

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**103234Orig1s5166**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

# PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

BLA #: 103234 Supplement Type (e.g. SE5): Efficacy Supplement Number: 5166

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

HFD-107 Trade and generic names/dosage form: Epoetin alfa (Epoegen/Procrit)/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.  
 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.

**Section 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:

BLA 103234/5166

Page 3

*There are additional indications, please proceed to Attachment A. 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 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)**

## DEBARMENT CERTIFICATION

### PROCRIT<sup>®</sup> (epoetin alfa)

Johnson & Johnson Pharmaceutical Research & Development, L.L.C. certifies that we 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.

This certification applies to the EPO-INT-76 and EPO-CAN-15 studies. These studies were conducted during and after the submission of the previous two efficacy supplemental BLAs for three times weekly (30 July 1992) and once weekly dosing (29 August 2003). These supplements contained debarment certifications for the other studies referenced in this supplement.

Robyn Sterner, Pharm.D.

Robyn Sterner, Pharm.D.  
Senior Director  
Regulatory Affairs

16-Oct-07

16 October 2007

# ACTION PACKAGE CHECKLIST

## APPLICATION INFORMATION<sup>1</sup>

NDA # BLA # 103234	NDA Supplement # BLA STN # 5166	If NDA, Efficacy Supplement Type:
Proprietary Name: Epogen Established/Proper Name: epoetin alfa Dosage Form: injection		Applicant: Amgen, Inc. Agent for Applicant (if applicable):
RPM: Mona Patel		Division: DBOP/OODP
<p><b>NDA:</b>                  NDA Application Type: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)                  Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>                  Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature.  <input type="checkbox"/> This application relies on a final OTC monograph.  <input type="checkbox"/> Other (explain)</p> <p><b><u>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.</u></b></p> <p><b><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></b></p> <p><input type="checkbox"/> No changes    <input type="checkbox"/> Updated    Date of check:</p> <p><b>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.</b></p>
❖ <b>Actions</b>		
<ul style="list-style-type: none"> <li>• Proposed action</li> <li>• User Fee Goal Date is <u>May 23, 2011</u></li> </ul>		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR
<ul style="list-style-type: none"> <li>• Previous actions (<i>specify type and date for each action taken</i>)</li> </ul>		<input type="checkbox"/> None    CR 4/27/2010 CR 10/24/2008

<sup>1</sup> 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.

<p>❖ 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 <a href="http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf">http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf</a>). If not submitted, explain _____</p>	<p><input type="checkbox"/> Received</p>
<p>❖ Application Characteristics<sup>2</sup></p>	
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority                  Chemical classification (new NDAs only):</p> <p><input type="checkbox"/> Fast Track <input type="checkbox"/> Rx-to-OTC full switch  <input type="checkbox"/> Rolling Review <input type="checkbox"/> Rx-to-OTC partial switch  <input type="checkbox"/> Orphan drug designation <input type="checkbox"/> Direct-to-OTC</p> <p>NDA: Subpart H <span style="margin-left: 200px;">BLAs: Subpart E</span>  <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <span style="margin-left: 100px;"><input type="checkbox"/> Accelerated approval (21 CFR 601.41)</span>  <input type="checkbox"/> Restricted distribution (21 CFR 314.520) <span style="margin-left: 100px;"><input type="checkbox"/> Restricted distribution (21 CFR 601.42)</span></p> <p>Subpart I <span style="margin-left: 200px;">Subpart H</span>  <input type="checkbox"/> Approval based on animal studies <span style="margin-left: 100px;"><input type="checkbox"/> Approval based on animal studies</span></p> <p><input type="checkbox"/> Submitted in response to a PMR <span style="margin-left: 200px;">REMS: <input checked="" type="checkbox"/> MedGuide</span>  <input type="checkbox"/> Submitted in response to a PMC <span style="margin-left: 100px;"><input checked="" type="checkbox"/> Communication Plan</span>  <input type="checkbox"/> Submitted in response to a Pediatric Written Request <span style="margin-left: 100px;"><input type="checkbox"/> ETASU</span>  <span style="margin-left: 400px;"><input type="checkbox"/> REMS not required</span></p> <p>Comments:</p>	
<p>❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)</p>	<p><input checked="" type="checkbox"/> Yes, dates 6/27/2011</p>
<p>❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)</p>	<p><input type="checkbox"/> Yes <input checked="" type="checkbox"/> No</p>
<p>❖ Public communications (<i>approvals only</i>)</p>	
<p>• Office of Executive Programs (OEP) liaison has been notified of action</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Press Office notified of action (by OEP)</p>	<p><input checked="" type="checkbox"/> Yes <input type="checkbox"/> No</p>
<p>• Indicate what types (if any) of information dissemination are anticipated</p>	<p><input type="checkbox"/> None  <input type="checkbox"/> HHS Press Release  <input type="checkbox"/> FDA Talk Paper  <input type="checkbox"/> CDER Q&amp;As  <input type="checkbox"/> Other</p>

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

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

Answer the following questions for each paragraph IV certification:

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

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

Yes  No

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

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

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes    <input type="checkbox"/> No</p>
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**CONTENTS OF ACTION PACKAGE**

❖ Copy of this Action Package Checklist <sup>3</sup>	Included
<b>Officer/Employee List</b>	
❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list ( <i>approvals only</i> )	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included
<b>Action Letters</b>	
❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Complete Response Letter 4/27/2010 Complete Response Letter 10/24/08
<b>Labeling</b>	
❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
<ul style="list-style-type: none"> <li>• Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	3/22/2011 10/23/2009 12/20/2007
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.

<ul style="list-style-type: none"> <li>❖ Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)</li> </ul>	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input checked="" type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format.</li> </ul>	
<ul style="list-style-type: none"> <li>• Original applicant-proposed labeling</li> </ul>	3/22/2011 MG & PIU Included 10/23/2009 MG & PIU Included 12/20/2007 PIU Included
<ul style="list-style-type: none"> <li>• Example of class labeling, if applicable</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Labels (<b>full color</b> carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Most-recent draft labeling</li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Proprietary Name               <ul style="list-style-type: none"> <li>• Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>)</li> <li>• Review(s) (<i>indicate date(s)</i>)</li> </ul> </li> </ul>	N/A
<ul style="list-style-type: none"> <li>❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)</li> </ul>	<input type="checkbox"/> RPM 3/5/2008 <input type="checkbox"/> DMEPA <input type="checkbox"/> DRISK 3/25/2010, 3/15/2010 <input checked="" type="checkbox"/> DDMAC 3/17/2010, 1/14/2010 & 10.20.08 (Cancer), 3/16/2010 & 1/14/2010 (DHP), 3/16/2010 & 1/14/2010 (MG) <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews 3/2/2010 & 10/14/2008 (SEALD), 2/1/2010 (Peds), 3.1.2010 & 10.22.2008 (MHT), 3/30/10 (OBP)
<b>Administrative / Regulatory Documents</b>	
<ul style="list-style-type: none"> <li>❖ Administrative Reviews (<i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)</li> </ul>	2/11/2008 RPM Filing Review/Memo of Filing Meetin
<ul style="list-style-type: none"> <li>❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte</li> <li>❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)</li> </ul>	<input checked="" type="checkbox"/> Not a (b)(2) <input type="checkbox"/> Not a (b)(2)
<ul style="list-style-type: none"> <li>❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)</li> </ul>	<input type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Application Integrity Policy (AIP) Status and Related Documents <a href="http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm">http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</a></li> </ul>	
<ul style="list-style-type: none"> <li>• Applicant is on the AIP</li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> <li>• This application is on the AIP               <ul style="list-style-type: none"> <li>○ If yes, Center Director's Exception for Review memo (<i>indicate date</i>)</li> <li>○ If yes, OC clearance for approval (<i>indicate date of clearance communication</i>)</li> </ul> </li> </ul>	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No  <input type="checkbox"/> Not an AP action

<sup>4</sup> Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

<ul style="list-style-type: none"> <li>❖ Pediatrics (<i>approvals only</i>)             <ul style="list-style-type: none"> <li>• Date reviewed by PeRC _____ If PeRC review not necessary, explain: _____</li> <li>• Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>)</li> </ul> </li> </ul>	<input checked="" type="checkbox"/> Included
<ul style="list-style-type: none"> <li>❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)</li> </ul>	<input type="checkbox"/> Verified, statement is acceptable
<ul style="list-style-type: none"> <li>❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)</li> </ul>	<ul style="list-style-type: none"> <li>❖ 6/15/11 Meeting Summary</li> <li>❖ 6/15/11 FDA Proposed Change</li> <li>❖ 6/6/11 FDA Proposed Change</li> <li>❖ 6/5/11 FDA Proposed Change</li> <li>❖ 6/2/11 Meeting Summary</li> <li>❖ 6/1/11 Meeting Summary</li> <li>❖ 5/31/11 Meeting Summary</li> <li>❖ 5/31/11 FDA Advice</li> <li>❖ 5/19/11 FDA Advice</li> <li>❖ 5/18/11 FDA Request</li> <li>❖ 5/6/11 Meeting Summary</li> <li>❖ 5/6/11 FDA Proposed Changes</li> <li>❖ 5/6/11 FDA Proposed Changes</li> <li>❖ 4/26/11 FDA Proposed Changes</li> <li>❖ 4/6/11 Acknowledgement Letter</li> <li>❖ 3/16/11 Revised labeling email</li> <li>❖ 3/3/11 FDA Advice</li> <li>❖ 2/23/2011 Meeting Summary</li> <li>❖ 2/16/11 Revised PI &amp; MG</li> <li>❖ 1/19/11 Revised PI &amp; MG</li> <li>❖ 12/9/2010 Meeting Summary of Amgen telecon</li> <li>❖ 3/10/2010 Revised PI email</li> <li>❖ 3/4/2010 Revised MG email</li> <li>❖ 3/3/2010 Revised PI email</li> <li>❖ 11/10/2009 Acknowledgement letter</li> <li>❖ 2/13/2009 FDA Draft Responses for 2/17/2009 Type A Meeting</li> <li>❖ 10/9/2008 Revised labeling email</li> <li>❖ 5/28/2008 Information Request letter</li> <li>❖ 3/7/2008 74-Day Letter</li> <li>❖ 2/21/2008 60-Day Letter</li> <li>2/01/2008 Acknowledgement Letter</li> <li>Meeting Summary of 9/25/2007 telecon</li> <li>10/25/2007 Meeting Summary of 10/19/2007 telecon</li> </ul>

<ul style="list-style-type: none"> <li>❖ Internal memoranda, telecons, etc.</li> </ul>	<ul style="list-style-type: none"> <li>❖</li> <li>❖ 5/31/11 Internal Meeting</li> <li>❖ 5/26/11 Internal Meeting</li> <li>❖ 5/26/11 Internal Meeting</li> <li>❖ 5/6/11 Internal Meeting</li> <li>❖ 4/27/11 Internal Meeting</li> <li>❖ 4/26/11 Internal Meeting</li> <li>❖ 4/5/11 Planning Meeting</li> <li>❖ 1/11/11 Internal meeting</li> <li>❖ 3/17/2010 Wrap-Up Meeting</li> <li>❖ 1/19/2010 Mid-Cycle Meeting</li> <li>❖ 11/9/2009 First Committee Meeting</li> <li>❖ 1/28/2008 First Committee Meeting</li> <li>❖</li> </ul>
<ul style="list-style-type: none"> <li>❖ Minutes of Meetings</li> </ul>	
<ul style="list-style-type: none"> <li>• Regulatory Briefing (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)</li> </ul>	<input checked="" type="checkbox"/> N/A or no mtg
<ul style="list-style-type: none"> <li>• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg July 25, 2007
<ul style="list-style-type: none"> <li>• EOP2 meeting (<i>indicate date of mtg</i>)</li> </ul>	<input type="checkbox"/> No mtg
<ul style="list-style-type: none"> <li>• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>❖ Advisory Committee Meeting(s)</li> </ul>	<input type="checkbox"/> No AC meeting
<ul style="list-style-type: none"> <li>• Date(s) of Meeting(s)</li> </ul>	9/7/07 & 5/31/07
<ul style="list-style-type: none"> <li>• 48-hour alert or minutes, if available (<i>do not include transcript</i>)</li> </ul>	
<b>Decisional and Summary Memos</b>	
<ul style="list-style-type: none"> <li>❖ Office Director Decisional Memo (<i>indicate date for each review</i>)</li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>• Division Director Summary Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None 6/24/11,4/27/2010, 10/24/2008
<ul style="list-style-type: none"> <li>• Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)</li> </ul>	<input type="checkbox"/> None
<ul style="list-style-type: none"> <li>• PMR/PMC Development Templates (<i>indicate total number</i>)</li> </ul>	<input type="checkbox"/> None
<b>Clinical Information<sup>5</sup></b>	
<ul style="list-style-type: none"> <li>❖ Clinical Reviews</li> </ul>	
<ul style="list-style-type: none"> <li>• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)</li> </ul>	
<ul style="list-style-type: none"> <li>• Clinical review(s) (<i>indicate date for each review</i>)</li> </ul>	5/16/2011 DHP Review w/secondary concurrence 4/22/2011 DBOP Review w/secondary concurrence 3/22/2010 DBOP Review 3/10/2010 DHP Review w/secondary concurrence 10/23/2008 DBOP Review

<sup>5</sup> Filing reviews should be filed with the discipline reviews.

	w/secondary concurrence 10/20/2008 DMIHP Review 4/22/08 Filing Review
<ul style="list-style-type: none"> <li>Social scientist review(s) (if OTC drug) <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not <i>(indicate date of review/memo)</i></li> </ul>	Page 7 of clinical review dated 10/23/08
<ul style="list-style-type: none"> <li>❖ Clinical reviews from immunology and other clinical areas/divisions/Centers <i>(indicate date of each review)</i></li> </ul>	<input checked="" type="checkbox"/> None
<ul style="list-style-type: none"> <li>❖ Controlled Substance Staff review(s) and Scheduling Recommendation <i>(indicate date of each review)</i></li> </ul>	<input checked="" type="checkbox"/> Not applicable
<ul style="list-style-type: none"> <li>❖ Risk Management                             <ul style="list-style-type: none"> <li>REMS Documents and Supporting Statement <i>(indicate date(s) of submission(s))</i></li> <li>REMS Memo(s) and letter(s) <i>(indicate date(s))</i></li> <li>Risk management review(s) and recommendations (including those by OSE and CSS) <i>(indicate date of each review and indicate location/date if incorporated into another review)</i></li> </ul> </li> </ul>	<input type="checkbox"/> 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 concurrence
<ul style="list-style-type: none"> <li>❖ DSI Clinical Inspection Review Summary(ies) <i>(include copies of DSI letters to investigators)</i></li> </ul>	<input checked="" type="checkbox"/> None requested
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Microbiology Team Leader Review(s) <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None
Clinical Microbiology Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Statistical Division Director Review(s) <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None
Statistical Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Statistical Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 3/26/2010 with secondary concurrence 10/16/2008 with secondary concurrence, 2/11/08 Filing Review
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
<ul style="list-style-type: none"> <li>❖ Clinical Pharmacology Division Director Review(s) <i>(indicate date for each review)</i></li> </ul>	<input type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None
Clinical Pharmacology review(s) <i>(indicate date for each review)</i>	<input type="checkbox"/> None 2/4/2010 with secondary concurrence & 10/20/2008 with secondary concurrence, 2/15/08 Filing Review
<ul style="list-style-type: none"> <li>❖ DSI Clinical Pharmacology Inspection Review Summary <i>(include copies of DSI letters)</i></li> </ul>	<input type="checkbox"/> None

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

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

<sup>6</sup> 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.



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## 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**

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**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

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**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

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**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

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**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 Page(s) of Draft REMS has been Withheld in Full  
immediately following this page as B4 (CCI/TS)

**Patel, Mona**

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**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



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**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 Page(s) of Draft REMS has been Withheld in Full immediately following this page as B4 (CCI/TS)

**Patel, Mona**

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**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)



6/6/2011



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## 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,



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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.



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## 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.



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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



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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.



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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.

**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

6/1/2011

**Response to comment 1**

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

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

**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.

## Patel, Mona

---

**From:** Ramanadham, Mahesh  
**Sent:** Friday, May 27, 2011 4:12 PM  
**To:** Patel, Mona; CDER-TB-EER; Pohlhaus, Timothy  
**Cc:** Keegan, Patricia; Jones, Karen  
**Subject:** RE: Urgent Re-Request: Complete Response Resubmission: TB EER Requests: Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

**Attachments:** STN 103234s5166 final.doc

Dear Mona,

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for STN 103234/5166. Please see the attached form for individual site compliance statuses. Although the compliance status of AML Puerto Rico is initially OAI, NGDMT does not feel that the nature of the deficiencies at this firm affect the approvability of the supplement. There are no pending or ongoing compliance actions that prevent approval of this supplement.



STN 103234s5166  
final.doc (36 ...)

Sincerely,

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

---

**From:** Patel, Mona  
**Sent:** Friday, May 27, 2011 10:13 AM  
**To:** CDER-TB-EER; Pohlhaus, Timothy  
**Cc:** Keegan, Patricia; Jones, Karen  
**Subject:** Urgent Re-Request: Complete Response Resubmission: TB EER Requests: Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

Hello,

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

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

Mona

---

**From:** CDER-TB-EER  
**Sent:** Friday, April 22, 2011 11:50 AM  
**To:** Patel, Mona; Pohlhaus, Timothy  
**Cc:** CDER-TB-EER  
**Subject:** RE: Complete Response Resubmission: TB EER Requests: Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-

EER below. Please see the attached form to find the current compliance status of each facility. There are no pending or ongoing compliance actions that would prevent approval of STN 103234/5166 at this time.

<< File: STN 103234s5166 final.doc >>

Sincerely,

**Marisa Stock**

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

---

**From:** Patel, Mona  
**Sent:** Monday, April 18, 2011 11:56 AM  
**To:** Pohlhaus, Timothy  
**Cc:** CDER-TB-EER  
**Subject:** Complete Response Resubmission: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

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

The action due date is May 23, 2011.

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

Mona

---

**From:** Pohlhaus, Timothy  
**Sent:** Monday, March 29, 2010 12:50 PM  
**To:** Patel, Mona  
**Cc:** CDER-TB-EER; Pohlhaus, Timothy  
**Subject:** RE: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for Amgen, Inc.'s STN 103234/5166. Please see the attached response for the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of STN 103234/5166 at this time.

<< File: 103234-5166 TB-EER response.doc >>

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

## Patel, Mona

---

**From:** Patel, Mona  
**Sent:** Friday, May 27, 2011 10:13 AM  
**To:** CDER-TB-EER; Pohlhaus, Timothy  
**Cc:** Keegan, Patricia; Jones, Karen  
**Subject:** Urgent Re-Request: Complete Response Resubmission: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

**Attachments:** STN 103234s5166 final.doc; 103234-5166 TB-EER response.doc

Hello,

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

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

Mona

---

**From:** CDER-TB-EER  
**Sent:** Friday, April 22, 2011 11:50 AM  
**To:** Patel, Mona; Pohlhaus, Timothy  
**Cc:** CDER-TB-EER  
**Subject:** RE: Complete Response Resubmission: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER below. Please see the attached form to find the current compliance status of each facility. There are no pending or ongoing compliance actions that would prevent approval of STN 103234/5166 at this time.



STN 103234s5166  
final.doc (37 ...)

Sincerely,

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

---

**From:** Patel, Mona  
**Sent:** Monday, April 18, 2011 11:56 AM  
**To:** Pohlhaus, Timothy  
**Cc:** CDER-TB-EER  
**Subject:** Complete Response Resubmission: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

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

The action due date is May 23, 2011.

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

Mona

---

**From:** Pohlhaus, Timothy  
**Sent:** Monday, March 29, 2010 12:50 PM

**To:** Patel, Mona  
**Cc:** CDER-TB-EER; Pohlhaus, Timothy  
**Subject:** RE: TB EER Requests:Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for Amgen, Inc.'s STN 103234/5166. Please see the attached response for the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of STN 103234/5166 at this time.



103234-5166  
B-EER response.do.

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



DEPARTMENT OF HEALTH AND HUMAN SERVICES  
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Center for Drug Evaluation and Research

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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

---

**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.



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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.

**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 L...

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 7<sup>th</sup> 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 PROCIT 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.

5/18/2011

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 22<sup>nd</sup>.

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: (b) (6)  
[adang@amgen.com](mailto: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 voicemail. 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](mailto:mona.patel@fda.hhs.gov) (email)  
Please consider the environment before printing this e-mail

5/18/2011

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 *[Signature]* 5/16/2011  
SUBJECT: PLR label conversion with edits to CKD section  
Via: Robert Kane, MD, Medical Officer; Division of Hematology Products, OODP; CDER *[Signature]* 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.

2.

(b) (4)

3. [Redacted] (b) (4)  
4. [Redacted]

[Redacted] (b) (4)

-----

## Patel, Mona

---

**From:** Patel, Mona  
**Sent:** Friday, May 06, 2011 3:56 PM  
**To:** '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 ... :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)



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**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](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

6/6/2011

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

Hi Mona,

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

Teleconference Information:

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

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 8<sup>th</sup> (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]

6/6/2011

**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  
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6/6/2011



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Public Health Service  
Food and Drug Administration  
Center for Drug Evaluation and Research

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## 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



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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.



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Memorandum

**Date:** May 6, 2011

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

**Subject:** STN BL 103234/5266 (5166) and 103951/5258 (5173): Internal meeting to determine path for Amgen to submit REMS modifications in light of April 22, 2011 email from Amgen

---

**FDA Attendees:**

Mona Patel-DBOP  
Grace Carmouze-DBOP  
Kaushik Shastri-DBOP  
Jeff Summers-DBOP  
Patricia Keegan-DBOP  
Karen Jones-DBOP  
Suzanne Berkman-OSE  
Claudia Karwoski-OSE  
Amarilys Vega-OSE

---

The purpose of this internal team meeting was to determine path for Amgen to submit REMS modifications

**Discussion:** The team reviewed the proposal submitted by Amgen, discussed path forward, and agreed with proposed changes.



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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  
**Date:** 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.

na



FDA Proposed  
Changes Epogen MG



FDA Proposed  
Changes Epogen PI



FDA Proposed  
Changes Procrit M



FDA Proposed  
Changes Procrit P



FDA Proposed  
Changes Aranesp M



FDA Proposed  
Changes Aranesp P



FDA Proposed  
Changes Aranesp P



FDA Proposed  
Changes Aranesp P



FDA Proposed  
Change Aranesp PI



FDA Proposed  
Changes Epogen PI

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Center for Drug Evaluation and Research

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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.

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**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.

**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:** 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.

6/1/2011

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

**Patel, Mona**

---

**From:** Patel, Mona  
**Sent:** Monday, April 18, 2011 11:56 AM  
**To:** Pohlhaus, Timothy  
**Cc:** CDER-TB-EER  
**Subject:** Complete Response Resubmission: TB EER Requests: Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

**Attachments:** 103234-5166 TB-EER response.doc

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

The action due date is May 23, 2011.

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

Mona

---

**From:** Pohlhaus, Timothy  
**Sent:** Monday, March 29, 2010 12:50 PM  
**To:** Patel, Mona  
**Cc:** CDER-TB-EER; Pohlhaus, Timothy  
**Subject:** RE: TB EER Requests: Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for Amgen, Inc.'s STN 103234/5166. Please see the attached response for the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of STN 103234/5166 at this time.



103234-5166  
B-EER response.do.

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



Our STN: BL 103234/5166

**ACKNOWLEDGE COMPLETE RESPONSE**

Amgen, Incorporated  
Attention: Annie Dang, J.D.  
Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop: 17-2-B  
Thousand Oaks, CA 91320

April 6, 2011

Dear Mrs. Dang:

We have received your March 22, 2011, resubmission to your biologics license application for Epopro/Procrit (epoetin 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

**Patel, Mona**

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**From:** Patel, Mona  
**Sent:** 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



FDA Proposed



FDA Proposed



FDA Proposed



FDA Proposed



FDA Proposed



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  
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Patel, Mona

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**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  
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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. [REDACTED] (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**

---

**From:** Patel, Mona  
**Sent:** Wednesday, February 16, 2011 12:31 PM  
**To:** Dang, Annie  
**Cc:** Shamon-Taylor, Lisa; Ali Ibrahim, Ebla  
**Subject:** Epogen PI & MG: PLR (STN 103234.5166)

**Attachments:** Epogen MG 2.16.11.doc; Epogen PI 2 16 11.doc; Epogen-FDA Response (DHP) 2.16.11.doc

Annie,

DBOP and DHP have finished reviewing the ESA PI and MG, and I have attached them here with an accompanying DHP rationale for you to consider. We are requesting a response from you by 12:30pm EST, Wednesday, February 23, 2011.

Please make parallel changes to Aranesp labeling.

Please acknowledge receipt.

Mona



Epogen MG

2.16.11.doc (98 KB)



Epogen PI 2 16

11.doc (442 KB)...



Epogen-FDA

Response (DHP) 2.16

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  
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## 2. Cross-Indication Proposals

### 2.1 Limitations of Use

*Epogen/PROCRIT (1.5) and Aranesp (1.3)*

Amgen/J&JPRD proposal

[ESA] has not been shown (b) (4)-to improve- (b) (4) quality of life, fatigue, or patient well-being.

#### **FDA Response:**

**DHP accepts your changes except for your proposal to change the word “shown” to (b) (4). DHP prefers the word “shown” because it clearly and simply expresses the point being made. (b) (4) is not as well understood by users of the PI.**

### 2.2 Patent Statement

*Epogen/PROCRIT and Aranesp*

Amgen/J&JPRD proposal

*Aranesp: This product, the process of its manufacture, or its use, may be covered by one or more U.S. Patents, including U.S. Patent No. 7,217,689.*

*Epogen/PROCRIT: This product, the process of its manufacture, or its use, may be covered by one or more U.S. Patents, including U.S. Patent No. 5,441,868; 5,547,933; 5,618,698; 5,756,349; and 5,955,422.*

#### **FDA Response:**

**DHP does not object.**

3. (b) (4)

3.1 INDICATIONS AND USAGE, (b) (4)  
*Epogen/PROCRIT (1.1)*

Amgen/J&JPRD proposal

(b) (4)

**FDA Response:**

In regard to your proposal to retain (b) (4)  
to the Epogen label is not acceptable. (b) (4)

**3.2 DOSAGE AND ADMINISTRATION, Preparation and Administration**

*Epogen/PROCRIT (2.6)*

Amgen/J&JPRD Proposal

Do not dilute. Do not mix with other drug solutions **except for admixing as described below:**

Preservative-free Epogen from single-use vials may be admixed in a syringe with bacteriostatic 0.9% sodium chloride injection, USP, with benzyl alcohol 0.9% (bacteriostatic saline) in a 1:1 ratio using aseptic technique at the time of administration, (b) (4). Risks are associated with benzyl alcohol in neonates, infants, pregnant women, and nursing mothers [see *Use in Specific Populations (8.1, 8.3, 8.4)* (b) (4)].

**FDA Response:**

The claim ,... (b) (4) is not supported by substantial evidence of safety and efficacy. Therefore it should be removed.

**3.3 CLINICAL STUDIES, Chronic Renal Failure Patients**

*Epogen/PROCRIT (14.1)*

FDA 27 April 2010 proposal

(b) (4)

Amgen/J&JPRD Proposal

The Companies agree to FDA's deletion of the above paragraph from the Clinical Studies section with the exception of the phrase [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

**FDA Response:**

**In regard to your proposal to retain the sentence [REDACTED] (b) (4)**

[REDACTED]  
[REDACTED] **is not acceptable. The sentence should not be retained.**

**Here is DHP's reason:**

[REDACTED] (b) (4)  
[REDACTED]

**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

---

**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 (b)(4) section, sent to us for the December 9, 2010 telecon 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 (b)(4) 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

3/2/2011

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](mailto:rmagavi@amgen.com)

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

(b) (4)

(b) (4)

## 2 Dosage and Admin (as revised by DHP in PLR format)

### 2.1 Evaluation of Iron Stores

Evaluate the iron status in all patients before and during treatment and maintain iron repletion. Correct or exclude other causes of anemia (e.g., vitamin deficiency, chronic inflammatory conditions, etc.) before initiating Aranesp [see *Warnings and Precautions (5.10)*].

### 2.2 Patients with Chronic Kidney Disease

[Redacted] (b) (4)

#### For patients with CKD not on dialysis:

[Redacted] (b) (4)

#### For patients with CKD on dialysis:

- The recommended starting dose is 0.45 mcg/kg intravenously or subcutaneously as a weekly injection or 0.75 mcg/kg once every 2 weeks. The intravenous route is recommended for patients on hemodialysis.

[Redacted] (b) (4)

When treating patients who have chronic kidney disease and cancer, physicians should refer to

**Warnings and Precautions:**

[see *Warnings and Precautions (5.1 and 5.3)*].



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

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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.

**December 9, 2010 Teleconference Discussion Points**

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

Oncology



(b) (4)



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

December 9, 2010

**Meeting:**  
**Date**

---

**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

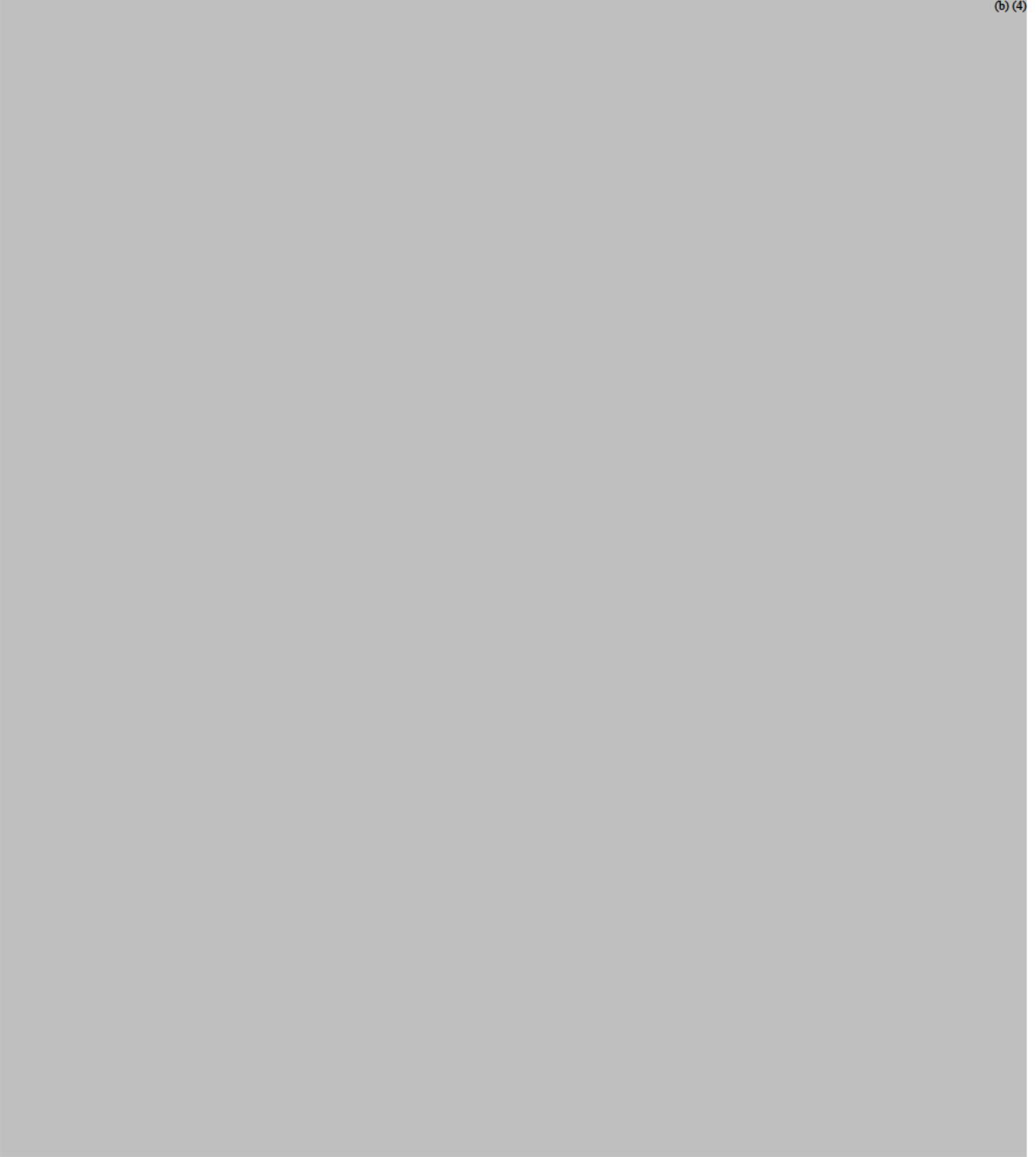
FDA requested a teleconference with Amgen to informally discuss the outstanding issues with the Aranesp and Epogen efficacy supplements submitted to FDA on December 20, 2007 and

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)



5.

6.

Call concluded.

## Patel, Mona

---

**From:** Patel, Mona  
**Sent:** Thursday, March 18, 2010 12:50 PM  
**To:** CDER-TB-EER  
**Subject:** TB EER Requests: Complete Response Resubmissions for PLR Supplements (Efficacy): Epogen (BL STN 103234/5166)

**Attachments:** Epogen BLA 103234.5166 (3.18.2010).doc; Epogen BLA 103234.5166 356h attachment.doc.pdf

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

The action due date is April 27, 2010.



Epogen BLA

03234.5166 (3.18..33234.5166 356h a.



Epogen BLA

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  
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**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**

---

**Subject:** FDA PROPOSED CHANGES March 10, 2010: & Epogen STN BL 103234/5166:

---

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

**Sent:** Wednesday, March 10, 2010 9:53 AM

**To:** Dang, Annie

**Subject:** FDA PROPOSED CHANGES March 10, 2010: & Epogen STN BL 103234/5166:

Annie,

Please find a clean version of the Epogen PI containing additional changes (tracked). Please integrate these FDA revisions of March 10, 2010 to the 3.3.2010 redlined Epogen PI we sent to you already.

Please confirm receipt of this email.

<<FDA Proposed Changes Epogen PI Clean 3.10.2010.doc>>

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

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3/10/2010

**Patel, Mona**

---

**Subject:** FW: MedGuide Attached: Epogen STN 103234/5166

**Attachments:** FDA Proposed Changes Epogen MedGuide Redline 3 4 2010.doc

---

**From:** Patel, Mona

**Sent:** Thursday, March 04, 2010 2:56 PM

**To:** 'Dang, Annie'

**Subject:** MedGuide Attached: Epogen STN 103234/5166

FDA's proposed changes to Epogen Medguide are attached. Please plan on providing your response to FDA by 2:30pm EST, Thursday, March 11, 2010

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

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**Patel, Mona**

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**From:** Patel, Mona  
**Sent:** Wednesday, March 03, 2010 4:26 PM  
**To:** Dang, Annie  
**Subject:** Epogen STN 103234/5166  
**Attachments:** FDA Proposed Changes Epogen PI Redline 3.3.2010.doc

Hi Annie,

Please see attached the revised label for Epogen Supplement 103234/5166 with FDA's proposed changes.

Please provide us with your comments by 3:30pm EST, Wednesday, March 10, 2010.

Thank you,

Mona



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  
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**FILE AMENDMENT**

**Amendment Date:** 02/02/2010

**PM:** Ebla Ali Ibrahim

**TO BLA:** 103234

**Submission Date:** 10/23/2009

**FDA Received Date:** 10/26/2009

**SDN / SN:** 103234/5166

**Network path in edr:** <\\cbsap58\M\leCTD\_Submissions\STN103234\103234.enx>

**FROM:** Saleh Ayache, MD, Medical Reviewer, Division of Imaging and Hematology Product

*[Signature]* 3/10/2010

**SUBJECT:** PLR prior approval supplement review for Epogen/Procrit for sponsor re-submission following CR Letter

**Via:** Robert Kane, MD, team leader, DDOP, OODP

*[Signature]* 3/10/2010

**BACKGROUND:** On October 23, 2009, Amgen resubmitted a revised Prior Approval Supplement for the physician labeling rule (PLR) conversion for Epogen/Procrit, in response to FDA's Complete Response Letter dated October 24, 2008. The original submission was reviewed by Dr. Minh-Ha Tran from DMIHP dated 10-20-2008.

**ISSUES:**

Amgen made the following changes to the 2008 FDA proposed label of Epogen/Procrit:



(b) (4)

**II. Boxed Warning: See the Box Warning in highlight sections**

**III. Label Sections:**

The sponsor made some changes in the instructions for hypo-responder patients as follow:

- Do not administer higher Epogen doses and (use the lowest dose that will ....)
- Evaluate and treat for other causes of anemia.
- Thereafter, hemoglobin should continue to be monitored and if responsiveness improves, Epogen dose adjustments should be made as described above.

The sponsor's reasoning for the additions are this language is in the current approved USPI and was generated in collaboration with the FDA after the 2007 CRDAC meeting.

- 2.3. Cancer Patients: *See Oncology Review.*
- 2.4. Zidovudine-treated HIV-infected Patients: No changes
- 2.5. Surgery Patients: No changes.
- 2.6. Preparation and Administration: *See CMC Review*

3. **DOSAGE FORMS AND STRENGTHS:**  
*See CMC Review.*

4. **CONTRAINDICATIONS:**  
Changes are already discussed in highlights section.

5. **WARNINGS AND PRECAUTIONS**

**5.8. Serious Allergic Reactions:** The sponsor added allergic bronchospasm to the serious allergic reactions.

**5.9. Albumin (Human):** (see CMC review)

**5.10.** (b) (4) The sponsor added this section.

**5.11. Dialysis Management:** No changes

**5.12. Laboratory Monitoring:** The statement regarding iron evaluation was moved (b) (4) to 5.11 where it is more appropriate.

**6. ADVERSE REACTIONS:**

**6.1. Clinical Trial Experience:**

- The sponsor added a paragraph under CRF in adult patients about the demographic of patients with CRF on dialysis. The sponsor's reason for this change is that there are some unique adverse events in patients with dialysis differ from that in patients not on dialysis.

- In Table 2 the sponsor made the following changes:

- Added arthralgia and muscle spasm.

There is no change in adverse reactions in pediatric patients.

6.3. Immunogenicity: No changes.

7. **DRUG INTERACTIONS:** (see *Clinical Pharmacology review*)

8. **USE IN SPECIFIC POPULATIONS:**

8.1. Pregnancy: (see *PMHT review*)

8.2.

8.3. Nursing Mothers: (see *PMHT review*).

8.4. Pediatric Use: (see *PMHT review*).

8.5. Geriatric Use: The sponsor added a new study results (PR97-19-002) to the 5 studies already in the current label. However the sponsor did not explain where derived that the total number of 4553 patients in 6 studies.

Study PR97-19-002: This was a Phase 4, open-label, randomized, parallel-group, multicenter study conducted to evaluate the incidence of deep vein thrombosis (DVT) in subjects receiving a peri-surgical regimen of epoetin alfa as compared to subjects receiving the standard of care (SOC) for blood conservation management. Subjects had to have hemoglobin of >10 g/dL and ≤13 g/dL at baseline.

9. if no change to this section – just state "no changes made"

10. **OVERDOSAGE:**

The sponsor deleted the (b) (4)

11. **DESCRIPTION:** (see *CMC review*)

12. **CLINICAL PHARMACOLOGY:** (see *Clinical Pharmacology review*)

13. **NONCLINICAL TOXICOLOGY:**

13.1. Carcinogenesis, Mutagenesis, Impairment of Fertility: (see *Nonclinical Pharmacology Review*)

13.2. Pharmacodynamics: (see *Pharmacology Review*)

13.3. Reproductive and Developmental Toxicology: (see *Nonclinical Pharmacology Review*)

14. **CLINICAL STUDIES:**

14.1. (b) (4) The sponsor added the following:

(b) (4)

(b) (4)

- Under Adult Patients on Dialysis: The sponsor added this statement

(b) (4)

(b) (4)

14.2. (b) (4) No changes.

14.3. (b) (4) (See DBOP Review)

14.4. Surgery Patients: No changes.

15.

16. HOW SUPPLIED/STORAGE AND HANDLING: (see CMC review)

**ACTIONS RECOMMENDED:** We recommend the following changes for Epogen/Procrit labels:

- 1- Change "events" back to reactions in Box Warning and in the Warning and Precautions sections.
- 2- Change this sentence [Patients experienced greater risks for death and serious cardiovascular events when administered erythropoiesis-stimulating agents (ESAs) to target higher versus lower hemoglobin levels (13.5 vs. 11.3 g/dL; 14 vs. 10 g/dL) in two clinical studies] with this [patients experienced greater risks for death, serious cardiovascular reactions, and stroke when erythropoiesis-stimulating agents (ESAs) were used to target hemoglobin levels of  $\geq 13$  g/dL and above].
- 3- Add that Epogen/Procrit is not indicated in patient undergoing cardiac surgery.
- 4- Add the Limitation of Use.
- 5- Keep our previous statement (b) (4) under the limitation of use.
- 6- Delete (b) (4) in CONTRAINDICATION section and add PRCA that begins after treatment with Epogen or other erythropoietin protein drugs instead.
- 7- Replace this statement (b) (4): If severe anemia and low reticulocyte count develop during Epogen treatment, withhold Epogen and evaluate for PRCA) in the WARNING AND PRECAUTIONS section.

- 8- Ask the sponsor to clarify and justify changes in the incidence of adverse reactions in the current label.
- 9- Change the dose adjustment description to start with dose reduction followed by the increase in dose.
- 10- Modified the instructions statement for hypo-responder patients as follow:



- 11- Delete [redacted] (b) (4)
- 12- Delete section [redacted] (b) (4)
- 13- Change [redacted] (b) (4) to porphyria under Postmarketing Experience (6.2).
- 14- The sponsor should provide explanation to changes in incidence rate of adverse reactions in Table 3 and table 5 from the current approved label.
- 15- The sponsor should clarify which 6 studies (with a total of 4553) included in geriatric section (8.5).
- 16- Retain the chronic overdosage statement in section (10).
- 17- The sponsor additions in regard to reduction of transfusion and the expected Hb increase under CRF in section (14.1) are acceptable.
- 18- The sponsor should quantify proportion of patients that experienced RBCs transfusion reduction while on dialysis in section (14.1) under CRF patients on dialysis.

**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.

Division of Drug Marketing,  
Advertising, and Communications

# Internal Consult

**\*\*\*Pre-decisional Agency Information\*\*\***

To: Mona Patel, Pharm.D., Regulatory Project Manager  
Division of Biologic Oncology Products (DBOP)  
Office of Oncology Drug Products

From: Carole C. Broadnax, R.Ph., Pharm.D. *CB 1/14/10*  
Division of Drug Marketing, Advertising and Communications, CDER

Date: January 14, 2010

Re: **Epogen/Procrit (epoetin alfa)**  
**STN BL 103234/5166**  
**Comments on draft product labeling**

---

In response to DBOP's Request for Consultation dated November 25, 2009, DDMAC has reviewed the draft product labeling (PI) sent by electronic mail from DBOP on January 11, 2010, for Epogen and offers the following comments. Please apply these comments to the draft Procrit labeling sent by electronic mail from DBOP on January 13, 2010, as the labeling changes for Epogen and Procrit are the same.

This draft product labeling converts the Epogen/Procrit PI into the Physician Labeling Rule format. The draft labeling also includes TREAT (Trial to Reduce Cardiovascular Events with Aranesp Therapy) study data.

These comments are limited to those sections of the draft PI that DBOP has responsibility for review based on the plan discussed at the pre-Mid-Cycle meeting on January 7, 2010.

Comments are included in the attached draft labeling.

23 Page(s) of Draft Labeling has been  
Withheld in Full immediately following this  
page as B4 (CCI/TS)



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration  
Silver Spring MD 20993

Our STN: BL 103234/5166

**ACKNOWLEDGE COMPLETE RESPONSE**

Amgen, Incorporated  
Attention: Annie Dang, J.D.  
Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop: 17-2-B  
Thousand Oaks, CA 91320

Nov 10 2009

Dear Mrs. Dang:

We have received your October 23, 2009, resubmission to your biologics license application for epoetin alfa (Epogen/Procrit) 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,

A handwritten signature in cursive script that reads "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 *ML*  
**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. Lanionu | 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 PROCRT:

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

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**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.

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## 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.

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## 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.



Our STN: BL 103234/5166

Amgen, Incorporated  
Attention: Neal Storm, M.S., M.B.A.  
Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop: 17-2-B  
Thousand Oaks, CA 91320

MAY 28 2008

Dear Mr. Storm:

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

We refer to STN BL 103234/5166, submitted December 20, 2007, and to the amendments submitted January 18, 2008, January 31, 2008, and April 23, 2008. Please note that the revised labeling submitted April 23, 2008, is still under review.

The clinical study reports for multiple studies are incomplete. We note that the appendices are missing. The appendices contain key information including, but not limited to, the clinical protocol, statistical analysis plan, case report forms, and data listings for all efficacy and safety endpoints. Without this information, a complete review of the study results cannot be conducted. Provide the missing information for the following studies, as requested during the April 30, 2008 meeting between Amgen representatives and the FDA:

1. For each study, provide study-specific datasets containing all primary data captured on case report forms associated with the study, provide copies of case report forms for all deaths and dropouts, and provide narrative summaries for each patient with a serious adverse event.
2. **Study I88-036, I87-018/OEO-U24, I87-019/OEO-U25 (Study MR-02685):** "A Double-Blind, Placebo-Controlled study to determine the safety and Efficacy of PROCIT, Administered Subcutaneously, in Patients with Anemia Secondary to Advanced Cancer and Cisplatin Chemotherapy"
  - a. Provide the Appendices 1 through 30 to the unified Clinical Study Report for the three studies. The information submitted in the April 23, 2008 amendment to this supplement does not contain appropriate links to the study report in the supplement submitted December 20, 2007. Until these links are corrected, we do not consider your response acceptable for review.

- b. Explain why data from OEO-U22, OEO-U23, OEO-U24 and OEO-U25 were included in the pas metadatasets and your analyses without providing any information on these studies or subjects in these studies.
3. **Study I88-037, I87-016, I87-017 (Study MR-002676):** “A Double-Blind, Placebo-Controlled study to determine the safety and Efficacy of PROCRIT, Administered Subcutaneously, in Patients with Anemia Secondary to Advanced Cancer and Aggressive Cyclic Chemotherapy”
  - a. Provide the Appendices 1 through 30 to the unified Clinical Study Report for the three studies. The information submitted in the April 23, 2008 amendment to this supplement does not contain appropriate links to the study report in the supplement submitted December 20, 2007. Until these links are corrected, we do not consider your response acceptable for review.
  - b. Explain why in the metadatasets provided in this supplement, the number of subjects in study I88-037 is 87, while in the study report, the number of subjects is 72.
4. **Study J89-040:** “The Effect of Subcutaneous r-HuEPO in Patients with Chronic Lymphocytic Leukemia: Results from North America Only”
  - a. Provide the Appendices 1 through 31 and Attachments 1 through 11 to the Clinical Study Report.
5. **Study EPO INT-1** “Randomized, Double-Blind Study on the Effect of EPOETIN ALFA in Subjects with Ovarian Cancer Receiving Cylic Platinum-based Chemotherapy Regimens” (Protocol CC 2574-P-416; Phase 3)
  - a. Provide the Appendices 1.1 through 3.11, Attachments 1 through 7 and the referenced Tables and Figures.
6. **Study EPO-CAN 15** “A Randomized, Double-blind, Placebo-controlled Study to Evaluate the Impact of Maintaining Hemoglobin Levels Using EPREX (Epoetin alfa) in Limited Disease Small Cell Lung Cancer (LD SCLC) Patients Receiving Combined Chemotherapy and Radiation Therapy”
  - a. Provide a complete clinical study report (missing pages 120 through 1295) including all the appendices that contain the study protocol and amendments, statistical methods, randomization code and schedule, subject data listings and narrative summary of deaths, serious adverse events and narratives for thrombovascular events. The information submitted in the February 18, 2008, (eCTD sequence No. 0135) as general correspondence to the BLA 103234, does not contain appropriate reference and links to the study report in the supplement submitted December 20, 2007. Because these links are not established and the submission has not been specifically cross-referenced nor identified as an

amendment to this prior approval supplement, information contained in the submission dated February 18, 2008 will not be reviewed under the BLA supplement submitted December 20, 2007.

7. **Study EPO-INT-76 (BEST)** “A Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Impact of Maintaining Hemoglobin Using Eprex® (Epoetin Alfa; RWJPRI-22512) in Metastatic Breast Carcinoma Subjects Receiving Chemotherapy”
  - a. Please provide SAS programs that are used to create the derived datasets and the SAS programs that are used for efficacy data analyses.

With regard to analyses pertaining to multiple studies, please provide the following information.

8. Please provide SAS programs for the following analyses described in Summary of Clinical Safety (module 2.7.4) of the submission:
  - a. Table 2, page 10
  - b. Figure 2, page 11
  - c. Figure 5, page 14
  - d. Figure 8, page 16
  - e. Figure 11, page 22
  - f. Tables 9 and 10, page 43
  - g. Figure 19, page 44
  - h. Figure 20, page 45
9. Provide the raw AE data sets and methodology for deriving the ADR table in the proposed label. Please include justification for inclusion of the specific studies in deriving the ADR table.
10. Provide the sub-study reports for the analysis of quality of life data for all the studies included in the submission for which quality of life information was collected (EPO-CC2574-P-174 (EPO-P-INT-174), EPO-CAN-15, EPO-INT-1, EPO-INT-2 (CC2574-P-467), EPO-INT-3 (CC 2574-P-034), EPO-INT-10, EPO-INT-76, i88-036-mr92013, i88 036-mr92014, J89-040, PR-27-008) Please provide (or ensure that the quality of life sub-study reports contain) a description of the instruments utilized for data collection, a discussion of the methodology utilized for data analysis, and primary datasets containing raw and derived variables collected in accordance with the quality of life instruments.
11. Please submit the methodology utilized in compiling and analyzing tumor outcome and survival data for studies CC2574-P-174, EPO-INT1 (CC2574-P-416), and EPO-INT-2 (CC2574-P-467).

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.

Please also note that, with respect to your supplement, STN BL 103234 (b) (4), submitted February 15, 2008, comments regarding the Final Study Report (FSR) for Study 20010145 will be provided in a separate letter.

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,

A handwritten signature in cursive script that reads "Patricia Keegan".

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



Our STN: BL 103234/5166

**FILING ISSUES**

**MAR 07 2008**

Amgen, Incorporated  
Attention: Neal Storm, M.S., M.B.A.  
Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop: 17-2-B  
Thousand Oaks, CA 91320

Dear Mr. Storm:

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 epoetin alfa (Epogen/Procrit). Also refer to our filing letter dated February 11, 2008. While conducting our filing review we identified the following potential review issues:

**STATISTICAL:**

1. 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.
2. Provide separate, individual study datasets, containing both raw data in the define document file, for each study included in the pooled dataset and analyses.
3. Provide the protocols for study 88-036 (MR92013) and (MR92014).

**REGULATORY: PLR LABELING FORMAT**

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

4. "Epogen (epoetin alfa)" appears under the highlights limitation statement, however, <sup>(b) (4)</sup> 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." <sup>(b) (4)</sup>

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.
10. Please further revise the highlights section to ensure it meets the ½ page requirement.

***With Respect to the FULL PRESCRIBING INFORMATION:***

11. 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***

12. The black box warning currently reads “WARNINGS: INCREASED MORTALITY, SERIOUS CARDIOVASCULAR and THROMBOEMBOLIC EVENTS, and TUMOR PROGRESSION.” [REDACTED] (b) (4)

***DOSAGE AND ADMINISTRATION:***

13. We recommend avoiding use of Latin abbreviations such as IV, while you do define IV in the first sentence of this section; you subsequently use the abbreviation throughout the label. We recommend always using [REDACTED] (b) (4) instead of “IV” to avoid a greater potential for medication errors should the abbreviation be misread.
14. 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.

15. Please revise section 2.5 to state, “Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, (b) (4)

**CONTRAINDICATIONS:**

16. 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:**

17. Please revise section 5.10, Albumin (Human), to include the following verbatim statement: "This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases. A theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD) also is considered extremely remote. No cases of transmission of viral diseases or CJD have ever been identified for albumin." (*See Guidance for Industry: Revised Preventive Measures to Reduce the Possible Risk of Transmission of Creutzfeldt-Jakob Disease (CJD) and Variant Creutzfeldt-Jakob Disease (vCJD) by Blood and Blood Products.*)

**ADVERSE REACTIONS:**

18. (b) (4)  
This is ultimately a review issue and will be discussed further during labeling negotiations.
19. 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 Epogen/Procrit with the incidence of antibodies to other products may be misleading.”

**OTHER COMMENTS:**

20. Please note that the revision date at the end of the highlights section replaces the “revision” or “issue” date at the end of the package insert or the attached patient

package insert. Please delete the “Issue Date” from the end of the patient package insert.

21. The manufacturing information should not be located at the end of the package insert. The patient package insert should immediately follow the package insert and the manufacturing information should be at the end of the patient package insert, at the end of the labeling.
22. You have not included proposed draft labeling for Procrit in this submission. We remind you that you must include all labeling in your submissions. Please submit both your proposed labeling revisions in the Procrit package insert and patient package insert in a timely manner. The proposed content of labeling [21 CFR 601.14(b)] in structured product labeling (SPL) format, as described at <http://www.fda.gov/oc/datacouncil/spl.html>, for Procrit is not included in your supplement.

This supplement is under review. We have no specific requests for additional 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,

A handwritten signature in cursive script that reads "Patricia Keegan". The signature is written in black ink and is positioned above the printed name and title.

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research



**FILING COMMUNICATION**

Our STN: BL 103234/5166

**FEB 21 2008**

Amgen, Incorporated  
Attention: Neal Storm, M.S., M.B.A.  
Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop: 17-2-B  
Thousand Oaks, CA 91320

Dear Mr. Storm:

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 epoetin alfa (Epogen/Procrit).

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.

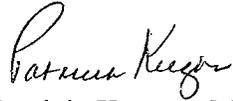
While conducting our filing review, we identified potential review issues and will be communicating them to you on or before March 9, 2008.

We acknowledge your request for a waiver of the requirement that the Highlights of Prescribing Information be limited to no more than one-half page. We will consider your request during labeling discussions. In the meantime, we encourage you to submit revised labeling that meets the half page requirement.

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,

A handwritten signature in cursive script, appearing to read "Patricia Keegan".

Patricia Keegan, M.D.

Director

Division of Biologic Oncology Products

Office of Oncology Drug Products

Center for Drug Evaluation and Research

**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  
Dwayne 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.*

# BLA/BLS Regulatory Filing Review

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CDER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy. An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD)..

Where an application contains more than one indication for use, it may be complete and potentially approvable for one indication, but inadequate for one or more additional indications. The agency may accept for filing those parts of the application that are complete for a particular indication, but refuse to file those parts of the application that are obviously incomplete for other indications.

CDER management may, for particularly critical biological products, elect not to use the RTF procedure, even where it can be invoked, if it believes that initiating the full review at the earliest possible time will better advance the public health.

STN: 1032241/15111111 (b)(4) Product: Epoehtn alfa Applicant: Amgen

Final Review Designation (circle one): Standard Priority

Submission Format (circle all that apply): Paper Electronic Combination

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 2/11/08 Committee Recommendation (circle one): File RTF

For BLA and Efficacy BLS: Were any potential review issues identified? Yes No

RPM: [Signature]  
(signature/date)

### Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
  - Part A - RPM
  - Part B - Product/CMC/Facility Reviewer(s): \_\_\_\_\_
  - Part C - Non-Clinical Pharmacology/Toxicology Reviewer(s): Zhao
  - Part D - Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers Shashin Lee
- Memorandum of filing recommendation:
  - Part B - Product/CMC/Facility Reviewer(s): \_\_\_\_\_
- Memo of Filing Meeting

105234/546

|                  |                                                                  |
|------------------|------------------------------------------------------------------|
| Applicant:       | <u>epinephrine</u>                                               |
| Short Summary:   | <u>to review the PE + PDE based on Recommendation of 5/10/07</u> |
| RPM:             | <u>Manually</u>                                                  |
| Office/Division: | OODP/DBOP                                                        |

**Filing worksheet Part A. Regulatory Project Manager (RPM)**

| CTD Module 1 Contents                                                                             | Present?                           |                         | If not, justification, action & status           |
|---------------------------------------------------------------------------------------------------|------------------------------------|-------------------------|--------------------------------------------------|
| Cover Letter                                                                                      | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| Form 356h completed                                                                               | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> including list of all establishment sites and their registration numbers | <input checked="" type="radio"/> Y | <input type="radio"/> N | <u>-Submitted upon request as an annex but</u>   |
| <input type="checkbox"/> If foreign applicant, US Agent signature.                                | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| Comprehensive Table of Contents                                                                   | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| Debarment Certification with correct wording (see * below)                                        | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| User Fee Cover Sheet                                                                              | <input checked="" type="radio"/> Y | <input type="radio"/> N | <u>N/A</u>                                       |
| User Fee payment received                                                                         | <input checked="" type="radio"/> Y | <input type="radio"/> N | <u>N/A</u>                                       |
| Financial certification &/or disclosure information                                               | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| Environment assessment or request for categorical exclusion (21 CFR Part 25)                      | <input checked="" type="radio"/> Y | <input type="radio"/> N | <u>Not included. Need to request from Agency</u> |
| Pediatric rule: study, waiver, or deferral                                                        | <input type="radio"/> Y            | <input type="radio"/> N | <u>N/A</u>                                       |
| Labeling:                                                                                         | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> PI -non-annotated                                                        | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> PI -annotated                                                            | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> PI (electronic)                                                          | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> Medication Guide                                                         | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> Patient Insert                                                           | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> package and container                                                    | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> diluent                                                                  | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> other components                                                         | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> established name (e.g. USAN)                                             | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |
| <input type="checkbox"/> proprietary name (for review)                                            | <input checked="" type="radio"/> Y | <input type="radio"/> N |                                                  |

\* The Debarment Certification must have correct wording, e.g. "I, the undersigned, hereby certify that XXX Co. 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 the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge..."

| Examples of Filing Issues                                                                                                                 | Yes?                                                       | If not, justification, action & status |
|-------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------------------------------|----------------------------------------|
| Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?:<br>Examples include: | <input checked="" type="radio"/> Y <input type="radio"/> N |                                        |

| Examples of Filing Issues                                                                                  | Yes?  | If not, justification, action & status |
|------------------------------------------------------------------------------------------------------------|-------|----------------------------------------|
| <input type="checkbox"/> legible                                                                           | (Y) N |                                        |
| <input type="checkbox"/> English (or translated into English)                                              | (Y) N |                                        |
| <input type="checkbox"/> compatible file formats                                                           | (Y) N |                                        |
| <input type="checkbox"/> navigable hyper-links                                                             | (Y) N |                                        |
| <input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays               | (Y) N |                                        |
| <input type="checkbox"/> summary reports reference the location of individual data and records             | (Y) N |                                        |
| <input type="checkbox"/> protocols for clinical trials present                                             | (Y) N |                                        |
| <input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance) | (Y) N |                                        |
| companion application received if a shared or divided manufacturing arrangement                            | Y (N) |                                        |
| if CMC supplement:                                                                                         |       |                                        |
| <input type="checkbox"/> description and results of studies performed to evaluate the change               | Y (N) |                                        |
| <input type="checkbox"/> relevant validation protocols                                                     | Y (N) |                                        |
| <input type="checkbox"/> list of relevant SOPs                                                             | Y (N) |                                        |
| if clinical supplement:                                                                                    |       |                                        |
| <input type="checkbox"/> changes in labeling clearly highlighted                                           | (Y) N |                                        |
| <input type="checkbox"/> data to support all label changes                                                 | (Y) N |                                        |
| <input type="checkbox"/> all required electronic components, including electronic datasets (e.g. SAS)      | (Y) N |                                        |
| if electronic submission:                                                                                  |       |                                        |
| <input type="checkbox"/> required paper documents (e.g. forms and certifications) submitted                | (Y) N |                                        |

List any issue not addressed above which should be identified as a reason for not filing the BLA/BLS. Also provide additional details if above charts did not provide enough room (or attach separate memo).

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Has orphan drug exclusivity been granted to another drug for the same indication?  
 If yes, review committee informed? NO

Does this submission relate to an outstanding PMC? NO

STN

103224/5244  
105234

(b)(4)

Product

epuehafa

Part A Page 3

If an Advisory Committee (AC) discussion may be needed, list applicable AC meetings scheduled to occur during the review period:

- Name: N/A
- Dates: \_\_\_\_\_

Recommendation (circle one): File RTF

RPM Signature:

[Signature] 2/11/03

Chief, Project Management Staff concurrence: \_\_\_\_\_



Our STN: BL 103234/5166

Amgen, Incorporated  
Attention: Neal Storm, M.S., M.B.A.  
Manager, Regulatory Affairs  
One Amgen Center Drive  
Mail Stop: 17-2-B  
Thousand Oaks, CA 91320-1799

FEB 01 2008

Dear Mr. Storm:

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 103234/5166 | Epoetin alfa/Epogen; Procrit |

**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,

A handwritten signature in cursive script that reads "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  
Dwayne 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 (b) (4)

(b) (4)

# RMS/BLA - Product Information Sheet for TBP

STN:

103234/5166

Reg. Coordinator:

Mana Patel

Document Date: \_\_\_\_\_

FDA Rcvd Date: \_\_\_\_\_

CBER Rcvd Date: \_\_\_\_\_

Applicant

Amgen

Product

Epoetin alfa

Proprietary/Trade Name(s)

Epogen

## Complete a box for each indication

Indication

PI attached

Dose

Age groups - check all that apply

- Adult 18+    All    Child 3-12    Geriatric 65+    Pediatric 0-3    Young Adult 13-18    Other \_\_\_\_\_

Indication Product Use - check all that apply

- Ancillary    Diagnostic/Therapeutic    Therapeutic    Prophylaxis    Other \_\_\_\_\_
- Further Manufacturing Injectable    Further Manufacturing Non Injectable

Indication

PI attached

Dose

Age groups - check all that apply

- Adult 18+    All    Child 3-12    Geriatric 65+    Pediatric 0-3    Young Adult 13-18    Other \_\_\_\_\_

Indication Product Use - check all that apply

- Ancillary    Diagnostic/Therapeutic    Therapeutic    Prophylaxis    Other \_\_\_\_\_
- Further Manufacturing Injectable    Further Manufacturing Non Injectable

## Guidance for completion of this form

Indication/Usage -- As stated in the P.I. This should also go into the short summary under the submission screen

Dose -- From the "Dosage and Administration" section of P.I. -- This is what the patient actually gets.

Dosage/Physical Form Details -- From the "How Supplied" section of P.I. -- Enter final dosage strengths; Potency & Units are important for user fee information

# Product Information Sheet - Dosage/Physical Form

Complete one sheet for each physical form, potency, and fill size.

STN:

Reg. Coordinator: \_\_\_\_\_

\* Dosage/Physical Forms \_\_\_\_\_ (See back page for Valid Values)

## Dosage

Potency (measurement of activity or strength) 2,000-40,000 Units/ml (See back page for Valid Values)

Duration (length of time dosage will remain stable) <sup>(b) (4)</sup>                      single-dose (months)

Temperature 2-8 °C <sup>(b) (4)</sup>                      multi-dose

## Container Type

- Ampule (Glass)  Ampule (Plastic)  Bag Bulk  Bottle  Pump Spray  
 Other\*\* \_\_\_\_\_  Syringe  Tube  Vial

## Container Closure

- Heat Seal  Plunger  Screw Cap Closure  Stopper (Dry Natural Rubber)  
 Stopper (Synthetic)  Stopper (Unknown)  Other

Container Fill Size 1ml and 2ml (Volume)

Route of Administration IV and Sub Q (See back page for Valid Values)

Dosage/Physical Forms \_\_\_\_\_ (See back page for Valid Values)

## Dosage

Potency (measurement of activity or strength) \_\_\_\_\_ Units \_\_\_\_\_ (See back page for Valid Values)

Duration (length of time dosage will remain stable) \_\_\_\_\_ (months)

Temperature \_\_\_\_\_

## Container Type

- Ampule (Glass)  Ampule (Plastic)  Bag Bulk  Bottle  Pump Spray  
 Other\*\* \_\_\_\_\_  Syringe  Tube  Vial

## Container Closure

- Heat Seal  Plunger  Screw Cap Closure  Stopper (Dry Natural Rubber)  
 Stopper (Synthetic)  Stopper (Unknown)  Other

Container Fill Size \_\_\_\_\_ (Volume)

Route of Administration \_\_\_\_\_ (See back page for Valid Values)

# Product Information Sheet - Dosage/Physical Form

## Listing of Valid Values

### Dosage/Physical Forms

- |                                                                              |                                                                          |
|------------------------------------------------------------------------------|--------------------------------------------------------------------------|
| <input type="checkbox"/> Inhalant Solution                                   | <input type="checkbox"/> Powder for Reconstitution                       |
| <input checked="" type="checkbox"/> Injectable Solution                      | <input type="checkbox"/> Solution                                        |
| <input type="checkbox"/> Injectable Solution Concentrate                     | <input type="checkbox"/> Solution for In Vitro Test                      |
| <input type="checkbox"/> Injectable Suspension                               | <input type="checkbox"/> Suspension for In Vitro Test                    |
| <input type="checkbox"/> Lyophilized Powder for In Vitro Test                | <input type="checkbox"/> Spray                                           |
| <input type="checkbox"/> Lyophilized Powder for Injectable Solution          | <input type="checkbox"/> Tablet                                          |
| <input type="checkbox"/> Lyophilized Powder for Injectable Suspension        | <input type="checkbox"/> Powder for Injectable Solution                  |
| <input type="checkbox"/> Lyophilized Powder for Scarification                | <input type="checkbox"/> Powder and Solvent for Suspension for Injection |
| <input type="checkbox"/> Lyophilized Powder to be suspended for Instillation | <input type="checkbox"/> Repository Injection                            |
| <input type="checkbox"/> Nasal Spray Suspension                              | <input type="checkbox"/> Other _____                                     |

### Potency Units

- |                                   |                                   |                                    |                                          |                                  |
|-----------------------------------|-----------------------------------|------------------------------------|------------------------------------------|----------------------------------|
| <input type="checkbox"/> AU/.5mL  | <input type="checkbox"/> mg/.8 mL | <input type="checkbox"/> dil.      | <input type="checkbox"/> mg/vial         | <input type="checkbox"/> ug/.4mL |
| <input type="checkbox"/> AU/mL    | <input type="checkbox"/> other    | <input type="checkbox"/> g         | <input type="checkbox"/> Percent         | <input type="checkbox"/> ug/.5mL |
| <input type="checkbox"/> BAU/mL   | <input type="checkbox"/> TCID     | <input type="checkbox"/> g/tube    | <input type="checkbox"/> u/.5mL          | <input type="checkbox"/> ug/.6mL |
| <input type="checkbox"/> IU/.1 mL | <input type="checkbox"/> TU/mL    | <input type="checkbox"/> mL        | <input type="checkbox"/> u/2mL           | <input type="checkbox"/> ug/g    |
| <input type="checkbox"/> IU/mL    | <input type="checkbox"/> U/.75mL  | <input type="checkbox"/> mg        | <input checked="" type="checkbox"/> u/mL | <input type="checkbox"/> ug/mL   |
| <input type="checkbox"/> IU/vial  | <input type="checkbox"/> cell/mL  | <input type="checkbox"/> mg/0.5 mL | <input type="checkbox"/> u/tube          | <input type="checkbox"/> ug/vial |
| <input type="checkbox"/> Lf/.5mL  | <input type="checkbox"/> cfu/mL   | <input type="checkbox"/> mg/2 mL   | <input type="checkbox"/> u/vial          |                                  |
| <input type="checkbox"/> MIU/mL   | <input type="checkbox"/> cfu/tab  | <input type="checkbox"/> mg/5 mL   | <input type="checkbox"/> ug              |                                  |
| <input type="checkbox"/> MIU/vial | <input type="checkbox"/> conc.    | <input type="checkbox"/> mg/mL     | <input type="checkbox"/> ug/.3mL         |                                  |

### Route of Administration

- |                                         |                                                 |                                                  |
|-----------------------------------------|-------------------------------------------------|--------------------------------------------------|
| <input type="checkbox"/> Dental         | <input type="checkbox"/> Intranasal             | <input type="checkbox"/> Needle Free Injection   |
| <input type="checkbox"/> Implantation   | <input type="checkbox"/> Intraperitoneal        | <input type="checkbox"/> Oral                    |
| <input type="checkbox"/> Inhalation     | <input type="checkbox"/> Intrathecal            | <input type="checkbox"/> Percutaneous            |
| <input type="checkbox"/> Intracoronary  | <input type="checkbox"/> Intratracheal          | <input type="checkbox"/> Prick Test              |
| <input type="checkbox"/> Intradermal    | <input checked="" type="checkbox"/> Intravenous | <input type="checkbox"/> Scratch Test            |
| <input type="checkbox"/> Intralesional  | <input type="checkbox"/> Intravesical           | <input type="checkbox"/> Spinal                  |
| <input type="checkbox"/> Intralymphatic | <input type="checkbox"/> Nasal Spray            | <input checked="" type="checkbox"/> Subcutaneous |
| <input type="checkbox"/> Intramuscular  | <input type="checkbox"/> Other _____            |                                                  |

# Product Information Sheet - Components

STN:

1032341

Reg. Coordinator: \_\_\_\_\_

Name Epoetin alfa

**Component Type**  
 Formulation Ingredient     Product     In Process Ingredient     Kit Component

**Ingredient Role -- (Pick one when Component Type "Formulation" is used)**  
 Active     Additive     Diluent     Preservative     Stabilizer

Source \_\_\_\_\_      Subsource \_\_\_\_\_

Name Human Serum Albumin

**Component Type**  
 Formulation Ingredient     Product     In Process Ingredient     Kit Component

**Ingredient Role -- (Pick one when Component Type "Formulation" is used)**

Source \_\_\_\_\_      Subsource \_\_\_\_\_

(b) (4)

Name Sodium citrate

**Component Type**  
 Formulation Ingredient     Product     In Process Ingredient     Kit Component

**Ingredient Role -- (Pick one when Component Type "Formulation" is used)**

Source \_\_\_\_\_      Subsource \_\_\_\_\_

(b) (4)

# Product Information Sheet - Components

STN: 1032341

Reg. Coordinator: \_\_\_\_\_

Name Sodium phosphat (monobasic and dibasic)

Component Type  
 Formulation Ingredient     Product     In Process Ingredient     Kit Component

Ingredient Role -- (Pick one when Component Type "Formulation" is used)

(b) (4)

Source \_\_\_\_\_                      Subsource \_\_\_\_\_

Name Sodium chloride

Component Type  
 Formulation Ingredient     Product     In Process Ingredient     Kit Component

Ingredient Role -- (Pick one when Component Type "Formulation" is used)

(b) (4)

Source \_\_\_\_\_                      Subsource \_\_\_\_\_

Name Benzyl alcohol

Component Type  
 Formulation Ingredient     Product     In Process Ingredient     Kit Component

Ingredient Role -- (Pick one when Component Type "Formulation" is used)

(b) (4)

Source \_\_\_\_\_                      Subsource \_\_\_\_\_

# Product Information Sheet - Components

STN:

1032341

Reg. Coordinator: \_\_\_\_\_

Name Water for injection

**Component Type**

- Formulation Ingredient     Product     In Process Ingredient     Kit Component

**Ingredient Role -- (Pick one when Component Type "Formulation" is used)**

(b) (4)

Source \_\_\_\_\_

Subsource \_\_\_\_\_

Name \_\_\_\_\_

**Component Type**

- Formulation Ingredient     Product     In Process Ingredient     Kit Component

**Ingredient Role -- (Pick one when Component Type "Formulation" is used)**

- Active     Additive     Diluent     Preservative     Stabilizer

Source \_\_\_\_\_

Subsource \_\_\_\_\_

Name \_\_\_\_\_

**Component Type**

- Formulation Ingredient     Product     In Process Ingredient     Kit Component

**Ingredient Role -- (Pick one when Component Type "Formulation" is used)**

- Active     Additive     Diluent     Preservative     Stabilizer

Source \_\_\_\_\_

Subsource \_\_\_\_\_