednesday, May 18, 2011 10:44 AM
To: 'Dang, Annie'
Cc: Williams, Elizabeth
Subject: FDA Response: Marketing Partner Name Change-ESAs (Centocor)

Annie,

FDA is requesting Amgen to submit the marketing partner name change [Centocor Ortho Biotech Products L.P. (COBP) to Janssen Products, LP (JP)] as an amendment to the PLR supplements under STNs 103234.5166 & 103951.5173 with a cross-reference letter to the TREAT supplements. Please do not immediately re-submit the REMS materials as we will be sending additional proposed changes to the concise REMS document to provide brevity and clarity to the language involving the Medication Guide requirements.

Thank you,

Mona

From: Dang, Annie [mailto:adang@amgen.com]
Sent: Wednesday, May 18, 2011 2:24 AM
To: Patel, Mona
Cc: Williams, Elizabeth
Subject: RE: Follow-up to Voicemail

Dear Mona,

Amgen and Centocor Ortho Biotech seek FDA guidance on incorporating a marketing partner name change [Centocor Ortho Biotech Products L.P. (COBP) to Janssen Products, LP (JP)] into PROCRIT labeling documents and REMS materials. We have considered various proposals on how to submit the associated labeling and REMS changes, and an email was sent to FDA on May 10, 2011 providing 3 proposals. These proposals are outlined below, and we believe Proposal 1 may be easiest from both the FDA and Companies' perspective.

1. Submit the CBE for the USPI, PIU, cartons and vials along with the MG. The name change to the MG would be implemented as part of the CBE. In parallel, submit a PAS for all the REMS tools and screen shots for FDA review. An expedited review of the REMS PAS would not be needed. The labeling and packaging components would be implemented upon submission of the CBE, and the revised REMS materials would be implemented upon FDA approval of the PAS.

2. Submit a CBE for the labeling documents and submit a formal PAS supplement with all the REMS tools and screen shots that mark the replacement of the COBP name and logo with the new Janssen name and logo. We could request a priority review in an effort to implement this change effective 22 June 2011. This would time the change with the CBE change required for the USPI, PIU, cartons and vials.
3. Submit the CBE for the USPI, PIU, cartons and vials without the MG. We would leave the MG unchanged until after approval of the REMS materials.

In addition to the above proposals, we seek guidance on whether FDA suggests instead that labeling documents and REMS materials incorporating the marketing partner name change be submitted via an amendment to the PLR.

Labeling documents and REMS materials have been prepared with just the marketing partner name change (not PLR changes incorporated) and can be submitted via a CBE & PAS route within a few business days. If, however, FDA prefers to combine the PLR changes and the marketing partner name change into all documents as an amendment to PLR, this mechanism will require approximately 1-2 weeks to develop (via vendors) and submit the labeling and REMS materials. Implementation for the marketing name change can occur no earlier than June 22nd.

We thank the FDA for your consideration, and we look forward to receiving FDA's guidance on how to proceed with submission of labeling and REMS materials for the marketing partner name change.

If you have any questions, please do not hesitate to contact me at (805) 447-0115.

Thanks,
Annie

Annie Dang
Manager, Regulatory Affairs
Amgen Inc.
Direct Line: 805.447.0115
Mobile Phone: 805.490.1775
adang@amgen.com

From: Patel, Mona [mailto:Mona.Patel@fda.hhs.gov]
Sent: Tuesday, May 17, 2011 12:19 PM
To: Dang, Annie
Cc: Williams, Elizabeth
Subject: Follow-up to Voicemail

Annie,

I received your voicemessage. We have an internal meeting for the ESAs tomorrow and I will bring up if submitting to PLR is the best route. Feel free to email me any questions you have about the status of things from the DBOP perspective and I will try my best to get your questions answered.

Mona

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)

FILE MEMORANDUM

MEMO DATE:	May 12, 2011 PM: E Ali Ibrahim
Regarding:	Aranesp STN BL 103951/5173 and 103234/5166
Submission Date:	02/02/2011
Other reviewers:	DBOP clinical reviewers and OSE
FROM:	Saleh Ayache, MD, clinical reviewer, DHP 5/16/2011
SUBJECT:	PLR label conversion with edits to CKD section
Via:	Robert Kane, MD, Medical Officer; Division of Hematology Products, OODP; CDER R Kane 5/16/11

ISSUE:
Amgen submits a revised version of the Aranesp and Epoetin alfa labeling to effect a conversion in compliance with the PLR rule. In addition, Amgen proposes changes to the text pertaining to patients with chronic kidney disease (CKD) as described further below.

ACTIONS RECOMMENDED:
The proposed changes are acceptable to DHP and should be agreed upon with the sponsor.

SUMMARY OF REVIEWER FINDINGS:

Background:

The following text is restated from a meeting with Amgen in which Amgen identified revisions in two areas, "oncology" and (b) (4)

December 9, 2010 Teleconference Discussion Points

Epoetin alfa (Epogen®/PROCRIT®) and darbepoetin alfa (Aranesp®)
STN BL 103234/5166 and STN BL 103951/5173

Oncology

1. (b) (4)
2.

3. (b) (4)

4.

(b) (4)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

To:	File
From:	Mona Patel, Pharm.D., Regulatory Health Project Manager Division of Biologic Oncology Products
Through:	Patricia Keegan, M.D., Director of Division of Biologic Oncology Products
Date:	May6, 2011
Regarding:	Teleconference to discuss FDA recommendations for proposed REMS modifications related to BL STN 103234/5266 & 5166 & BL STN 103951/5258 & 5173

FDA Attendees:
Mona Patel, Regulatory Health Project Manager, DBOP
Jeff Summers, Deputy Director of Safety, DBOP
Patricia Keegan, Division Director, DBOP
Kaushik Shastri, Clinical Reviewer, DBOP
Karen Jones, Chief of Project Management Staff, DBOP
Claudia Karwoski, Director, DRISK
Sue Kang, OSE Regulatory Project Manager, OSE/DRISK
Suzanne Berkman Robottom, Team Leader, DRISK

Amgen:
Ed Burd, PhD – Director, Global Regulatory Affairs
Janet Franklin, MD, MPH – Clinical Research Medical Director, Global Development
Steven Galson, MD, MPH – VP, Global Regulatory Affairs
Bob Harris, PhD – Director, Global Regulatory Affairs
Danica Katz, MA – Director, Global Safety
Darshna Patel – Director, Global Regulatory Affairs and Safety Operations
Jerome Rossert, MD, PhD – Clinical Research Medical Director, Global Development
Elizabeth Williams, MS, RAC – Manager, Global Regulatory Affairs
Sunita Zalani, PhD – Executive Director, Global Regulatory Affairs

J&J:
Peter Bowers, MD – Sr. Director, Clinical Development
Mary Guilfoyle – Sr. Director, Compound Development Team Leader
Paul Percheson, MD – Medical Safety Assessment Physician, Global Medical Safety
Barbara Kolb – Sr. Director, Regulatory Affairs
Brian Maloney, RPh, MS – Director, Regulatory Affairs
Brenda Sarokhan, MPH – Sr. Director, Medical Education Science Communication

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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Teleconference Minutes

On October 14, 2010, Amgen submitted a First Assessment Report to the REMS approved on February 16, 2010 and a Prior Approval Supplement (PAS) describing proposed modifications to the ESA APPRISE Oncology Program Hospital Designee Enrollment Form and ESA APPRISE Oncology Program website.

Proposed REMS modifications were also included in the Complete Response resubmissions to the April 27, 2010 action under STNs 103234.5166 & 103951.5173 on March 22, 2011.

FDA requested a teleconference with Amgen to discuss FDA's recommendations for changes to the proposed REMS modifications under all supplements referenced above. Draft FDA recommendations were communicated to Amgen via electronic means on May 6, 2011 prior to the teleconference. The draft recommendations are attached.

Amgen provided assurances these changes would be considered for incorporation in the revised REMS materials.

FDA explained to Amgen that since the Complete Responses to the April 27, 2010, CR letter for STN 103234.5166 & 103951.5173 was still under review, FDA may recommend additional changes to REMS materials. Therefore, FDA requested that Amgen delay submission of the revised REMS documents until final labeling changes have been agreed under the March 22, 2011 resubmission to STNs 103234.5166 and 103951.5173. The revised REMS materials to be submitted from Amgen may be submitted to STNs 103234.5166 and 103951.5173 and a cross-reference to STNs 103234.5166 and 103951.5173 submitted to STN 103234.5266 and 103951.5258. Amgen agreed to follow FDA's recommended approach to submission of revised REMS materials with the caveat that it could take up to a week to submit the completed changes following agreement on final labeling due to the required website revisions. FDA acknowledged. FDA reminded Amgen to carefully annotate and reference their proposed changes.

Also discussed was Amgen's May 5, 2011 submission under (b) (4) informing FDA of the deregistration of the Human Serum Albumin formulation for Aranesp. Amgen proposed to remove the Aranesp albumin formulation from the PLR supplement due to discontinuation of the marketing of this formulation in the United States. FDA agreed with Amgen's proposal and stated that changes to the package insert to remove references to the albumin formulation should be included with other labeling changes under STN 103234.5166 & 103951.5173. Amgen agreed to do so.

Call concluded.

Patel, Mona

From: Patel, Mona
nt: Friday, May 06, 2011 3:56 PM
o: 'Williams, Elizabeth'; 'Dang, Annie'
Subject: Redlined Version: Follow-up to Telecon Today

Attachments: Section 2_HCP trainign module SBR AV (2).doc; ESAs_Webpage changes.doc

Elizbaeth and Annie,

I am attaching redlined versions of 2 documents to aid you when making the changes to the REMs docs.

Please acknowledge receipt.

Mona


Section 2_HCP trainign module ...


ESAs_Webpage changes.doc (71 K...

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)

5 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Patel, Mona

From: Patel, Mona
Sent: Friday, May 06, 2011 10:58 AM
To: 'Williams, Elizabeth'
Subject: RE: STN 103951/5173: Deregistration of the Aranesp albumin formulation and proposal to incorporate changes into the PLR supplement

Elizabeth,

We prefer you remove language of SureClick and albumin formulation now in the PLR supplements currently under review. Please email me a copy of the cover letter for the formal submission which informed us that this albumin formulation was no longer to be marketed and a statement that there is no remaining product on the U.S. market (or if there is, the date when any Aranesp in this formulation is scheduled to expire).

Mona

From: Williams, Elizabeth [mailto:ewilliam@amgen.com]
Sent: Tuesday, May 03, 2011 3:50 PM
To: Patel, Mona
Cc: Jones, Karen; Williams, Elizabeth
Subject: STN 103951/5173: Deregistration of the Aranesp albumin formulation and proposal to incorporate changes into the PLR supplement

Hi Mona,

I am copying Karen as well since you said you were out of the office until Thursday. In follow-up to our phone call on April 27th, where FDA requested Amgen remove the SureClick language from the Aranesp label and REMS materials within the PLR supplement, it has been brought to my attention that Amgen will also deregister the Aranesp albumin formulation. Since this change will affect the Aranesp USPI and MG, Amgen would like to propose that we remove this language within the PLR supplement as we feel that it is an analogous change to the removal of the SureClick language. To facilitate incorporation of this change into the current PLR timeline, the deregistration notification will be submitted to DHP this Thursday.

The only change required within the MG would be the removal of the reference to the albumin solution under Inactive Ingredients on the last page. The removal of the albumin language would not affect any of the other REMS materials. This change does not apply to Epoetin alfa USPI or MG.

The changes required within the Aranesp USPI would only affect the following sections where albumin is referenced:
Section 3 DOSAGE FORMS AND STRENGTHS
Section 5.9 Albumin (Human) under WARNINGS AND PRECAUTIONS (entire section would be removed as it is a theoretical warning pertaining specifically to albumin)
Section 11 DESCRIPTION
Section 16 HOW SUPPLIED/STORAGE AND HANDLING

Please provide guidance on whether FDA would prefer the removal of the albumin language within the PLR supplement or would prefer us to wait until PLR is approved before submitting this change for review.

I appreciate your time and consideration of this proposal. Thank you.

Elizabeth

~~~~~~~~~~~~~~~~~~~~~~~~~~

Elizabeth Williams, MS, RAC
Manager, Global Regulatory Affairs
One Amgen Center Drive
Mailstop: 17-2-B
Thousand Oaks, CA 91320

Office: (805) 447-8363
Cell: (b)(6)
FDA Fax: (805) 480-1330
General Fax: (805) 499-6296
Email: ewilliam@amgen.com
~~~~~~~~~~~~~~~~~~~~~~~~~~

Patel, Mona

From: Patel, Mona
Sent: Friday, May 06, 2011 10:18 AM
To: 'Williams, Elizabeth'
Cc: 'Dang, Annie'
Subject: Draft Comments Attached: FDA Requests TCON: Friday, May 6, 2011
Attachments: STN 1003234.5266 (5166) & 103951.5258 (5173) REMS MODS.doc

Elizabeth,

I misspoke. It looks like we do have comments to share with you prior to our telecon.

Mona

Please acknowledge receipt.

From: Patel, Mona
Sent: Friday, May 06, 2011 9:33 AM
To: 'Williams, Elizabeth'
Cc: Dang, Annie
Subject: RE: FDA Requests TCON: Friday, May 6, 2011

We will not have documents to share at this time. We will send them out after the meeting.

From: Williams, Elizabeth [mailto:ewilliam@amgen.com]
Sent: Friday, May 06, 2011 9:08 AM
To: Patel, Mona
Cc: Williams, Elizabeth; Dang, Annie
Subject: RE: FDA Requests TCON: Friday, May 6, 2011

Good morning Mona,

Welcome back! I hope you had a good vacation.

You previously mentioned that you would try to send a list of items that would be discussed during the tcon today. I'm just following up to see if that will be possible? Thanks very much!

Elizabeth

From: Williams, Elizabeth
Sent: Thursday, April 28, 2011 10:51 PM
To: Patel, Mona; Dang, Annie

Subject: RE: FDA Requests TCON: Friday, May 6, 2011

Hi Mona,

I am confirming that May 6th at 12pm EST will work for us. Below is the call-in information.

Teleconference Information:

Domestic (US) Dial-in: (b) (4)
International Dial-in:
Conference Code:

Your email below states that this tcon will be to discuss the proposed REMS modifications submitted in the October 14, 2010 and March 22, 2011 submissions. Would you please also confirm that we will discuss how best to include the REMS modifications related to the TREAT proposals received April 8th (reference is made to my email on 4/22)?

Thank you.

Elizabeth

From: Patel, Mona [mailto:Mona.Patel@fda.hhs.gov]
Sent: Thursday, April 28, 2011 12:03 PM
To: Dang, Annie; Williams, Elizabeth
Subject: RE: FDA Requests TCON: Friday, May 6, 2011

Thank you for clarifying.

From: Dang, Annie [mailto:adang@amgen.com]
Sent: Thursday, April 28, 2011 2:34 PM
To: Patel, Mona; Williams, Elizabeth
Subject: RE: FDA Requests TCON: Friday, May 6, 2011

Hi Mona,

Thanks for taking the call to clarify representation at the teleconference.

Per our discussion, a separate teleconference is not requested. Both Aranesp and Epogen/PROCRIT teams will be represented at the May 6, 2011 call at 12 PM EST. I will likely not be on the May 6 call, however there will be other regulatory representation for Epogen/PROCRIT at this meeting, and I continue to be your primary contact for Epogen/PROCRIT.

Please let me know if you have any further questions.

Thanks,
Annie

From: Patel, Mona [mailto:Mona.Patel@fda.hhs.gov]

Sent: Thursday, April 28, 2011 11:10 AM
To: Williams, Elizabeth; Dang, Annie
Subject: RE: FDA Requests TCON: Friday, May 6, 2011

Can you please clarify? We have held telecons before with both Epogen and Aranesp before as these submissions (STN 103951.5258 and STN 103234.5266 are in parallel) and the items to discuss pertain to both Epogen and Aranesp. Are you requesting separate teleconferences?

Mona

From: Williams, Elizabeth [mailto:ewilliam@amgen.com]
Sent: Thursday, April 28, 2011 1:39 PM
To: Patel, Mona; Dang, Annie
Subject: RE: FDA Requests TCON: Friday, May 6, 2011

Hi Mona,

I acknowledge receipt of your email. I am currently checking team members availability and will confirm acceptance and provide the call-in information by tomorrow morning at the latest.

Please note that Annie Dang will not be on the call however epoetin alfa will be represented by other team members.

Will you be able to provide a list of FDA participants before the meeting?

Elizabeth

From: Patel, Mona [mailto:Mona.Patel@fda.hhs.gov]
Sent: Thursday, April 28, 2011 9:48 AM
To: Williams, Elizabeth; Dang, Annie
Subject: FDA Requests TCON: Friday, May 6, 2011

Hello,

As mentioned to Elizabeth yesterday during our conversation yesterday, we are requesting a 45 minute teleconference for May 6, 2011 between 12-12:45pm EST with both of your teams to discuss the proposed REMS modifications submitted in the October 14, 2010 and March 22, 2010 submission.

Can you confirm acceptance and provide call-in information.

I will try to send you items we will be planning to discuss/reach agreement before the telecon.

Please note I will be out of the office with little to no email access from May 2-5, 2011. With hopes of trying to finalize logistics by tomorrow, I'd like to receive confirmation from you on time by sometime today or tomorrow morning.

Please acknowledge receipt of email.

Mona
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)

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 27, 2011

From: Mona Patel, Pharm.D., Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: STN BL 103234/5166 and 103951/ 5173: Internal meeting to discuss March 22, 2011 resubmission to PLR supplements under Epogen and Aranesp.

FDA Attendees:
Mona Patel-DBOP
Grace Carmouze-DBOP
Kaushik Shastri-DBOP
Jeff Summers-DBOP
Patricia Keegan-DBOP
Karen Jones-DBOP

The purpose of this internal team meeting was to discuss the March 22, 2011 resubmission to the PLR supplements under Epogen and Aranesp.

Discussion: The team reviewed the pending issues with the PLR labeling under the March 22, 2011 resubmission for Epogen and Aranesp and discussed a path forward.

Patel, Mona

From: Patel, Mona
Sent: Tuesday, April 26, 2011 10:00 AM
To: 'Williams, Elizabeth'; Dang, Annie
Subject: FDA Proposed Changes ESA Labeling (STNs 103234.5166 & 103951.5173) 4.26.11

Attachments: FDA Proposed Changes Epogen MG 4.26.11.doc; FDA Proposed Changes Epogen PIU 4.26.11.doc; FDA Proposed Changes Procrit MG 4.26.11.doc; FDA Proposed Changes Procrit PIU 4.26.11.doc; FDA Proposed Changes Aranesp MG 4.26.11.doc; FDA Proposed Changes Aranesp PIU SDV 4.26.11.doc; FDA Proposed Changes Aranesp PIU SD Prefilled 4.26.11.doc; FDA Proposed Changes Aranesp PIU Autoinjector 4.26.11.doc; FDA Proposed Change Aranesp PI 4.26.11 (conjoined).doc; FDA Proposed Changes Epogen PI 4-26-11 (conjoined).doc

Hello,

I have attached FDA proposed changes to ESA labeling. These changes reflect DBOP changes. Please clean up and insert in tracked changes any changes you are proposing that you would like DBOP to review. Also, from the 3.22.2011 submission, I noted a few minor changes you made in some of the PIU's . Please-re-include them here in tracked changes once you have cleaned up document and note that these changes were communicated to FDA for consideration on 3.22.2011.

I will be calling you shortly to touch base.

DBOP is requesting a response back within 24 hours.

Please acknowledge receipt.

ɔna

FDA Proposed hanges Epogen MG..
FDA Proposed Changes Epogen PI..
FDA Proposed Changes Procrit M...
FDA Proposed Changes Procrit P...
FDA Proposed hanges Aranesp M..
FDA Proposed Changes Aranesp P..
FDA Proposed Changes Aranesp P..
FDA Proposed Changes Aranesp P..
FDA Proposed Change Aranesp PI...
FDA Proposed hanges Epogen PI..

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)

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56 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: April 26, 2011

From: Mona Patel, Pharm.D., Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: STN BL 103234/5166 (5266) and 103951/5173 (5258): Internal meeting to discuss Amgen's Proposed REMS modifications originally submitted under STN 103234.5266 & STN 103951.5258 on October 14, 2010 and included in resubmissions to April 27, 2010 Complete Response action under STN 103234.5166 & 103951.5173 on March 22, 2011.

FDA Attendees:
Mona Patel-DBOP
Grace Carmouze-DBOP
Kaushik Shastri-DBOP
Jeff Summers-DBOP
Amarilys Vega-OSE
Suzanne Robottom Berkman-OSE
Sue Kang-OSE

The purpose of this internal team meeting was to discuss Amgen's proposed REMS modifications originally submitted under STN 103234.5266 & STN 103951.5258 on October 14, 2010 and included in the resubmissions to April 27, 2010 Complete Response action under STN 103234.5166 & 103951.5173 on March 22, 2011.

Discussion: The team reviewed the various documents submitted by Amgen, discussed proposed changes, and agreed to set up a teleconference with Amgen for May 6, 2011 to discuss the proposed changes.

Patel, Mona

From: Williams, Elizabeth [ewilliam@amgen.com]
Sent: Friday, April 22, 2011 6:12 PM
To: Patel, Mona
Cc: Dang, Annie; Shamon-Taylor, Lisa; Williams, Elizabeth
Subject: Pending ESA labeling changes: Proposal for further REMS modifications under PLR and TREAT-related PI and MG changes

Hi Mona,

Recent discussions with FDA regarding incorporation of TREAT into the ESA PLR labeling have concluded, and formal submissions to DHP are forthcoming. During these discussions, changes to the PIs and Medication Guides have occurred. Since these changes impact the REMS, Amgen has the following proposal for managing the REMS modifications:

1. With regard to the Medication Guide changes proposed since the March 22, 2011 PLR complete response submission: these changes have been formally agreed upon by Amgen and DHP. Per a communication from Ebla Ali Ibrahim to Amgen, DHP is requesting that the Medication Guide be submitted separately to DBOP as a REMS Modification, with reference to the TREAT PAS.

2. In the proposal received from DHP on April 8, 2011, Amgen noted that the word "myelosuppressive" was added to the oncology indication statement within the full prescribing information (making it consistent with the Highlights section). This change affects the concise REMS and certain REMS tools, as the indication statement within the PLR FPI was used as the basis for the REMS language in the PLR complete response submission. Therefore, Amgen are requesting to amend the PLR PAS (with cross reference to the REMS PAS) to incorporate the word "myelosuppressive" into the USPI and the REMS materials. Under the PAS amendment, the following change would be made to the indication statement:

   > "Aranesp is indicated for the treatment of anemia in patients with non-myeloid malignancies where anemia is due to the effect of concomitant myelosuppressive chemotherapy, and upon initiation, there is a minimum of two additional months of planned chemotherapy."

   In addition, the following REMS materials would be revised to incorporate "myelosuppressive" where it is currently not included within the indication statement:

   - REMS Concise document
   - HCP enrollment form
   - HCP training module
   - Hospital designee training module
   - Website screenshots: to change ISI language on each page and wherever else the indication statement is referenced

Both of these submissions could occur by April 29, 2011.

Thank you for your consideration of this proposal, and we welcome discussion with FDA on any alternate suggestions you may have for managing the REMS modifications.

We look forward to your response. Please note that I will be out of the office on Monday April 25, so please copy Lisa when responding.

Elizabeth

~~~~~~~~~~~~~~~~~~~~~~~~~

Elizabeth Williams, MS, RAC
Manager, Global Regulatory Affairs
One Amgen Center Drive
Mailstop: 17-2-B
Thousand Oaks, CA 91320

Office: (805) 447-8363
Cell: (b) (6)
FDA Fax: (805) 480-1330
General Fax: (805) 499-6296
Email: ewilliam@amgen.com
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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 103951/5173

ACKNOWLEDGE COMPLETE RESPONSE

Amgen, Incorporated
Attention: Elizabeth Williams
Manager, Regulatory Affairs
One Amgen Center Drive
Mail Stop: 17-2-B
Thousand Oaks, CA 91320

April 6, 2011

Dear Ms. Williams:

We have received your March 22, 2011, resubmission to your biologics license application for Aranesp (darbepoetin alfa) on March 23, 2011.

The resubmission contains a revised package insert, medication guide, patient instructions for use and REMS that you submitted in response to our April 27, 2010 complete response letter.

We consider this a complete, class 1 response to our action letter. Therefore, the user fee goal date is May 23, 2011.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Mona Patel, at (301) 796-4236.

Sincerely,

/Patricia Keegan/
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

sBLA 103951/5173 and 103234/5166
Complete Response Resubmission
darbepoetin alfa (Aranesp) and epoetin alfa (Epogen/Procrit)
Planning Meeting Summary
April 5, 2011

Attendees:
Mona Patel, Regulatory Project Manager, DBOP
Ebla Ali Ibrahim, Regulatory Project Manager, DHP
Kaushik Shastri, Clinical Reviewer, DBOP
Saleh Ayache, Clinical Reviewer, DHP
Claudia Karwoski, Director, OSE
Suzanne Berkman Robottom, Team Leader, OSE
Sharon Mills, Safety Reviewer, OSE
Barbara Fuller, Lead Safety Reviewer, OSE
Kristen Miller, FDAAA Project Manager, OC
Patricia Zettler, Assistant Chief Counsel for Drugs, OC
Sean Bradley, Team Leader-Safety Regulatory Project Manager, OSE

Items covered:

1. Discussion of whether supplements are Class 1 or 2 resubmissions: *Class 1*

2. Discuss approach for expected action for PLR supplements and proposed REMS modifications: *Was discussed and internal goals were set.*

3. **Milestones for Application Received on March 23, 2011**:
   a. First Committee Meeting: Scheduled for April 5, 2011
   d. Continued below under Dates Milestone Letters Must Issue

4. **Dates Milestone Letter's Must Issue**:
   a. Action Letter: May 23, 2011 (Class 1)
   b. Action Letter: September 22, 2011 (Class 2)

4. **Upcoming Internal Team Meetings**:
   a. Internal meetings: *Ad hoc. Review team and consultants decided to hold internal meeting(s) to discuss proposed REMS modification, limited to revisions to the MG for consistency with revisions to the PI under these efficacy supplements*
   b. Mid-Cycle Meeting: *Not required (class 1 resubmission)*
   c. Labeling Meetings: *As needed*
   d. Final Wrap Up Meeting: *Not required (class 1 resubmission)*

5. Confirmation that Division Director is signatory authority: *Yes*

6. Would the teams like to have monthly team meetings to discuss the progress of the review and identify major issues? *No, ad hoc*

7. Is an updated consult form required for the OSE reviewer? Do we have specific questions for OSE?
   Discussion: *Updated consult form not required*

8. Is an updated consult form required for the DDMAC reviewer? Do we have specific questions for DDMAC?
Discussion: *No*

9. Discuss any issues that have been identified during the review to date or need to request additional information:

   a. Clinical

   Discussion: *Cross-division reviews, considering pending CBE supplement in DHP were discussed*

10. Any other issues related to this application that requires discussion?
Discussion: *Internal action dates were discussed*

Patel, Mona

From: Patel, Mona
t: Wednesday, March 16, 2011 9:16 AM
To: 'Dang, Annie'; Elizabeth Williams (ewilliam@amgen.com)
Cc: 'Shamon-Taylor, Lisa'
Subject: FDA Proposed Changes: ESA Labeling (STN 103234.5166 & 103951.5173)

Attachments: FDA Proposed Changes Aranesp PIU Single-dose Vial 3-8-11.doc; FDA Proposed Changes Epogen MG 3-8-11.doc; FDA Proposed Changes Aranesp MG 3-8-11.doc; FDA Proposed Changes Aranesp PIU Autoinjector 3-8-11.doc; FDA Proposed Changes Epogen PI 3-8-11.doc; FDA Proposed Changes Aranesp PI 3-8-11.doc; FDA Proposed Changes Aranesp PIU Prefilled Syringe 3-8-11.doc; FDA Proposed Changes Epogen PIU 3-8-11.doc

Hello,

I have attached FDA Proposed Change labeling for the PI, MG, and PIU for the ESAs to be submitted formally in your response to the April 27, 2010 Complete Response action taken on Aranesp (STN 103951.5173) and Epogen (STN 103234.5166).

We are requesting receipt of a formal submission no later than Tuesday, March 22, 2011.

Please confirm receipt of this email, attachments, and timeline.

Also, please be sure to remove vertical line marks before submitting.

Mona







FDA Proposed Changes Aranesp P.. | FDA Proposed Changes Epogen MG.. | FDA Proposed Changes Aranesp M.. | FDA Proposed Changes Aranesp P.. | FDA Proposed Changes Epogen PI.. | FDA Proposed Changes Aranesp P.. | FDA Proposed Changes Aranesp P..

FDA Proposed Changes Epogen PI..

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

49 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Patel, Mona

From: Patel, Mona
Sent: Thursday, March 03, 2011 2:54 PM
To: 'Dang, Annie'; Elizabeth Williams (ewilliam@amgen.com)
Cc: 'Shamon-Taylor, Lisa'
Subject: Path Forward for Pending Regulatory Submissions for ESAs

Annie and Elizabeth,

For your resubmission to the CR Letters issued on April 27, 2010, for STN BL 103234/5166 and STN BL 103951/5173 (PLR supplements), FDA requests that Amgen formally submit all labeling components (PI, medication guide, and PIU) sent via email on February 23, 2011, as well as all proposed REMS modifications, the justification for those modifications and the updated REMS materials, including updated PAF modification guidelines. Please also send a letter of cross-reference to STN BL 103234/5266 and STN BL 103951/5258 (REMS modification supplements) indicating that updated REMS materials have been submitted to the PLR supplements.

In your resubmission to the PLR supplements, please summarize the changes being made to the REMS materials and reference all REMS-related communications that have occurred since April 27, 2010. FDA anticipates receiving these submissions within one week's time, COB Thursday, March 10, 2011.

Please acknowledge receipt.

Mona.

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)


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MEMORANDUM OF MEETING MINUTES

MEETING DATE:	February 23, 2011
TIME:	11:15 AM – 11:30 AM
LOCATION:	CDER White Oak, Bldg 22, Conf Room 5440
APPLICATION:	STN BL 103951/5173 & 5248 and STN BL 103234/5166 &5256
DRUG NAME:	Aranesp and Epogen/Procrit
MEETING CHAIR:	Ann Farrell, M.D.
MEETING RECORDER:	Diane Leaman

FDA ATTENDEES:

Ann Farrell, Acting Division Director [Office of Oncology Drug Products/Division of Hematology Products (OODP/DHP)]
Patricia Keegan, Division Director, Office of Oncology Drug Products/Division of Biologic Oncology Products (OODP/DBOP)
Robert Kane, Acting Deputy Division Director for Safety (OODP/DHP)
Saleh Ayache, Medical Officer (OODP/DHP)
Ryan Qin, Clinical Team Leader (OODP/DHP)
Diane Leaman, Safety Regulatory Health Project Manager (OODP/DHP)
Ebla Ali-Ibrahim, M.S., Regulatory Health Project Manager (OODP/DHP)
Kaushikkumar Shastri, Medical Officer (OODP/DBOP)
Jeff Summers, Deputy Division Director for Safety (OODP/DBOP)
Karen Jones, Chief, Project Management Staff (OODP/DBOP)
Grace Carmouze, Safety Regulatory Health Project Manager (OODP/DBOP)
Mona Patel, Regulatory Health Project Manager (OODP/DBOP)

EXTERNAL ATTENDEES:

Amgen, Inc.
Susan Boynton – Executive Director, Global Regulatory Affairs
Janet Franklin, M.D., MPH – Clinical Research Medical Director, Global Development
Danica Katz, M.A. - Director, Safety
Steven Galson, M.D., MPH – VP, Regulatory Affairs
Rekha Garg, M.D., M.S. – Executive Director, Safety
Reshma Kewalramani, M.D., FASN – VP, Global Development
Jerome Rossert, M.D., Ph.D. - Clinical Research Medical Director
Lisa Shamon-Taylor, Ph.D. – Director, Regulatory Affairs
Elizabeth Williams, M.S., RAC- Manager Regulatory Affairs
Sunita Zalani, Ph.D. - Executive Director, Regulatory Affairs

J&J
Mary Guilfoyle – Sr. Director, CDTL

Brian Maloney, RPh, MS – Director, Regulatory Affairs
Brenda Sarokhan, MPH – Sr. Director, Medical Education Science Communication

BACKGROUND:

On August 10, 2010 Amgen submitted a labeling supplement with clinical data from the TREAT study for Aranesp (STN BL 103951/5248 and for Epogen/PROCRIT (STN BL 103234/5256). On February 10, 2011, Amgen received a Complete Response action for both supplements.

As requested by FDA, Amgen initiated informal labeling negotiations intended to reach agreement on final labeling as requested in FDA's April 27, 2010, Complete Response letters for Epogen/Procrit (STN BL 103234/5166) and for Aranesp STN BL 103951/5173). On February 2, 2011 Amgen sent a proposed product labeling and the rationale for the changes to the labeling attached to the CR letters as an informal response via e-mail. On February 16, 2011, DBOP responded with an informal proposal containing proposed revisions to the Feb 2, 2011, proposed product labeling. Amgen responded by email on February 23, 2011.

MEETING OBJECTIVES:

- To discuss the path forward to response to CR letter for the efficacy supplement (103234/5166 and 103951/5173)
- To facilitate completion of the labeling supplements (103234/5256 and 103951/5248) to include data from the TREAT trial, for which a CR letter issued February 11, 2011.

DISCUSSION POINTS:

With regard to the pending efficacy supplements containing proposed REMS modifications, FDA informed Amgen that the February 2, 2011, e-mail from Amgen containing their proposed approach for response to the Complete Response letters of April 27, 2010 were still being evaluated, however it appeared that most of the areas of disagreement had been resolved. FDA advised Amgen to submit their response to FDA's April 27, 2010 CR letters to 103234/5166 and 103951/5173 as soon as possible.

FDA indicated the possibility of approval of the safety labeling supplements (103234/5256 and 103951/5248) at the same time as the approval actions on the efficacy supplements and REMS modification supplements (103234/5266 and 103951/5258). FDA stated that if agreement on the safety labeling changes was not reached at the time approval of the efficacy and REMS modifications supplements, Amgen should not to print large numbers of the approved package inserts until the safety labeling changes to include the TREAT information were also approved. Amgen noted that it will take time to implement revised labeling, and they would prefer to not circulate the new product labels and then be required to revise it a few weeks later.

With regard to safety labeling supplements, FDA requested that Amgen further consider the findings from the TREAT trial with patients with chronic kidney disease (CKD). FDA noted that a safe and effective dose schedule is not known. The TREAT study was confounded by transfusions and heterogeneous patient populations. The Aranesp control arm from the TREAT

trial appears to be the safest dosing schedule. (b) (4) [redacted] FDA asked Amgen to submit concept proposals for future trials to include dialysis and non-dialysis patient populations separately. FDA will review the proposals and provide Amgen with comments.

Amgen asked for clarification on the process.

FDA will review the potential timing of approval actions and respond to Amgen with the recommended pathway for updating the package insert to accommodate all pending labeling changes under the efficacy supplements, REMS modification supplements, and the safety labeling changes to incorporate the TREAT study results.

DECISIONS (AGREEMENTS) REACHED:

The proposed labeling submitted on Feb. 23, 2011 would support resubmissions for the efficacy and REMS modifications supplements and should be submitted as soon as possible.

FDA and Amgen will work together on proposed language to update the Epogen/Procrit and Aranesp labels with data from the TREAT trial that might be acceptable to support a resubmission. FDA and Amgen will identify the established evidence on which to base labeling changes and to decide on required postmarketing trial designs that can address outstanding safety concerns.

UNRESOLVED ISSUES OR ISSUES REQUIRING FURTHER DISCUSSION:

Logistics for submitting updated labeling incorporating the TREAT study data into the Epogen labeling.

ACTION ITEMS:

Follow-up of above issues.

ATTACHMENTS/HANDOUTS:

None

Patel, Mona

Subject: FW: FDA Discussion Material

Attachments: Aranesp PI 1 13 2011 (STN 103951 5173).doc; Aranesp MG 1 13 2011 (STN 103951 5173).doc; Epogen PI 1 13 2011 (STN 103234 5166).doc; Epogen MG 1.13.2011 (STN 103234.5166).doc; Jan 19, 2011 Telecon Discussion Points.docx; Aranesp PI section Dosage and Admin JAN 19-2011.doc

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From: Ali Ibrahim, Ebla
Sent: Wednesday, January 19, 2011 12:06 PM
To: 'Magavi, Ravi'
Subject: FDA Discussion Material

Hello Ravi,

Please find attached the FDA proposed PI, Medguide, revised language for the nephrology section, sent to us for the December 9, 2010 tecon and proposed language for Section 2.1 and 2.2. These documents should serve as discussion points for tomorrow's meeting. Thank you.

Ebla Ali Ibrahim, MS
Regulatory Health Project Manager
Division of Hematology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research
Food and Drug Administration
10903 New Hampshire Avenue, Rm 2159
Silver Spring, MD 20903

Tel: 301-796-3691
Fax: 301-796-9849

From: Magavi, Ravi [mailto:rmagavi@amgen.com]
Sent: Tuesday, January 18, 2011 2:47 PM
To: Ali Ibrahim, Ebla
Subject: Handout: Discussion points for 20 Jan 2011 telecon

Hi Ebla,

Attached please find a handout to facilitate the 20 January 2011 teleconference discussion of the salient issues with regards to the outstanding PLR label.

The handout contains selected nephrology labeling statements taken verbatim from the USPIs provided by FDA with the 27 April 2010 complete response letters (STN BL 103234/5166 and STN BL 103951/5173), and specific text has been highlighted in red to signify the areas on which we would like

to focus.

Please note that these are the issues we believe to be key. Amgen will provide a few additional proposed revisions that are editorial in nature in the formal written response.

Please contact me if you have questions or need additional information.

Thanks,
Ravi

Ravi Magavi, MS
Senior Manager, Regulatory Affairs
Amgen Inc.
Direct Line: 805.447.4326
Mobile: (b) (6)
E-mail: rmagavi@amgen.com

30 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 19, 2011

From: Mona Patel, Pharm.D., Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: BL STN 103951/5173 & 103234/5166

Meeting: Date December 9, 2010

FDA Attendees:
Mona Patel, Regulatory Health Project Manager
Kaushik Shastri, Clinical Reviewer
Jeff Summers
Karen Jones
Hong Zhao
Grace Carmouze
Ingrid Markovic

Amgen Attendees:
Paul Eisenberg – Vice President of Global Regulatory Affairs & Safety
Susan Boynton – Executive Director, Regulatory Affairs
Annie Dang – Manager, Regulatory Affairs
Steven Galson – Vice President, Global Regulatory Affairs
Sanja Gauthier – Medical Director, Global Safety
Robert Harris – Director, Regulatory Affairs
Reshma Kewalramani – Vice President, Global Development
Richard Markus – Executive Medical Director, Global Development
Allan Pollock – Executive Medical Director, Clinical Development
Lisa Shamon-Taylor – Director, Regulatory Affairs
Sunita Zalani – Executive Director, Regulatory Affairs

Johnson & Johnson
Brian Maloney – Director, Regulatory Affairs
Barbara Kolb – Senior Director, Regulatory Affairs
Melanie Rothschild – Manager, Regulatory Affairs
Jerry Retwa – Manager, Regulatory Affairs
Michael Romano – Associate Director, Regulatory Affairs
Peter Bowers – Senior Director, Clinical Leader

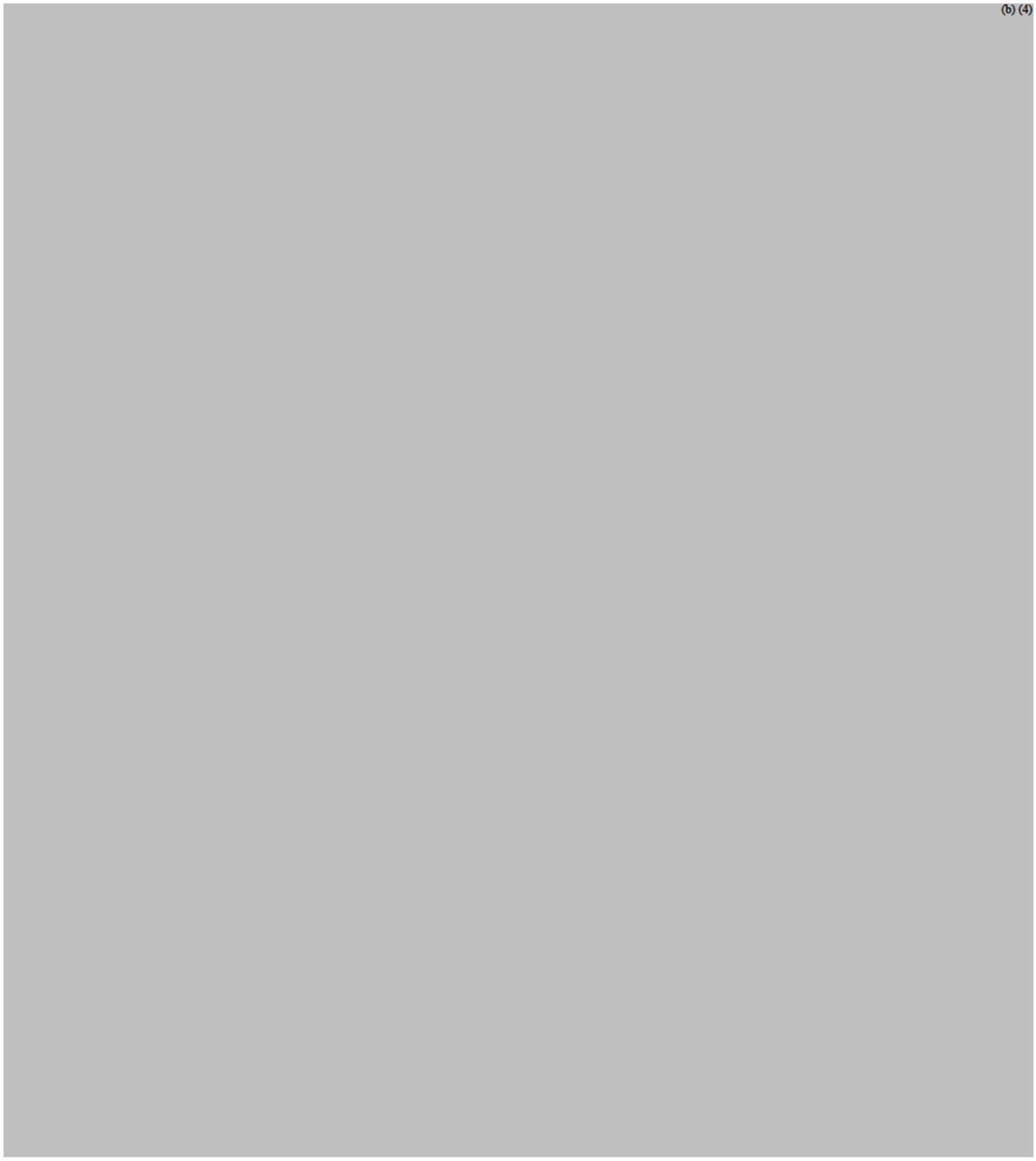
FDA requested a teleconference with Amgen to informally discuss the outstanding issues with the Aranesp and Epogen efficiacy supplements submitted to FDA on December 20, 2007 and

resubmitted on October 23, 2009. Amgen was issued a Complete Response letter on October 24, 2008 and April 27, 2009.

On December 9, 2010, Amgen sent via electronic communication, a handout outlining the outstanding issues with the Aranesp & Epogen supplements as copied below. Discussion is captured for each item below. Items highlighted in red is language proposed by Amgen.

Oncology

(b) (4)



Call concluded.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: January 11, 2011

From: Mona Patel, Pharm.D., Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: STN BL 103234/5166 (5256) and 103951/ 5173 (5248): Internal meeting with/DHP to discuss open TREAT and PLR supplements under Epogen and Aranesp.

FDA Attendees:
Mona Patel-DBOP
Grace Carmouze-DBOP
Kaushik Shastri-DBOP
Jeff Summers-DBOP
Patricia Keegan-DBOP
Karen Jones-DBOP
Ann Farrell-DHP
Robert Kane-DHP
Saleh Ayache-DHP
Ebla Ali Ibrahim-DHP

The purpose of this internal team meeting was to discuss with DHP open TREAT and PLR supplements under Epogen and Aranesp, and to determine path forward.

Discussion: The team reviewed the outstanding issues with open supplements under Epogen and Aranesp and discussed path forward.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

Memorandum

Date: March 24 & March 25, 2010

From: Mona Patel, Pharm.D., Regulatory Health Project Manager
DBOP/OODP/OND/CDER/FDA

Subject: BL STN 103951/5173

FDA Attendees:
Mona Patel, Regulatory Health Project Manager
Yuan Li Shen, Biometrics Reviewer
Kaushik Shastri, Clinical Reviewer

Amgen Attendees:
Lisa-Shamon Taylor
Cristina Damatarca
Richard Markus
Jason Legg

On March 22, 2010, Amgen submitted a response to FDA proposed PLR changes to Aranesp labeling sent to them on February 22, 2010, March 3, 2010, and March 10, 2010. In this submission, Amgen proposed a revised Table 4 in the Oncology ADR section, stating that in Amgen's original proposal for Table 4 in the Adverse Reactions section (Thrombovascular Adverse Reactions in Patients Receiving Chemotherapy), a programming error resulted in the inclusion of adverse events that are usually excluded from such analyses (b) (4) This error was corrected in their proposed revised table. On March 24, 2010, FDA participants, Drs. Mona Patel, Kaushik Shastri, and Yuan Li Shen requested a brief teleconference with Amgen to request the data supporting the proposed change to Table 4 under Section 6.1 of the Aranesp Package Insert related to thrombovascular adverse reactions. Amgen was asked to provide separate adverse events dataset (c aepool) and key variable dataset (p keyvar) for the 145 study and the pooled studies represented in the table. Amgen was also requested to create a coded variable for the treatment (1) and placebo (0).

Amgen submitted the datasets via e-mail on 3/24/10. However, one of the files (a_key145.xpt) could not be opened. In a response to the e-mail query from Dr. Shastri on 3/25/10, Amgen indicated that the problem was a formatting issue on their part and they would work to resolve it and provide a new file. The corrected file was provided via e-mail on 3/25/10. A follow-up call was initiated by Dr. Kaushik Shastri to Amgen (attended by Dr. Shastri from FDA and Lisa Shamon-Taylor, Jason Legg and Matt Ness from Amgen) to clarify some of the variable definitions since a variable definition file was not provided with the datasets. Also Amgen was asked to provide an updated version of the AE datasets since the AE datasets did not contain

the variable for unique subject ID (USUBID). Amgen provided the updated datasets on 3/25/10 via e-mail. These datasets were also subsequently submitted to the BLA.

sBLA 103951/5173 and 103234/5166
Complete Response Resubmission
darbepoetin alfa (Aranesp) and epoetin alfa (Epogen/Procrit)
Wrap-Up Meeting Summary
Held on: 3/17/2010

Attendees:
Mona Patel
Ebla Ali Ibrahim
Cynthia Collins
Michelle Safarik
Carole Broadnax
Patricia Keegan
Rafel Rieves
Robert Kane
Kaushik Shastri
Saleh Ayache
Kathy Robie Suh
Richardae Araojo
Haleh Saber
Mark Rothmann
Yuan Li Shen
Kyung Y Lee
Andrew Mcdougal
Anne Pilaro
Diane Leaman
Ann Farrell
Grace Carmouze
Sharon Mills
Melissa Hulett
Sue Kang
Sarah Simon
Ingrid Markovic
Kimberly Rains

The wrap-up meeting was held on March 17, 2010, to discuss the reviewers' findings, draft labeling, and any problems that surfaced or remained since the Mid-Cycle meeting for the Amgen Aranesp and Epogen/Procrit Complete Response resubmissions to convert the labeling into PLR format.

Dr. Mona Patel gave a brief introduction. Drs. Kaushik Shastri, Saleh Ayache, Kyung Yul Lee, and Yuan Li Shen spoke briefly of their clinical and statistical reviews. Dr Andrew Mcdougal spoke briefly on the nonclinical review. Drs. Cynthia Collins and Carole Broadnax and Ms. Michelle Safarik spoke briefly of the Division of Drug Marketing, Advertising, and Communications review of the labeling. Dr. Richardae Araojo gave a presentation of the Maternal Health Team's review. Drs. Melissa Hulett and Ms. Mills spoke briefly on the Office of Surveillance and Epidemiology/Division of Risk Management review.

Patel, Mona

From: Hulett, Melissa
nt: Thursday, March 11, 2010 10:27 AM
To: Patel, Mona; Mills, Sharon; Simon, Sarah
Cc: Griffiths, LaShawn
Subject: RE: Followup from 3.9.2010 Aranesp meeting

Mona,
We wanted to draw your attention to four differences we noted between the MG guide that was discussed and revised on 3-9-10 and the one sent to Amgen on 3-4-10.

(b) (4)

If you have any questions regarding these differences between the versions or our comments regarding them please let us know.
Melissa
'/R
Melissa Hulett MSBA, BSN, RN
Lieutenant US Public Health Service

FDA/OSE/DRISK/ Patient Product Information Reviewer
10903 New Hampshire Ave, Bldg 22, Room 2491
Silver Spring, MD 20993
Email: melissa.hulett@fda.hhs.gov
Phone: 301.796.4897 Fax: 301-796-9837

V/R
Melissa
301-796-4897

From: Patel, Mona
Sent: Tuesday, March 09, 2010 5:42 PM
To: Mills, Sharon; Simon, Sarah; Hulett, Melissa
Cc: Griffiths, LaShawn
Subject: Followup from 3.9.2010 Aranesp meeting
Importance: High

Sharon,

Attached below is the IFU we agreed upon at today's meeting which is going to be sent to Amgen.
< File: Aranesp PIU Single Use Vial (redline) 3.9.2010.doc >> << File: Aranesp PIU Prefilled Syringe 03.9.2010 (redline).doc >> << File: FDA Proposed Changes Aranesp PIU Autoinjector for Injection Redline 03.9.2010.doc >>

Attached is the Aranesp MG with 2 embedded DRISK comments for you to address. Do you think you can address these tomorrow? I'd like to try and send the revised Aranesp MG to Amgen by tomorrow COB.

<< File: Aranesp MG 03.9.2010 (redline).doc >>

Attached below is the Aranesp MG we sent to Amgen on 3.4.2010 (I have highlighted those areas that we changed from the version sent to you originally on 2.23.2010.

<< File: Highlighted FDA Proposed Changes Medguide Aranesp Redline 3 4 2010.doc >>
Mona

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

Patel, Mona

Subject: FDA PROPOSED CHANGES March 10, 2010: Followup: Aranesp STN BL 103951/5173 & Epogen STN BL 103234/5166: PI and Medguide

-----Original Message-----
From: Patel, Mona [mailto:Mona.Patel@fda.hhs.gov]
Sent: Wednesday, March 10, 2010 9:39 AM
To: Shamon-Taylor, Lisa
Subject: FDA PROPOSED CHANGES March 10, 2010: Followup: Aranesp STN BL 103951/5173 & Epogen STN BL 103234/5166: PI and Medguide

Lisa,

We had an internal meeting with OSE and further revisions have been made.

Please find attached the latest version of the Aranesp Medguide to work off of. I have dated it March 10, 2010.

Please also find a clean version of the Aranesp PI containing additional changes (tracked). Please integrate these FDA revisions of March 10, 2010 to the 2.22.2010 redlined Aranesp PI we sent to you already.

Please find attached FDA's proposed changes to the 3 Patient Instructions for Use.

Please provide us with the labels back by Noon, Tuesday, March 16, 2010.

Please confirm receipt of this email.

Thank you,

Mona

50 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Patel, Mona

Subject: FDA Revise Aranesp Medguide: Aranesp STN BL 103951/5173: PI and Medguide

Attachments: FDA Proposed Changes Medguide Aranesp Redline 3 4 2010.doc

FDA Proposed Changes Medguide ..

-----Original Message-----
From: Patel, Mona
Sent: Thursday, March 04, 2010 2:58 PM
To: 'Shamon-Taylor, Lisa'
Subject: FDA Revise Aranesp Medguide: Aranesp STN BL 103951/5173: PI and Medguide

Lisa,

FDA made further revisions to Aranesp MG to reflect those changes made for Epogen MG. Please use this version.

Mona

5 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

Patel, Mona

From: Patel, Mona
Sent: Monday, February 22, 2010 5:26 PM
To: 'Shamon-Taylor, Lisa'
Subject: Aranesp STN BL 103951/5173: PI and Medguide

Attachments: FDA Proposed Changes Medguide Aranesp Redline 2 22 2010.doc; FDA Proposed Changes Aranesp PI Redline 2.22.2010.doc


FDA Proposed Changes Medguide ..


FDA Proposed Changes Aranesp P..

Hi Lisa,

Please see attached the revised label for Aranesp Supplements 103951/5173 with FDA's proposed changes.

Please provide us with your comments by 5pm EST, Monday, March 1, 2010.

Thank you,

Mona

34 pages of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

sBLA 103951/5173 and 103234/5166
Complete Response Resubmission
darbepoetin alfa (Aranesp) and epoetin alfa (Epogen/Procrit)
Mid-Cycle Meeting Summary
Held on: 1/19/2010

Attendees:

Mona Patel
Karen Jones
Ebla Ali Ibrahim
Raymond Chiang
Vaishali Jarral
Patricia Keegan
Rafel Rieves
Robert Kane
Kaushik Shastri
Saleh Ayache
Kathy Robie Suh
Aakanksha Khandelwal
Hong Zhao
Yanli Ouyang
Mark Rothmann
Yuan Li Shen
Kyung Y Lee
Andrew Mcdougal
Carole Broadnax
Michelle Safarik
Cynthia Collins
Richardae Araojo
Jeanine Best
Karen Feibus
LaShawn Griffiths
Melissa Hulett
Catherine Carr
Iris Masucci
Grace Carmouze
Jeffrey Summers

The mid-cycle review meeting was held on January 19, 2010, to discuss the status of the reviews for the Amgen Aranesp and Epogen/Procrit Complete Response resubmissions to convert the labeling into PLR format.

Dr. Mona Patel gave a presentation on the regulatory history. Drs. Kaushik Shastri, Saleh Ayache, Kyung Yul Lee, and Yuan Li Shen gave presentations of their clinical and statistical reviews. Dr Andrew Mcdougal gave a presentation of the nonclinical review. Dr. Aakanksha Khandelwal gave a presentation of the clinical pharmacology review. Dr. Cynthia Collins gave a presentation of the Division of Drug Marketing, Advertising, and Communications review of the medication guide. Dr. Richardae Araojo gave a presentation of the Maternal Health Team's review. Dr. Jeanine Best gave a presentation of the Pediatric review. Dr. LaShawn Griffiths gave a presentation on the Office of Surveillance and Epidemiology/Division of Risk Management review.

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

Our STN: BL 103951/5173

ACKNOWLEDGE COMPLETE RESPONSE

Amgen, Incorporated
Attention: Lisa Shamon-Taylor, Ph.D.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Nov 10 2009

Dear Dr. Shamon-Taylor:

We have received your October 23, 2009 resubmission to your biologics license application for darbepoetin alfa (Aranesp) on October 26, 2009.

The resubmission contains additional revisions to the package insert beyond those recommended in our October 24, 2008, complete response letter, and new changes to the Medication Guide.

We consider this a complete, class 2 response to our action letter. Therefore, the user fee goal date is April 27, 2010

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Mona Patel, at (301) 796-4236.

Sincerely,

Patricia Keegan

/Patricia Keegan/s/
Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

sBLA 103951/5173 and 103234/5166
Complete Response Resubmission
darbepoetin alfa (Aranesp) and epoetin alfa (Epogen/Procrit)
First Committee Meeting Summary
Held on: 11/9/09

Attendees:
Mona Patel
Monica Hughes
Patricia Keegan
Rafel Rieves
Kaushik Shastri
Ann Farrell
Saleh Ayache
Aakanksha Khandelwal
Hong Zhao
Yanli Ouyang
Mark Rothmann
Yuan Li Shen
Kyung Y Lee
Andrew Mcdougal
Anne Pilaro
Ebla Ali Ibrahim

DBOP and DMIHP elected to work collaboratively to review these Complete Response resubmissions which were determined to be Class 2 submissions and will fall under a 6 month review clock.

DBOP and DMIHP Review Teams were discussed:

DBOP Reviewers:
Mona Patel, Regulatory Project Manager
Kaushik Shastri,Clinical Reviewer
Ingrid Markovic, Product Reviewer
Aakanksha Khandelwal, Clinical Pharmacology Reviewer
Andrew McDougal, Pharm-Tox Reviewer
Kyung Yul Lee (Epogen/Procrit) Yuan Li Shen (Aranesp), Statistical Reviewer
Carole Broadnax, DDMAC Reviewer
Cynthia Collins, DDMAC Reviewer

DMIHP Reviewers:
Ebla Ali Ibrahim, Regulatory Project Manager
Saleh Ayache, Clinical Reviewer
Yanli Ouyang, Pharm-Tox Reviewer
Michelle Safarik, DDMAC Reviewer

Items covered:

1. **Dates Milestone Letter's Must Issue**:
   a. Action Letter: Due April 27, 2010

2. **Upcoming Internal Team Meetings**:
   a. Internal Meeting Prior to Mid-Cycle Meeting
   The team decided that the internal meeting should be held in December
   b Mid-Cycle Meeting: Scheduled for _____
   The team decided that the Mid-Cycle meeting should be held in January.
   c. Labeling Meeting #1: Scheduled for _____
   The team decided that labeling meetings should begin in January.
   d. Labeling Meeting #2: Scheduled for _____
   e. Labeling Meeting #3: Scheduled for _____
   f. Labeling Meeting#4: Scheduled for _____
   g. Labeling Meeting #5: Scheduled for _____
   h. Final Wrap Up Meeting: Scheduled for _____

5. Consults required for this application were discussed as follows:
   a. Will a Maternal health consult be required?
   The team decided yes.
   b. Would you like to request a formal consult for OSE reviewer? Do we have specific questions for OSE? *The team decided yes for changes in the medication guide.*

7. Would the team like to have monthly team meetings to discuss the progress of the review and identify major issues? *The team decided to establish one prior to Mid-Cycle meeting.*

8. Discuss any issues that have been identified during the review to date or need to request additional information:

   a. CMC
   b. Clinical
   c. Statistical
   d. Clinical Pharmacology

   None were discussed during this meeting.

9. Any other issues related to this application that requires discussion?
   None discussed.

DEPARTMENT OF HEALTH & HUMAN SERVICES
Public Health Service
Food and Drug Administration
Rockville, MD 20857

FDA DRAFT RESPONSES

DRAFT COMMENTS SENT:	February 13, 2009
MEETING DATE:	February 17, 2009
TIME:	1:00 PM-2:00 PM ET
LOCATION:	White Oak Bldg 22, conference room 2201
APPLICATION:	BL STN 103234/5166 (Epogen/Procrit) and 103951/5173 (Aranesp)
DRUG NAME:	Epoetin alfa (Epogen/Procrit) and Darbepoetin alfa (Aranesp)
TYPE OF MEETING:	Teleconference
MEETING CHAIR:	Patricia Keegan, M.D.
MEETING RECORDER:	Monica Hughes, M.S.
SUBJECT:	Draft FDA Responses to Amgen's questions submitted on January 14, 2009, along with the request for a Type A meeting to discuss the Agency's October 24, 2008, complete responses letters.

TENTATIVE LIST OF FDA ATTENDEES:

Office of Oncology Drug Products
Division of Biologic Oncology Products

Patricia Keegan	Division Director, Acting Team Leader
Kaushikkumar Shastri	Medical Officer
Andrew McDougal	Pharmacology/Toxicology Reviewer
Anne M. Pilaro	Pharmacology/Toxicology Supervisor
Monica Hughes	Lead Regulatory Project Manager
Jeff Summers	Deputy Director, Safety

Office of Oncology Drug Products
Division of Medical Imaging and Hematology Products

Dwaine Rieves	Division Director
Kassa Ayalew	Medical Officer, Team Leader
Minh Ha Tran	Medical Officer
Yanli Ouyang	Pharmacology/Toxicology Reviewer
Adebayo A. Laniyonu	Pharmacology/Toxicology Supervisor

Office of Clinical Pharmacology
Division of Clinical Pharmacology V

Hong Zhao	Clinical Pharmacology Team Leader
Aakanksha Khandelwal	Clinical Pharmacology Reviewer

Office of Biostatistics
Division of Biostatistics 5

Mark Rothmann	Statistical Team Leader
Yuan Li Shen	Statistical Reviewer
Kyung Yul Lee	Statistical Reviewer

Office of Medical Policy
Division of Drug Marketing, Advertising, and Communications
Carole Broadnax
Iris Masucci (SEALD)

TENTATIVE LIST OF AMGEN AND J&J PRD ATTENDEES

Tentative Amgen Attendees representing Epogen and Aranesp:

Cheryl Anderson, MBA	Director, Regulatory Affairs
Jeff Borenstein, MD	Director, Clinical Development
Cheryl Byun, PharmD	Manager, Labeling
Cristina Damatarca, MD	Director, Global Safety
Annie Dang, JD	Manager, Regulatory Affairs
Alex Fleishman	Senior Manager, Biostatistics
Robert Harris, PhD	Director, Regulatory Affairs
Sarah Khalil	Director, Promotions
Reshma Kewalramani, MD	Executive Director, Clinical Development
Ravi Magavi, PharmD	Senior Manager, Regulatory Affairs
Richard Markus, MD	Director, Clinical Development
Kurt Olson	Director, Biostatistics
Desmond Padhi	Executive Director, Clinical Pharmacology
Allan Pollock, MD	Director, Clinical Development
Erik Poulsen, PhD	Director, Regulatory Affairs
Ian Pyrah	Executive Director, Toxicology
Jerome Rossert, MD, PhD, MSc	Director, Global Safety
Lisa Shamon Taylor, PhD	Senior Manager, Regulatory Affairs
Dianne Tomita	Director, Biostatistics
Stacey Tosadori	Director, Promotions
Yow-Ming Wang	Director, Pharmacokinetics

Tentative J&J PRD Attendees representing PROCRIT:
Dina Anand
Peter Bowers
Bhupesh Desai
Min Fu
Mary Jean Fusco
Tony Greway
Cindy Hardiman
Sera LaCasse
Brian Maloney
Paul Percheson
Sudhakar Rao
Linda Tatem
Teresa Romaine
Michael Romano
Robyn Sterner
Steven Sun
Kristen Von Seggern
Marsha Wolfson

Disclaimer: This material consists of our preliminary responses to your questions and any additional comments in preparation for the discussion at the meeting scheduled for February 17, 2009, between Amgen and J&J PRD and the Division of Biologic Oncology Products. This material is shared to promote a collaborative and successful discussion at the meeting. The minutes of the meeting will reflect agreements, key issues, and any action items discussed during the formal meeting and may not be identical to these preliminary comments.

If these answers and comments are clear to you and you determine that further discussion is not required, you have the option of canceling the meeting (contact the Regulatory Project Manager). It is important to remember that some meetings, particularly milestone meetings, are valuable even if the pre-meeting communications are considered sufficient to answer the questions. Please note that if there are any major changes to your development plan, the purpose of the meeting, or questions (based on our responses herein), we may not be prepared to discuss or reach agreement on such changes at the meeting. If any modifications to the development plan or additional questions for which you would like FDA feedback arise prior to the meeting, contact the Regulatory Project Manager to discuss the possibility of including these for discussion at the meeting.

At the end of the meeting, key discussion points, agreements, clarifications, and action items will be summarized. We request that you take the responsibility for summarizing what you have heard at the meeting. This will help ensure that there is mutual understanding of the advice given and meeting outcomes and actions.

No meeting briefing packages were submitted for this teleconference.

Meeting Purpose: To discuss and clarify questions Amgen and J&J PRD have regarding the FDA Complete Response letters and to the proposed revisions to the Epogen/Procrit and Aranesp package inserts that were issued to Amgen October 24, 2008.

These draft FDA comments were sent to Amgen on February 13, 2009.

1.0 BACKGROUND

Supplements BL STN 103234/5166 for Epogen/Procrit and BL STN 103951/5173 for Aranesp were submitted on December 20, 2007. These supplements proposed to revise the package insert and patient package insert labeling based on recommendations from the May 10, 2007, Oncology Advisory Committee Meeting (ODAC) as supported by new analyses of pooled data from multiple studies and to convert the package insert to meet the requirements as specified in 21 CFR 201.56-57.

On October 24, 2008, FDA issued complete response letters to both supplements BL STN 103234/5166 for Epogen/Procrit and BL STN 103951/5173 for Aranesp. In these letters FDA acknowledged that while Amgen's original submission included proposed revisions to the patient package insert, during the review of these supplements, separate supplements were submitted to convert the patient package insert to a medication guide, therefore FDA would not provide comments regarding patient labeling but rather attached a copy of the medication guides that were under review and subsequently approved on November 19, 2008. FDA provided comments in redlined track changes format to both the Epogen/Procrit and Aranesp package inserts along with the complete response letters.

On January 14, 2009, Amgen submitted a request for a joint Type A teleconference to discuss the Agency's October 24, 2008, complete response letters for BL STN 103234/5166 for Epogen/Procrit and BL STN 103951/5173 for Aranesp.

2.0 DISCUSSION

Sponsor Submitted Questions and FDA Response:

SAFETY QUESTIONS: ALL INDICATIONS

1. **Questions 5 through 11 of the 24 October 2008 Complete Response letter relate to a requested Safety Update. Would FDA please clarify the terms "new safety data," "newly completed studies," proposed indication," and "initial submission" and explain whether all of the requests in this section are applicable to the current supplement, as the supplement is not an efficacy supplement?**

   FDA RESPONSE: Items 5-12 of the October 24, 2008, Complete Response letters for BL STN 103234/5166 and 103951/5173 are standard language included in FDA Complete Response letters. FDA considers both of these supplements to be efficacy supplements. If there is no new safety information available at the time of the submission, please indicate that in your response.

If FDA confirms that Questions 5 through 11 are applicable to the current supplement, further clarification is requested on Questions 8 and 11.

2. **In question 8 of the 24 October 2008 Complete Response letter, the Agency has requested certain case report forms and narrative summaries. The Agency has also requested the safety update to "include data from all clinical studies." Would the FDA please clarify the scope of "all clinical studies" (e.g., randomized controlled studies, registry studies, studies after 200X)? Does the request apply only to oncology studies, as the data submitted in this supplement were focused on oncology studies? Please note that meeting this request in full may not be possible for Epogen/PROCRIT due to data availability as many of the studies were performed approximately 20 years ago.**

   FDA RESPONSE: FDA requests that Amgen limit the scope of the response to the studies included in the supplements as of December 20, 2007, for the oncology indication. If complete clinical study reports (CSRs), containing narratives for patients experiencing serious and unexpected adverse events, case report forms for patients who discontinued treatment due to toxicity (dropouts), and primary patient-level data in a SAS-compatible format for all protocol specified data collection cannot be provided, please state so in your response. In addition, identify studies for which you cannot respond, provide the reason for lack of availability of information and identify the specific information that is deficient in the study report.

3. **In question 11 of the 24 October 2008 Complete Response letter, the Agency has requested a summary of "worldwide experience on the safety of the drug." Because Epoetin alfa that is manufactured by Amgen is sold in the US only, Amgen seeks FDA concurrence that this request applies only to darbepoetin alfa.**

   FDA RESPONSE: If worldwide experience is limited, then please state there is no experience with Amgen-manufactured epoetin alfa outside of the U.S. If there is worldwide experience, then please state so and provide this information as requested.

4. **What criteria did FDA use in generating the ADR tables? Specifically, what is the search strategy being used? Were Standardized MedDRA Queries (SMQs), medical concepts, or a combination of these used? If SMQs were used, what are their IDs and the MedDRA version?**

   FDA RESPONSE: With respect to Epogen/Procrit, the ADR table was based on the incidence table generated using the adverse events data provided and as described in the FDA proposed label.

   With respect to Aranesp, both broad and narrow scope SMQs were generated using Amgen-supplied datasets and the MAED program. Selection of individual components was based on medical judgment of the potential relatedness to Aranesp by the medical reviewer.

SAFETY QUESTION: ONCOLOGY

5. **In determining ADRs for oncology, what is (a) the cut-off for incidence of ADRs and (b) the difference in incidence between an AE considered ADR and placebo?**

   FDA RESPONSE:

   (a) This information was provided in the proposed revisions to the Epogen/Procrit label. For the Aranesp label, an incidence cut-off of $\geq 1\%$ was used because of the severity of the adverse events being assessed and,

   (b) Any adverse event for which the rate in the ESA arm was higher when compared to placebo was included in the ADR table.

GENERAL QUESTIONS

6. **Does the 24 October 2008 Complete Response letter include the final comments by other FDA Divisions, specifically the Study Endpoints and Labeling Division (SEALD) and the Division of Drug Marketing, Advertising and Communications (DDMAC)? We would like to ensure that we have received a comprehensive list of questions from all Divisions so that we can address all concerns.**

   FDA RESPONSE: The proposed revisions to the labeling included preliminary comments from the review divisions, the SEALD team, and DDMAC. We will need to review your proposed revised labeling in response to the complete response letters and we may have additional comments at that time.

7. **Based on our understanding of eCTD structure and guidance, previously submitted documents to the licenses in the XML backbone should be cross-referenced rather than resubmitted. Does the FDA agree?**

   FDA RESPONSE: No, FDA does not agree with Amgen's proposal to cross reference documents rather than resubmitting the documents because the application files for Epogen/Procrit and Aranesp contain multiple errors as discussed during our working meetings held on April 30, 2008, and information can be very difficult to locate. Therefore, all information must be resubmitted as we cannot rely on the information in the eCTD files in its current form.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103951/5173

AUG 1 9 2008

Amgen, Incorporated
Attention: Lisa Shamon-Taylor, Ph.D.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Shamon-Taylor:

This letter is in regard to the supplement to your biologics license application for darbepoetin alfa (Aranesp) submitted under Section 351 of the Public Health Service Act.

We refer to STN BL 103951/5173, submitted December 20, 2007, and to the amendments submitted January 18, 2008, and April 18, 2008. Please note that the revised labeling submitted April 18, 2008, is still under review.

We have the following questions and requests for additional information:

1. **Study 20010119:** "A Randomized, Double-blind, 5-way Crossover, ARANESP Vehicle Pain Study in Healthy Volunteers."

   Please clarify the relevance of this clinical study to the supplement submission. If information from this study is intended to support revisions or specific information in product labeling, you must also provide study datasets limited to this study (i.e., not contained in the meta-dataset) containing primary study data for raw and derived variables, and all SAS programs utilized to generate analyses that are necessary to evaluate the study conduct and outcomes and as used in support of proposed labeling.

2. **Study 20000161:** "A Multicenter, Blinded, Placebo-controlled, Randomized Study of Novel Erythropoiesis Stimulating Protein (NESP) for the Treatment of Anemia in Subjects with Lymphoproliferative Malignancies Receiving Chemotherapy."

   a. You have identified this study as among the six studies justifying proposed labeling. We note that the supplement contains a synopsis report in section 2.7.6 (Synopses of Individual Studies) but that the final study report is not provided in section 5.3.5 (Reports of Efficacy and Safety Studies). However, two clinical study reports dated August 14, 2002 and April 5, 2005, respectively, can be accessed through a hyperlink in Table 5.2-2 that is contained in section 5.2 (Tabular Listing of All Clinical Studies). These clinical study reports are incomplete. You must provide a complete study report containing the clinical

protocol and all amendments, summary results of the study, datasets limited to this study (i.e., not contained in the meta-dataset) containing primary data for raw and derived variables, all SAS programs utilized to generate derived variables and analyses that are necessary to evaluate the study conduct and outcomes and as used in support of proposed labeling. The study report should also contain case report forms for each patient who died during the study or who did not complete the study due to an adverse event, regardless of whether the adverse event was believed to be drug-related or not drug-related. In addition, the study report should contain narrative summaries for all patients with serious adverse events.

b. Clarify whether use of an ESA was permitted during the study follow-up period. If yes, state whether data were collected on medications administered during the follow-up period.

3. **Study 20010103:** "A Multicenter, Randomised, Double-blind, Placebo-controlled Study of Darbepoetin Alfa for the Treatment of Anemia of Cancer."

a. You have identified this study as among the six studies justifying proposed labeling. We note that the supplement contains a synopsis report in section 2.7.6 (Synopses of Individual Studies) but that the final study report is not provided in section 5.3.5 (Reports of Efficacy and Safety Studies). However, a clinical study report dated April 2, 2007 can be accessed through a hyperlink in Table 5.2-2 that is contained in section 5.2 (Tabular Listing of All Clinical Studies). This clinical study report is incomplete. You must provide a complete study report containing the clinical protocol and all amendments, summary results of the study, datasets limited to this study (i.e., not contained in the meta-dataset) containing primary data for raw and derived variables, all SAS programs utilized to generate derived variables and analyses that are necessary to evaluate the study conduct and outcomes and as used in support of proposed labeling. The study report should also contain case report forms for each patient who died during the study or who did not complete the study due to an adverse event, regardless of whether the adverse event was believed to be drug-related or not drug-related. In addition, the study report should contain narrative summaries for all patients with serious adverse events.

b. Clarify whether use of an ESA was permitted during the study follow-up period. If yes, state whether data were collected on medications administered during the follow-up period.

c. State whether serum erythropoietin levels were obtained at study entry. If yes, submit the primary data in the study datasets.

4. **Study 980291 Schedules 1 and 2**: "A Randomized, Double-Blind, Placebo-Controlled, Dose-Finding Study of Novel Erythropoiesis Stimulating Protein (NESP) Administered by Subcutaneous Injection (SC) for the Treatment of Anemia in Subjects with Solid Tumors Receiving Multi-Cycle Chemotherapy."

   a. The study report should also contain case report forms for each patient who died during the study or who did not complete the study due to an adverse event, regardless of whether the adverse event was believed to be drug-related or not drug-related. In addition, the study report should contain narrative summaries for all patients with serious adverse events.

5. **Study 990114:** "A Multi-center, Blinded, Placebo-controlled, Randomised, Dose-finding Study of Novel Erythropoiesis Stimulating Protein Administered by Subcutaneous Injection for the Treatment of Anaemia in Subjects With Lymphoproliferative Malignancies Receiving Chemotherapy."

   a. The study report should also contain case report forms for each patient who died during the study or who did not complete the study due to an adverse event, regardless of whether the adverse event was believed to be drug-related or not drug-related. In addition, the study report should contain narrative summaries for all patients with serious adverse events.

   b. The analysis data sets and tabulation data sets have "Missing header in file" errors that do not allow the files to be opened with SAS 9.1 or JMP. Please use PROC COPY to re-create the SAS transport file (instead of using PROC CIMPORT).

   c. Please provide all SAS programs utilized to generate derived variables and analyses that are necessary to evaluate the study conduct and outcomes as used in support of proposed labeling.

6. **Study 20030232:** "A Randomized, Double-blind, Placebo-controlled Study of darbepoetin alfa for the Treatment of Anemia in Subjects with Non-myeloid Malignancy Receiving Multicycle Chemotherapy."

   a. The statistical analysis plan included in the study report is version 1.2. Provide the original statistical analysis plan and copies of all amendments.

   b. Provide the sample Case Report Forms/Instruments used for collection of patient-reported outcomes regarding quality of life (QOL). Include the instructions given to healthcare providers and/or patients regarding how to complete these forms.

   c. Please provide all SAS programs utilized to generate derived variables and analyses that are necessary to evaluate the study conduct and outcomes as used in support of proposed labeling.

d. State whether serum erythropoietin levels were obtained at study entry. If yes, submit the primary data in the study datasets.

e. The study report should also contain case report forms for each patient who died during the study or who did not complete the study due to an adverse event, regardless of whether the adverse event was believed to be drug-related or not drug-related. In addition, the study report should contain narrative summaries for all patients with serious adverse events.

7. **Study 980297:** "A Double-blind, Placebo-controlled, Randomised Study of Novel Erythropoiesis Stimulating Protein (NESP) for the Treatment of Anaemia in Lung Cancer Subjects Receiving Multicycle Platinum-containing Chemotherapy."

a. Clarify whether use of an ESA was permitted during the study follow-up period. If yes, state whether data were collected on medications administered during the follow-up period.

b. State whether serum erythropoietin levels were obtained at study entry. If yes, submit the primary data in the study datasets.

c. The hyperlink (m5/53-clin-stud-rep/537-crf-ipl/980297) in Appendix 1 to the June 6, 2001, clinical study report is not functional. Please revise this appendix to the study report to incorporate functional hyperlinks to the referenced case report forms.

d. Please provide all SAS programs utilized to generate derived variables and analyses that are necessary to evaluate the study conduct and outcomes and as used in support of proposed labeling.

8. **Study 20020149:** "A Multicenter, Double-blind, Placebo-controlled Rollover Study to Protocol 20010103 of Darbepoetin Alfa for the Treatment of Anemia of Cancer."

a. Submit individual clinical case report forms for each patient who died during the study or who did not complete the study due to an adverse event, regardless of whether the adverse event was believed to be drug-related or not drug-related.

b. Clarify whether use of an ESA was permitted during the study follow-up period. If yes, state whether data were collected on medications administered during the follow-up period.

9. Please provide SAS programs for the following analysis described in the Summary of Clinical Safety (module 2.7.4) in the submission:

1) Table 1, page 8
2) Figure 1, page 9
3) Figure 4, page 13
4) Figure 7, page 16
5) Figure 10, page 21
6) Figure 12, page 25
7) Figure 13, page 26
8) Table 4, page 26
9) Table 7, page 33
10) Figure 16 and figure 17, page 38

10. In response to your April 15, 2008, submission in which you provided derived datasets for study 20010145. Please provide documentation of how the variable LASTCONTACTDT was derived (including data involved and computation algorithm) and the SAS macro (getlastcontactdate) that was used to derive the LASTCONTACTDT. In addition, please provide the SAS program that was used to generate the OS results

(b) (4)

You should promptly submit a complete response to the items enumerated above within 15 days of the date of this letter. Failure to respond in a timely manner or submission of a partial response may result in a determination that your supplement is not approvable. Review of your supplement is continuing.

Please note that a separate letter will follow with additional requests for specific analyses involving individual studies.

(b) (4)

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Monica Hughes, M.S., Lead Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

DK Summers for Pat Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING ISSUES

Our STN: BL 103951/5173

MAR 0 7 2008

Amgen, Incorporated
Attention: Lisa Shamon-Taylor, Ph.D.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Shamon-Taylor:

Please refer to the supplement to your biologics license application (BLA), dated December 20, 2007, received December 26, 2007, submitted under section 351 of the Public Health Service Act, for darbepoetin alfa (Aranesp). Also refer to our filing letter dated February 11, 2008. While conducting our filing review we identified the following potential review issues:

STATISTICAL:

1. We cannot locate the define document for some of the individual studies (e.g. 20030232, 980291 schedules 1 and 2, 980297, 990114). Please provide for each study the define document(s) for the data or, if the define document is contained in the application, provide the precise location of the define document(s) for each study.

2. Provide the SAS programs that were used to produce derived variables in each of the analysis datasets. In addition, submit revised product labeling that is annotated to contain a link to the SAS programs used to generate each of the derived variables and analysis results included in the prescribing information.

3. We note that the application contains only a seendpt.xpt for study 20020149. Provide the raw datasets and additional derived datasets for study 20020149.

REGULATORY: PLR LABELING FORMAT

The following comments reflect only preliminary format-related comments. Comments on the content of the proposed labeling will be provided later, during labeling negotiations.

With Respect to the Highlights of Prescribing Information Section of the Package Insert:

4. "Aranesp (darbepoetin alfa)" appears under the highlights limitation statement, however, (b) (4) route of administration is NOT listed in the line below as required for biological products (21 CFR 600.3 (k)). Please revise.

5. The black box warning currently reads "WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION." (b) (4)

6. Under the INDICATIONS AND USAGE section, please define "ESA", Erythropoiesis stimulating agents, as the pharmacologic class.

7. Under WARNINGS AND PRECAUTIONS, you listed: Hypertension, PRCA, Allergic reactions, and Seizures. Please provide a justification for sections containing multiple discrete terms, such as "Increased Mortality, Serious Cardiovascular and Thromboembolic Events" and "Increased Mortality and/or Tumor Progression" or revise the package insert to discuss each discrete item under a separate subheading.

8. The "Revised:_____" date will need to be revised to reflect the date in which this supplement is ultimately approved.

9. Please note, the revision date at the end of the highlights section replaces the "revision" or "issued" date at the end of the labeling. It should not appear in both places, please delete the "Issued Date: ____" from the end of the label (patient package insert, PPI).

With Respect to the FULL PRESCRIBING INFORMATION:

10. Please review the Full Prescribing sections of the label for consistency with respect to reference citations. Please ensure all citations follow the following format: [*see Section referring to* (section number, e.g. 5.2)].

With Respect to the FULL PRESCRIBING INFORMATION: CONTENTS* and FULL PRESCRIBING INFORMATION Sections of the Package Insert:

BOXED WARNING: In both the TOC and the boxed Warning in the FPI

11. The black box warning currently reads "WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION." (b) (4)

DOSAGE AND ADMINISTRATION:

12. We recommend that you avoid the use of Latin abbreviations such as IV and instead use (b) (4)" to reduce the potential for medication errors, should the abbreviation be misread.

13. Immediately following the heading, you have inserted the following text: "IMPORTANT: See BOXED WARNINGS and WARNINGS: Increased Mortality, Serious Cardiovascular and Thromboembolic events." Please delete this sentence.

14. Please revise section 2.3 to state, "Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, (b) (4)

CONTRAINDICATIONS:

15. Each contraindication should have its own subheading. In addition, each contraindication, if not just a theoretical possibility, should also contain the type and nature of the expected adverse reaction along with information regarding its known prevalence rate.

WARNINGS AND PRECAUTIONS:

16. (b) (4)

ADVERSE REACTIONS:

17. (b) (4) This is ultimately a review issue and will be discussed further during labeling negotiations.

18. With respect to subsection "**6.3, Immunogenicity**", this section should be revised to include the verbatim statement: "As with all therapeutic proteins, there is potential for immunogenicity. [Insert data from PI.] The incidence of antibody formation is highly dependent on the sensitivity and the specificity of the assay. Additionally, the observed incidence of antibody (including neutralizing antibody) positivity in an assay may be influenced by several factors including assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to Aranesp with the incidence of antibodies to other products may be misleading."

This supplement is under review. We have no specific requests for additional clinical information at this time; however, we may identify during the ongoing review, aspects of the submission that will require clarification or submission of additional information.

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 supplement and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the supplement. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your supplement. Following a review of the supplement, we will advise you in writing of any action we have taken and request additional information if needed.

Please respond 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.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Monica Hughes, M.S., Lead Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

FILING COMMUNICATION

Our STN: BL 103951/5173

FEB 21 2008

Amgen, Incorporated
Attention: Lisa Shamon-Taylor, Ph.D.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320

Dear Dr. Shamon-Taylor:

This letter is in regard to your biologics license application (BLA), dated December 20, 2007, received December 26, 2007, submitted under section 351 of the Public Health Service Act, for darbepoetin alfa (Aranesp).

We have completed an initial review of your application to determine its acceptability for filing. Under 21 CFR 601.2(a), we have filed your application today. The review classification for this application is standard. Therefore, the user fee goal date is October 25, 2008. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before March 9, 2008.

Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, call Monica Hughes, M.S., Lead Regulatory Health Project Manager, at (301) 796-2320.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

sBLA 103951/5173 and 103234/5166
(b) (4)

darbepoetin alfa (Aranesp) and epoetin alfa (Epogen/Procrit)
Filing Meeting Agenda
Held on: 2/11/08

Attendees:
Monica Hughes
Patricia Keegan
Jeff Summers
Vinni Juneja
Richard Chen
Florence Moore
Andrew McDougal
Anne Pilaro
Mark Rothmann
Kyung Yul Lee
Yuan Li Shen
Leslie Kenna
Hong Zhao
Bill Pierce
Sean Bradley
Dwaine Rieves

Review Teams:
Monica Hughes, Regulatory Project Manager
Vinni Juneja (Epogen/Procrit) and Chaohong Fan (Aranesp), Clinical Reviewer
Ingrid Markovic, Product Reviewer
Hong Zhao, Clinical Pharmacology Reviewer
Andrew McDougal, Pharm-Tox Reviewer
Kyung Yul Lee (Epogen/Procrit) Yuan Li Shen (Aranesp), Statistical Reviewer
Carole Broadnax, DDMAC Reviewer
Betsy Scroggs, OSE Reviewer
Sharon Mills, OSE/DSRCS Reviewer

DMIHP Reviewers:
Florence Moore, Regulatory Project Manager
Leslie Kenna, Clinical Pharmacology Reviewer
Yuan Who Chen, Statistical Reviewer
Faranak Jamali, Clinical Reviewer
Yanli Ouyang, Pharm-Tox Reviewer
Sean Bradley, DDMAC Reviewer

Items covered:

1. **Milestones for Applications Received on December 26, 2007**:
   a. Committee Assignment: Complete
   b. First Committee Meeting: Completed 1-28-08
   c. Filing Meeting: Held Today
   d. Continued below under Dates Milestone Letter's Must Issue

2. **Dates Milestone Letter's Must Issue**:
   a. Filing Action Letter: Due February 24, 2008
   b. Deficiencies Identified Letter (74 day letter): Due March 9, 2008
   c. Action Letter: Due October 28, 2008

3. **Upcoming Internal Team Meetings**:
   a. Filing Meeting: Today
   b. Mid-Cycle Meeting: Scheduled for June 16, 2008
   c. Labeling Meeting #1: Scheduled for _____
   d. Labeling Meeting #2: Scheduled for _____
   e. Labeling Meeting #3: Scheduled for _____

4. ODAC: There is an ODAC meeting scheduled for March 13, 2008.

5. **Monthly Review Team Meetings are in the process of being set up, they will begin in April.**

6. **Discuss filing issues identified thus far by team discipline. Is this application filable?**

   Team decided that the first monthly team meeting will be used to divide up responsibilities to avoid redundant review of materials.

7. **RPM PLR labeling review using the LRT is under review, comments will be disseminated to the team in the near future.**

8. **Collect supervisor signed off, filing review forms.**
   Florence will collect all DMIHP forms. I will collect all DBOP forms.

9. **Any other issues related to this application that requires discussion?**
   None discussed.

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

Our STN: BL 103951/5173

Amgen, Incorporated
Attention: Lisa Shamon-Taylor, Ph.D.
Senior Manager, Regulatory Affairs
One Amgen Center Drive
Thousand Oaks, CA 91320-1799

FEB 01 2008

Dear Dr. Shamon-Taylor:

We have received your supplement to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act for the following biological product:

STN	Name of Biological Product
BL 103951/5173	Darbepoetin alfa/Aranesp

Reason for the submission: To revise the package insert and patient package insert labeling based on recommendations from the May 10, 2007, ODAC meeting.

Date of Supplement: December 20, 2007

Date of Receipt: December 26, 2007

Action Due Date: October 25, 2008

If you have not already done so, promptly submit the *content of labeling* (21 CFR 601.14(b)) in electronic format as described at the following website:
http://www.fda.gov/oc/datacouncil/spl.html

We will notify you within 60 days of the receipt date if the application is sufficiently complete to permit a substantive review.

We request that you submit all future correspondence, supporting data, or labeling relating to this application in triplicate, citing the above STN number. Please refer to http://www.fda.gov/cder/biologics/default.htm for information regarding therapeutic biological products, including the addresses for submissions.

This acknowledgment does not mean that this supplement has been approved nor does it represent any evaluation of the adequacy of the data submitted. Following a review of this submission, we shall advise you in writing as to what action has been taken and request additional information if needed.

If you have any questions, please contact the Lead Regulatory Health Project Manager, Monica Hughes, M.S., at (301) 796-2320.

Sincerely,

Patricia Keegan

Patricia Keegan, M.D.
Director
Division of Biologic Oncology Products
Office of Oncology Drug Products
Center for Drug Evaluation and Research

sBLA 103951/5173 and 103234/5166
darbepoetin alfa (Aranesp) and epoetin alfa (Epogen/Procrit)
First Committee Meeting Summary
Held on: 1/28/08

Attendees:
Monica Hughes
Patricia Keegan
Jeff Summers
Vinni Juneja
Chaohong Fan
Mark Rothmann
Kyung Yul Lee
Yuan Li Shen
Anne Pilaro
Andrew McDougal
William Pierce
Dwaine Rieves
Florence Moore
Faranack Jamali
Betsy Scroggs
Sean Bradley
Hong Zhao

DBOP and DMIHP elected to work collaboratively to review these supplements which contain multiple clinical study reports, data, and convert the labeling to PLR format.

DBOP and DMIHP Review Teams were discussed:

DBOP Reviewers:
Monica Hughes, Regulatory Project Manager
Vinni Juneja (Epogen/Procrit) and Chaohong Fan (Aranesp), Clinical Reviewer
Ingrid Markovic, Product Reviewer
Hong Zhao, Clinical Pharmacology Reviewer
Andrew McDougal, Pharm-Tox Reviewer
Kyung Yul Lee (Epogen/Procrit) Yuan Li Shen (Aranesp), Statistical Reviewer
Carole Broadnax, DDMAC Reviewer
Betsy Scroggs, OSE DDRE Reviewer

DMIHP Reviewers:
Florence Moore, Regulatory Project Manager
Leslie Kenna, Clinical Pharmacology Reviewer
Yuan Who Chen, Statistical Reviewer
Faranak Jamali, Clinical Reviewer
Yanli Ouyang, Pharm-Tox Reviewer
Sean Bradley, DDMAC Reviewer

Items covered:

1. **Milestones for Application Received on December 26, 2007**:
   a. Committee Assignment: Complete
   b. First Committee Meeting: Completed Today
   c. Filing Meeting: Scheduled for February 11, 2008
   d. Continued below under Dates Milestone Letter's Must Issue

2. **Dates Milestone Letter's Must Issue**:
   a. Filing Action Letter: Due February 24, 2008
   b. Deficiencies Identified Letter (74 day letter): Due March 9, 2008
   c. Action Letter: Due October 28, 2008

3. **Upcoming Internal Team Meetings**:
   a. Filing Meeting: Scheduled for February 11, 2007
   b. Mid-Cycle Meeting: Scheduled for _____
   The team decided that the Mid-Cycle meeting should be held in June.
   c. Labeling Meeting #1: Scheduled for _____
   The team decided that labeling meetings should begin in June.
   d. Labeling Meeting #2: Scheduled for _____
   e. Labeling Meeting #3: Scheduled for _____

4. ODAC: There is an ODAC meeting scheduled for March 13, 2008.

5. Consults required for this application were discussed as follows:
   a. Will DSI Inspections be required? *The team decided none were required.*
   b. Would you like to request a formal consult for OSE reviewer (Betsy Scoggs manages ESA files)? Do we have specific questions for OSE? *The team will submit questions as they arise during the review.*
   c. SEALD consults will be requested and invited to labeling meetings as needed.

   To DDMAC: the review teams want to ensure that we have input from the teams who would review direct to consumer adds to make sure we understand any implications the labeling could have in advertising.

6. Would the team like to set up standing weekly teleconferences with Amgen to begin after the mid-cycle meeting? *The team decided not to establish these.*

7. Would the team like to have monthly team meetings to discuss the progress of the review and identify major issues? *The team decided to establish these.*

8. Discuss any issues that have been identified during the review to date or need to request additional information:

   a. CMC
   b. Clinical
   c. Statistical
   d. Clinical Pharmacology

   None were discussed during this meeting.

9. Any other issues related to this application that requires discussion?
   None discussed.

10. Discuss labeling claims and (b) (4)

(b) (4)

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION[1]

NDA # BLA # 103951	NDA Supplement # BLA STN # 5173	If NDA, Efficacy Supplement Type:
Proprietary Name: Aranesp Established/Proper Name: darbepoetin alfa Dosage Form: injection		Applicant: Amgen, Inc. Agent for Applicant (if applicable):
RPM: Mona Patel		Division: DBOP/OODP

NDAs:
NDA Application Type: ☐ 505(b)(1) ☐ 505(b)(2)
Efficacy Supplement: ☐ 505(b)(1) ☐ 505(b)(2)

(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 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)

505(b)(2) Original NDAs and 505(b)(2) NDA supplements:
Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s)):

Provide a brief explanation of how this product is different from the listed drug.

If no listed drug, explain.
- ☐ This application relies on literature.
- ☐ This application relies on a final OTC monograph.
- ☐ Other (explain)

Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.

On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.

☐ No changes ☐ Updated Date of check:

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.

❖ Actions	
• Proposed action • User Fee Goal Date is May 23, 2011	☒ AP ☐ TA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☐ None CR 4/27/2010 CR 10/24/2008

[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.

❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain _____	☐ Received
❖ Application Characteristics [2]	

Review priority: ☒ Standard ☐ Priority
Chemical classification (new NDAs only):

☐ Fast Track
☐ Rolling Review
☐ Orphan drug designation
☐ Rx-to-OTC full switch
☐ Rx-to-OTC partial switch
☐ Direct-to-OTC

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

☐ Submitted in response to a PMR
☐ Submitted in response to a PMC
☐ Submitted in response to a Pediatric Written Request

REMS: ☒ MedGuide
☒ Communication Plan
☐ ETASU
☐ REMS not required

Comments:

❖ BLAs only: Ensure *RMS-BLA Product Information Sheet for TBP* and *RMS-BLA Facility Information Sheet for TBP* have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	☒ Yes, dates 6/27/2011
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 *(approvals only)*	☐ Yes ☒ No
❖ Public communications *(approvals only)*	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action (by OEP)	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☐ None ☐ HHS Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

[2] Answer all questions in all sections in relation 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	
• Is approval of this application blocked by any type of exclusivity?	☒ No ☐ Yes
• NDAs and BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *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.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application)? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? *(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.)*	☐ No ☐ Yes If yes, NDA # and date 10-year limitation expires:
❖ Patent Information (NDAs only)	
• 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.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• 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) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [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).	☐ No paragraph III certification Date patent will expire
• [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). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next section below (*Summary Reviews*)).*	☐ N/A (no paragraph IV certification) ☐ 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).*

(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? (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). *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*).* *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.*	☐ Yes ☐ No

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 *(approvals only)*	☒ Included
Documentation of consent/non-consent by officers/employees	☒ Included
Action Letters	
❖ Copies of all action letters *(including approval letter with final labeling)*	Action(s) and date(s) Complete Response Letter 4/27/2010 Complete Response Letter 10/24/08
Labeling	
❖ Package Insert *(write submission/communication date at upper right of first page of PI)*	
• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	• 03/22/2011 • 10/23/2009 12/20/2007
• Example of class labeling, if applicable	

[3] Fill in blanks with dates of reviews, letters, etc.

❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling *(write submission/communication date at upper right of first page of each piece)*	☒ Medication Guide ☐ Patient Package Insert ☒ Instructions for Use ☐ Device Labeling ☐ None
• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.	
• Original applicant-proposed labeling	3/22/2011 MG &PIU Included 10/23/2009 MG & PIU Included 12/20/2007 PIU Included
• Example of class labeling, if applicable	
❖ Labels (**full color** carton and immediate-container labels) *(write submission/communication date on upper right of first page of each submission)*	
• Most-recent draft labeling	N/A
❖ Proprietary Name • Acceptability/non-acceptability letter(s) *(indicate date(s))* • Review(s) *(indicate date(s))*	N/A
❖ Labeling reviews *(indicate dates of reviews and meetings)*	☐ RPM 3/3/2008 ☐ DMEPA ☒ DRISK 3/9/2010 & 3/11/2010 ☒ DDMAC 3/4/2010, 1/14/2010 & 10.20.08 (Cancer), 3/4/2010 & 1/14/2010 (DHP), 3/4/2010 & 1/14/2010 (MG) ☐ CSS ☒ Other reviews 2/18/2010 (SEALD), 2/1/2010 (Peds), 3.2.2010(MHT), 3.30.10 (OBP)
Administrative / Regulatory Documents	
❖ Administrative Reviews *(e.g., RPM Filing Review[4]/Memo of Filing Meeting) (indicate date of each review)* ❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte ❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment *(indicate date)*	2/11/2008 RPM Filing Review/Memo of Filing Meetin ☒ Not a (b)(2) ☐ Not a (b)(2)
❖ NDAs only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP o If yes, Center Director's Exception for Review memo *(indicate date)* o If yes, OC clearance for approval *(indicate date of clearance communication)*	☐ Yes ☒ No ☐ Not an AP action
❖ Pediatrics *(approvals only)* • Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____ • Pediatric Page/Record *(approvals only, must be reviewed by PERC before*	☒ Included

[4] Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

finalized)	
❖ 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 *(include certification)*	☐ Verified, statement is acceptable
❖ Outgoing communications *(letters (except action letters), emails, faxes, telecons)*	❖ 6/15/11 Meeting Summary ❖ 6/15/11 FDA Proposed Change ❖ 6/6/11 FDA Proposed Change ❖ 6/5/11 FDA Proposed Change ❖ 6/2/11 Meeting Summary ❖ 6/1/11 Meeting Summary ❖ 5/31/11 Meeting Summary ❖ 5/31/11 FDA Advice ❖ 5/19/11 FDA Advice ❖ 5/18/11 FDA Advice ❖ 5/6/11 Meeting Summary ❖ 5/6/2011 FDA Proposed Changes ❖ 5/6/2011 FDA Proposed Changes ❖ 5/6/11 FDA Email Communication ❖ 4/26/11 FDA Proposed Changes ❖ 4/6/11 Acknowledgement Letter ❖ 3/16/11 Revised labeling email ❖ 3/3/11 FDA Advice ❖ 2/23/11 Meeting Summary ❖ 1/19/11 Revised PI & MG ❖ 12/9/10 Mtg Summary ❖ 3/25/10 Meeting Summary of 3/24/10 and 3/25/10 telecon w/ Amgen ❖ 3/10/2010 Revised PI, MG, & PIU email ❖ 3/4/2010 Revised MG email ❖ 2/22/2010 Revised PI email ❖ 12/9/10 Mtg Summary ❖ 11/10/2009 Acknowledgement letter ❖ 2/13/2009 FDA Draft Responses for 2/17/2009 Type A Meeting ❖ 8/19/2008 Information Request letter ❖ 4/24/08 74-Day Letter ❖ 3/7/2008 74-Day Letter ❖ 2/21/2008 60-Day Letter ❖ 2/01/2008 Acknowledgement Letter ❖ 9/7/2007 Information Request

	Letter 5/31/2007 Information Request Letter
❖ Internal memoranda, telecons, etc.	❖ ❖ 5/31/11 Internal Meeting ❖ 5/26/11 Internal Meeting ❖ 5/26/11 Internal Meeting ❖ 5/6/11 Int Mtg Summary ❖ 4/27/11 Internal Meeting ❖ 4/26/11 Internal Meeting ❖ 4/5/11 Planning Meeting ❖ 1/11/11 Meeting Summary ❖ 3/17/2010 Wrap-Up Meeting ❖ 1/19/2010 Mid-Cycle Meeting ❖ 11/9/2009 First Committee Meeting ❖ 1/28/2008 First Committee Meeting ❖ 10/25/2007 Meeting Summary of 10/19/2007 telecon Meeting Summary of 9/25/2007 telecon
❖ Minutes of Meetings	
• Regulatory Briefing *(indicate date of mtg)*	☒ No mtg
• If not the first review cycle, any end-of-review meeting *(indicate date of mtg)*	☒ N/A or no mtg
• Pre-NDA/BLA meeting *(indicate date of mtg)*	☐ No mtg July 25, 2007
• EOP2 meeting *(indicate date of mtg)*	☐ No mtg
• Other milestone meetings (e.g., EOP2a, CMC pilots) *(indicate dates of mtgs)*	
❖ Advisory Committee Meeting(s)	☐ No AC meeting
• Date(s) of Meeting(s)	9/7/07 & 5/31/07
• 48-hour alert or minutes, if available *(do not include transcript)*	
Decisional and Summary Memos	
❖ Office Director Decisional Memo *(indicate date for each review)*	☒ None
Division Director Summary Review *(indicate date for each review)*	☐ None 6/24/11,4/27/2010, 10/24/2008
Cross-Discipline Team Leader Review *(indicate date for each review)*	☐ None
PMR/PMC Development Templates *(indicate total number)*	☐ None
Clinical Information[5]	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) *(indicate date for each review)*	
• Clinical review(s) *(indicate date for each review)*	5/16/2011 DHP Review w/secondary concurrence 4/22/2011 DBOP Review w/secondary concurrence

[5] Filing reviews should be filed with the discipline reviews.

	3/22/2010 DBOP Review 3/10/2010 DHP Review w/secondary concurrence 10/23/2008 DBOP Review w/secondary concurrence 10/20/2008 DMIHP Review 2/11/08 Filing Review
• Social scientist review(s) (if OTC drug) *(indicate date for each review)*	☐ None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here ☐ and include a review/memo explaining why not *(indicate date of review/memo)*	Page 10 of clinical review dated 10/23/08
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers *(indicate date of each review)*	☒ None
❖ Controlled Substance Staff review(s) and Scheduling Recommendation *(indicate date of each review)*	☒ Not applicable
❖ Risk Management • REMS Documents and Supporting Statement *(indicate date(s) of submission(s))* • REMS Memo(s) and letter(s) *(indicate date(s))* • Risk management review(s) and recommendations (including those by OSE and CSS) *(indicate date of each review and indicate location/date if incorporated into another review)*	☐ None 6/21/11 6/9/11 w/ secondary concurrence 6/8/11 (secondary review) 5/9/11 with/secondary concurrence 4/20/2011 with/secondary concurrence1
❖ DSI Clinical Inspection Review Summary(ies) *(include copies of DSI letters to investigators)*	☒ None requested
Clinical Microbiology ☒ None	
❖ Clinical Microbiology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Microbiology Review(s) *(indicate date for each review)*	☐ None
Biostatistics ☐ None	
❖ Statistical Division Director Review(s) *(indicate date for each review)*	☐ None
Statistical Team Leader Review(s) *(indicate date for each review)*	☐ None
Statistical Review(s) *(indicate date for each review)*	☐ None 3/18/2010 with secondary concurrence, 10/17/08 w/secondary concurrence, 10/16/2008 w/secondary concurrence, 2/11/08
Clinical Pharmacology ☐ None	
❖ Clinical Pharmacology Division Director Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology Team Leader Review(s) *(indicate date for each review)*	☐ None
Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None 2/4/2010 with secondary concurrence & 10/20/2008 with secondary concurrence 2/15/08 Filing Review
❖ DSI Clinical Pharmacology Inspection Review Summary *(include copies of DSI letters)*	☐ None

Nonclinical ☐ None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) *(indicate date for each review)*	☐ None
• Supervisory Review(s) *(indicate date for each review)*	☐ None
• Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	☐ None 3/24/2010 (with secondary concurrence) & 10/20/2008 with secondary cocnurrence (Cancer) 3/25/2010 with secondary concurrence & 10/20/2008 with secondary concurrence (Renal)
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer *(indicate date for each review)*	☒ None
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	☒ No carc
❖ ECAC/CAC report/memo of meeting	☒ None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary *(include copies of DSI letters)*	☒ None requested
Product Quality ☐ None	
❖ Product Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) *(indicate date for each review)*	☐ None
• Branch Chief/Team Leader Review(s) *(indicate date for each review)*	☐ None
• Product quality review(s) including ONDQA biopharmaceutics reviews *(indicate date for each review)*	☐ None 6/15/11 10/17/08 with secondary concurrence
❖ Microbiology Reviews ☐ NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) *(indicate date of each review)* ☐ BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) *(indicate date of each review)*	☒ Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer *(indicate date of each review)*	☐ None
❖ Environmental Assessment (check one) (original and supplemental applications)	
☒ Categorical Exclusion *(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)*	10/17/2008 CMC Review
☐ Review & FONSI *(indicate date of review)*	
☐ Review & Environmental Impact Statement *(indicate date of each review)*	

❖ Facilities Review/Inspection	
☐ NDAs: Facilities inspections (include EER printout) *(date completed must be within **2 years** of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites[6])*	Date completed: ☐ Acceptable ☐ Withhold recommendation ☐ Not applicable
☒ BLAs: TB-EER *(date of most recent TB-EER must be within **30 days** of action date) (original and supplemental BLAs)*	Date completed: 5/27/2011 ☒ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation *(check box only, do not include documents)*	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed (per review)

[6] I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix 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.