

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**BLA 125268**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**PEDIATRIC PAGE**

(Complete for all filed original applications and efficacy supplements)

BLA #: 125268/0 Supplement Type (e.g. SE5): N/A Supplement Number: N/A

Stamp Date: 10/23/07 PDUFA Goal Date: 4/23/08

HFD 160 Trade and generic names/dosage form: Nplate™ (romiplostim)

Applicant: Amgen Therapeutic Class: Hematology

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): N/A

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

Number of indications for this application(s): 1

**Indication #1:** Treatment of thrombocytopenia in adult patients with chronic Immune (idiopathic) Thrombocytopenic Purpura (ITP).

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 125268/0

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*If 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:**

*Florence O. Moore*

**Regulatory Project Manager**

cc: BLA 125268/0

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)**



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

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Memorandum *JM*

Debarment certification: verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent.

STN 125268/0 Romiplostim (Nplate)

**1. Debarment Certification**

Amgen hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Paul Eisenberg, MD, MPH, FACP, FACC  
Vice President, Global Regulatory Affairs and Safety

26 Sept 2007

Date

512 125268/0

**AMGEN**

## ACTION PACKAGE CHECKLIST

<b>APPLICATION INFORMATION<sup>1</sup></b>		
NDA # BLA # 125268	NDA Supplement # BLA STN # 0	If NDA, Efficacy Supplement Type:
Proprietary Name: Nplate Established/Proper Name: Romiplostim Dosage Form: Subcutaneous Injection		Applicant: Amgen, Inc. Agent for Applicant (if applicable):
RPM: Florence O. Moore, M.S.		Division: DMIHP
<p><b>NDAs:</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 NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)</p>		<p><b>505(b)(2) Original NDAs and 505(b)(2) NDA supplements:</b>            Listed drug(s) referred to in 505(b)(2) application (include NDA/ANDA #(s) and drug name(s)):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p><input type="checkbox"/> If no listed drug, check here and explain:</p> <p><b>Prior to approval, review and confirm the information previously provided in Appendix B to the Regulatory Filing Review by re-checking the Orange Book for any new patents and pediatric exclusivity. If there are any changes in patents or exclusivity, notify the OND ADRA immediately and complete a new Appendix B of the Regulatory Filing Review.</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> <p><b>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</b></p>
❖ User Fee Goal Date Action Goal Date (if different)		July 23, 2008 August 22, 2008
❖ Actions		
• Proposed action		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> AE <input type="checkbox"/> NA <input type="checkbox"/> CR
• Previous actions ( <i>specify type and date for each action taken</i> )		<input type="checkbox"/> None
❖ Advertising ( <i>approvals only</i> ) Note: If accelerated approval (21 CFR 314.510/601.41), advertising MUST have been submitted and reviewed ( <i>indicate dates of reviews</i> )		<input checked="" type="checkbox"/> Requested in AP letter <input type="checkbox"/> Received and reviewed

<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.

❖ 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 each <b>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
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**Officer/Employee List**

❖ 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/nonconsent by officers/employees	<input checked="" type="checkbox"/> Included

**Action Letters**

❖ Copies of all action letters ( <i>including approval letter with final labeling</i> )	Action(s) and date(s) Pending for July 23, 2008
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**Labeling**

❖ Package Insert ( <i>write submission/communication date at upper right of first page of PI</i> )	
❖ Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	August 22, 2008
❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	August 1, 2008
❖ Original applicant-proposed labeling	October 23, 2007
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide/Patient Package Insert/Instructions for Use ( <i>write submission/communication date at upper right of first page of each piece</i> )	<input checked="" type="checkbox"/> Medication Guide <input type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> None
❖ Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling)	

<sup>3</sup> Fill in blanks with dates of reviews, letters, etc.  
Version: 5/29/08

❖ Most recent submitted by applicant labeling (only if subsequent division labeling does not show applicant version)	
❖ Original applicant-proposed labeling	October 23, 2007
❖ Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Labels (full color carton and immediate-container labels) ( <i>write submission/communication date at upper right of first page of each submission</i> )	
❖ Most-recent division proposal for (only if generated after latest applicant submission)	
❖ Most recent applicant-proposed labeling	
❖ Labeling reviews ( <i>indicate dates of reviews and meetings</i> )	<input checked="" type="checkbox"/> RPM <input type="checkbox"/> DMEDP <input type="checkbox"/> DRISK <input checked="" type="checkbox"/> DDMAC February 28, 2008 <input type="checkbox"/> CSS <input checked="" type="checkbox"/> Other reviews DSRCS May 2, 2008; SEALD February 18, 2008; DMETS January 9, 2008; Memos of Meetings Included
<b>Administrative / Regulatory Documents</b>	
❖ Administrative Reviews ( <i>e.g., RPM Filing Review<sup>4</sup>/Memo of Filing Meeting</i> ) ( <i>indicate date of each review</i> )	First Committee: November 6, 2007 Designation: December 10, 2007 Filing: November 20, 2007 Midcycle: January 17, 2008
❖ NDAs only: Exclusivity Summary ( <i>signed by Division Director</i> )	<input type="checkbox"/> Included
❖ AIP-related documents <ul style="list-style-type: none"> <li>• Center Director's Exception for Review memo</li> <li>• If approval action, OC clearance for approval</li> </ul>	<input checked="" type="checkbox"/> Not on AIP
❖ Pediatric Page ( <i>approvals only, must be reviewed by PERC before finalized</i> )	<input checked="" type="checkbox"/> Included
❖ 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> )	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Postmarketing Requirement (PMR) Studies <ul style="list-style-type: none"> <li>• Outgoing communications (<i>if located elsewhere in package, state where located</i>)</li> <li>• Incoming submissions/communications</li> </ul>	<input type="checkbox"/> None Included (see memo, t-cons and emails) August 20, 2008
❖ Postmarketing Commitment (PMC) Studies <ul style="list-style-type: none"> <li>• Outgoing Agency request for postmarketing commitments (<i>if located elsewhere in package, state where located</i>)</li> <li>• Incoming submission documenting commitment</li> </ul>	<input type="checkbox"/> None
❖ Outgoing communications ( <i>letters (except previous action letters), emails, faxes, telecons</i> )	Included
❖ Internal memoranda, telecons, etc.	Included
❖ Minutes of Meetings <ul style="list-style-type: none"> <li>• Pre-Approval Safety Conference (<i>indicate date; approvals only</i>)</li> </ul>	<input type="checkbox"/> Not applicable April 22, 2008

<sup>4</sup> Filing reviews for other disciplines should be filed behind the discipline tab.  
Version: 5/29/08

• Regulatory Briefing ( <i>indicate date</i> )	<input type="checkbox"/> No mtg
• Pre-NDA/BLA meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg June 4, 2007
• EOP2 meeting ( <i>indicate date</i> )	<input type="checkbox"/> No mtg July 18, 2007
• Other (e.g., EOP2a, CMC pilot programs)	EOP1 - December 18, 2003; CMC - November 23, 2004, November 20, 2007 Orientation Meeting
❖ Advisory Committee Meeting(s)	<input type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	March 12, 2008
• 48-hour alert or minutes, if available	Included
<b>Decisional and Summary Memos</b>	
❖ Office Director Decisional Memo ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 16, 2008
Division Director Summary Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 14, 2008
Cross-Discipline Team Leader Review ( <i>indicate date for each review</i> )	<input type="checkbox"/> None July 14, 2008
<b>Clinical Information<sup>5</sup></b>	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) ( <i>indicate date for each review</i> )	May 20, 2008
• Clinical review(s) ( <i>indicate date for each review</i> )	May 20, 2008
• Social scientist review(s) (if OTC drug) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None
• Safety update review(s) ( <i>indicate location/date if incorporated into another review</i> )	May 20, 2008. See Clinical review section 7.5
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, review/memo explaining why not	May 20, 2008. See Clinical review section 3.3
❖ Clinical reviews from other clinical areas/divisions/Centers ( <i>indicate date of each review</i> )	<input type="checkbox"/> None MHPS March 5, 2008; DBOP March 5, 2008; QT-IRT May 6, 2008; HRQOL January 16, 2008.
❖ Controlled Substance Staff review(s) and Scheduling Recommendation ( <i>indicate date of each review</i> )	<input type="checkbox"/> Not needed
❖ REMS	<input type="checkbox"/> None
• REMS Document and Supporting Statement ( <i>indicate date(s) of submission(s)</i> )	Sponsor submission- final 8/1208 DRISK 2/12/08 and 8/22/08
• Review(s) and recommendations (including those by OSE and CSS) ( <i>indicate location/date if incorporated into another review</i> )	
❖ DSI Inspection Review Summary(ies) ( <i>include copies of DSI letters to investigators</i> )	<input type="checkbox"/> None requested
• Clinical Studies	April 1, 2008
• Bioequivalence Studies	
• Clinical Pharmacology Studies	
<b>Clinical Microbiology</b> <input type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) ( <i>indicate date for each review</i> )	<input type="checkbox"/> None

<sup>5</sup> Filing reviews should be filed with the discipline reviews.  
Version: 5/29/08

Clinical Microbiology Review(s) (indicate date for each review)	<input type="checkbox"/> None
<b>Biostatistics</b> <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
Statistical Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None April 14, 2008
Statistical Review(s) (indicate date for each review)	<input type="checkbox"/> None February 10, 2008
<b>Clinical Pharmacology</b> <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None April 18, 2008
Clinical Pharmacology Team Leader Review(s) (indicate date for each review)	<input type="checkbox"/> None April 18, 2008
Clinical Pharmacology review(s) (indicate date for each review)	<input type="checkbox"/> None April 18, 2008; April 21, 2008 (might be February 28, 2008)
❖ DSI Clinical Pharmacology Inspection Review Summary	<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 May 6, 2008
• Pharm/tox review(s), including referenced IND reviews (indicate date for each review)	<input type="checkbox"/> None
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (indicate date for each review)	<input type="checkbox"/> None
• Statistical review(s) of carcinogenicity studies (indicate date for each review)	<input type="checkbox"/> No carc
❖ ECAC/CAC report/memo of meeting	<input type="checkbox"/> None Included in P/T review, page
❖ DSI Nonclinical Inspection Review Summary	<input type="checkbox"/> None requested
<b>CMC/Quality</b> <input type="checkbox"/> None	
❖ CMC/Quality Discipline Reviews	
• ONDQA/OBP Division Director Review(s) (indicate date for each review)	<input type="checkbox"/> None
• Branch Chief/TeamLeader Review(s) (indicate date for each review)	<input type="checkbox"/> None April 30, 2008
• CMC/product quality review(s) (indicate date for each review)	<input type="checkbox"/> None April 25, 2008
• BLAs only: Facility information review(s) (indicate dates)	<input type="checkbox"/> None April 19, 2008
❖ Microbiology Reviews	
• NDAs: Microbiology reviews (sterility & pyrogenicity) (indicate date of each review)	<input type="checkbox"/> Not needed ?
• BLAs: Sterility assurance, product quality microbiology	
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer (indicate date for each review)	<input type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)	
<input type="checkbox"/> Categorical Exclusion (indicate review date)(all original applications and all efficacy supplements that could increase the patient population)	
<input type="checkbox"/> Review & FONSI (indicate date of review)	
<input type="checkbox"/> Review & Environmental Impact Statement (indicate date of each review)	April 14, 2008

<p>❖ Facilities Review/Inspection</p>	
<ul style="list-style-type: none"> <li>• NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date)</i></li> </ul>	<p>Date completed:</p> <p><input type="checkbox"/> Acceptable</p> <p><input type="checkbox"/> Withhold recommendation</p>
<ul style="list-style-type: none"> <li>• BLAs:             <ul style="list-style-type: none"> <li>➢ TBP-EER</li> <li>➢ Compliance Status Check (approvals only, both original and all supplemental applications except CBEs) <i>(date completed must be within 60 days prior to AP)</i></li> </ul> </li> </ul>	<p>Date completed:</p> <p><input type="checkbox"/> Acceptable</p> <p><input type="checkbox"/> Withhold recommendation</p> <p>Date completed: March 19, 2008</p> <p><input checked="" type="checkbox"/> Requested</p> <p><input checked="" type="checkbox"/> Accepted <input type="checkbox"/> Hold</p>
<p>❖ NDAs: Methods Validation</p>	<p><input type="checkbox"/> Completed</p> <p><input type="checkbox"/> Requested</p> <p><input type="checkbox"/> Not yet requested</p> <p><input type="checkbox"/> Not needed</p>

### Appendix A 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.

**Moore, Florence O**

**From:** Chang-Lok, Mei Ling [meilingc@amgen.com]  
**Sent:** Wednesday, August 20, 2008 4:44 PM  
**To:** Moore, Florence O  
**Cc:** Ali Ibrahim, Ebla  
**Subject:** FW: Information Request

Dear Florence,

Thank you for your email to clarify Amgen's proposed PMR language with timelines. Amgen would like to provide you with some background details. Amgen submitted PMR language to the FDA on May 22, 2008, (Sequence #0030) based on the language provided by FDA via email on May 16, 2008. On July 24, 2008, Amgen received a response from Dr Rieves regarding revising the dates for PMR #1. Amgen originally planned to submit the protocol for PMR #1 to FDA by 31 July 2008. Due to the delay in approval, Amgen revised the timelines for PMR #1. This information was emailed to FDA on 01 August 2008, and was formally submitted on August 14, 2008 (Sequence #0042).

Therefore, the two versions you have included only differ with respect to 1) the listed order of the studies and 2) the date of submission of the protocol # 20080009 to the FDA. Amgen requests that the PMR language and timelines you referred to in your email as the 8/6/08 version is the proposed language for FDA review and finalization as follows:

Nplate STN 125268/0 PMR

**POSTMARKETING REQUIREMENTS UNDER 505(o)**

1. To conduct trial 20080009, "A Prospective Phase IV, Open-Label, Multi-Center, Study Evaluating the Changes in Bone Marrow Morphology in Subjects Receiving Romiplostim for the Treatment of Thrombocytopenia associated with Immune (Idiopathic) Thrombocytopenia Purpura (ITP)." In the trial, at least 150 patients will receive romiplostim and undergo bone marrow evaluations prior to, during and following the completion of romiplostim administration. A similar evaluation schedule apply to the detection of antibody formation to romiplostim and thrombopoietin, as well as, the electrocardiographic (ECG) detection of cardiac conduction abnormalities. A first interim report will contain, in addition to any other items, an ECG and the results of bone marrow evaluations for patients who have completed 12 months of trial participation. This information will be updated for patients who have completed 24 months of trial participation and submitted in a second interim report.

You will conduct this trial according to the following timetable:

Protocol submission:	August 22, 2008
Trial start:	July 2009
First interim report submission:	June 2012
Second interim report submission:	June 2013
Final report submission:	December 2014

8/22/2008

2. To conduct an "Antibody Registry Study" that will enroll subjects who have received Romiplostim whose blood samples contain neutralizing antibodies to either romiplostim or thrombopoietin. The antibody assays will be performed by Amgen in response to spontaneously submitted requests for the post-marketing blood tests. As described in the romiplostim prescribing information, a lack of response to romiplostim should prompt the healthcare provider to search for causative factors, including neutralizing antibodies to romiplostim. In these situations, healthcare providers to submit blood samples to Amgen for detection of neutralizing antibodies to romiplostim and thrombopoietin. The Antibody Registry Study will collect follow-up platelet count and other clinical data sufficient to assess the long term consequences of the detected antibodies. Patients will be followed until the detected antibodies resolve or stabilize in titer over a several month period of time.

You will conduct this trial according to the following timetable:

Protocol Submission:	November 2008
Study Start:	May 2009
Final Report Submission:	Within six months of FDA notification that sufficient data has been collected.

3. To develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to romiplostim during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, bone marrow reticulin formation, thrombotic events, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA has acknowledged that sufficient data has been collected.

You will conduct this trial according to the following timetable:

Protocol Submission:	November 2008
Study Start:	May 2009
Final Report Submission:	Within six months of FDA notification that sufficient data had been collected

4. To conduct a milk only lactation study in the subset of women enrolled in the pregnancy registry who choose to breastfeed their infants. This study will be designed to detect the presence and concentration of romiplostim in breast milk and any effects on milk production and composition. The study will include a symptom diary for mothers to record any adverse effects in the breastfeeding infants. Annual interim reports will be submitted until FDA has acknowledged that sufficient data has been collected.

You will conduct this trial according to the following timetable:

Protocol Submission:	November 2008
Study Start:	May 2009
Final Report Submission:	Within six months of FDA notification that sufficient data has been collected.

---

**From:** Boynton, Susan  
**Sent:** Wednesday, August 20, 2008 12:46 PM  
**To:** Batra, Monica; Chang-Lok, Mei Ling; Lauritzen, Anne  
**Subject:** RE: Information Request

Thanks Anne.

Do you think we should highlight where the versions differ to help Florence?

Susan Boynton  
Executive Director,  
TA Head, Oncology Supportive Care  
Global Regulatory Affairs  
Amgen Inc.  
Work phone: (805) 447-8424  
Fax: (805) 499-9228  
Cell: (805) 573-0885  
Email: sboynton@amgen.com

8/22/2008

**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Wednesday, August 20, 2008 12:28 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Cc:** Ali Ibrahim, Ebla  
**Subject:** Information Request

**Importance:** High

**Follow Up Flag:** Follow up  
**Due By:** Wednesday, August 20, 2008 1:30 PM  
**Flag Status:** Flagged

Hi Mei Ling:

It seems the dates for PMRs were changed. Please confirm for me the correct dates that FDA and you agreed on.

A. Current dates we have:

1. To conduct an "Antibody Registry Study" that will enroll subjects who have received Romiplostim and whose blood samples contain antibodies to either romiplostim or thrombopoietin. The antibody assays will be performed by Amgen in response to spontaneously submitted requests for the post-marketing blood tests. As described in the romiplostim prescribing information, a lack or loss of response to romiplostim should prompt the healthcare provider to search for causative factors, including neutralizing antibodies to romiplostim. In these situations, healthcare providers are to submit blood samples to Amgen for detection of antibodies to romiplostim and thrombopoietin. The Antibody Registry Study will collect follow-up platelet count and other clinical data sufficient to assess the long term consequences of the detected antibodies. Patients will be followed until the detected antibodies resolve or stabilize in titer over a several month period of time.

You will conduct this study according to the following timetable:

Protocol Submission:	November 2008
Study Start:	May 2009
First interim report submission:	May 2010 then annually
Final Report Submission:	Within six months of FDA notification that sufficient data has been collected

2. To develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to romiplostim during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, bone marrow reticulatin formation, thrombotic events, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA has acknowledged that sufficient data have been collected.

You will conduct this study according to the following timetable:

Protocol Submission:	November 2008
Study Start:	May 2009

First interim report submission: May 2010 then annually  
Final Report: Within six months of FDA notification that sufficient data has been collected.

3. To conduct a milk only lactation study in the subset of women enrolled in the pregnancy registry that choose to breastfeed their infants. This study will be designed to detect the presence and concentration of romiplostim in breast milk and any effects on milk production and composition. The study will include a symptom diary for mothers to record any adverse effects in the breastfeeding infants. Annual interim reports will be submitted until FDA has acknowledged that sufficient data have been collected.

You will conduct this study according to the following timetable:

Protocol Submission: November 2008  
Study Start: May 2009  
First interim report submission: May 2010 then annually  
Final Report: Within six months of FDA notification that sufficient data has been collected.

4. To conduct trial 20080009, "A Prospective Phase IV, Open-Label, Multi-Center, Study Evaluating the Changes in Bone Marrow Morphology in Subjects Receiving Romiplostim for the Treatment of Thrombocytopenia associated with Immune (Idiopathic) Thrombocytopenia Purpura (ITP)." In this trial, at least 150 patients will receive romiplostim and undergo bone marrow evaluations prior to, during and following the completion of romiplostim administration. A similar evaluation schedule will apply to the detection of antibody formation to romiplostim and thrombopoietin as well as the electrocardiographic (ECG) detection of cardiac conduction abnormalities.

A first interim report will contain, in addition to any other items, ECG and the results of bone marrow evaluations for patients who have completed 12 months of trial participation. This information will be updated for patients who have completed 24 months of trial participation and submitted in a second interim report.

You will conduct this trial according to the following timetable:

Protocol submission: \_\_\_\_\_  
Trial start: \_\_\_\_\_  
First interim report submission: \_\_\_\_\_  
Second interim report submission: \_\_\_\_\_  
Final report submission: \_\_\_\_\_

OR  
B. 8/6/2008

1. To conduct trial 20080009, "A Prospective Phase IV, Open-Label, Multi-Center, Study Evaluating the Changes in Bone Marrow Morphology in Subjects Receiving Romiplostim for the Treatment of Thrombocytopenia associated with Immune (Idiopathic) Thrombocytopenia Purpura (ITP)." In this trial, at least 150 patients will receive romiplostim and undergo bone marrow evaluations prior to, during and following the completion of romiplostim administration. A similar evaluation schedule will apply to the detection of antibody formation to romiplostim and thrombopoietin as well as the electrocardiographic (ECG) detection of cardiac conduction abnormalities.

A first interim report will contain, in addition to any other items, ECG and the results of bone marrow evaluations for patients who have completed 12 months of trial participation. This information will be updated for patients who have completed 24 months of trial participation and submitted in a second interim report.

You will conduct this trial according to the following timetable:

Protocol submission:	August 22, 2008
Trial start:	July 2009
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Second interim report submission:	June 2013
Final report submission:	December 2014

2. To conduct an "Antibody Registry Study" that will enroll subjects who have received Romiplostim and whose blood samples contain antibodies to either romiplostim or thrombopoietin. The antibody assays will be performed by Amgen in response to spontaneously submitted requests for the post-marketing blood tests. As described in the romiplostim prescribing information, a lack or loss of response to romiplostim should prompt the healthcare provider to search for causative factors, including neutralizing antibodies to romiplostim. In these situations, healthcare providers are to submit blood samples to Amgen for detection of antibodies to romiplostim and thrombopoietin. The Antibody Registry Study will collect follow-up platelet count and other clinical data sufficient to assess the long term consequences of the detected antibodies. Patients will be followed until the detected antibodies resolve or stabilize in titer over a several month period of time.

You will conduct this study according to the following timetable:

Protocol Submission:	November 2008
Study Start:	May 2009
Final Report Submission:	Within six months of FDA notification that sufficient data has been collected

3. To develop and maintain a prospective, observational pregnancy exposure registry study conducted in the United States that compares the pregnancy and fetal outcomes of women exposed to romiplostim during pregnancy to an unexposed control population. The registry will detect and record major and minor congenital anomalies, spontaneous abortions, stillbirths, elective terminations, adverse effects on immune system development, platelet number and function, neoplasm formation, bone marrow reticulin formation, thrombotic events, and any serious adverse pregnancy outcomes. These events will be assessed among the enrolled women throughout the pregnancy. The events will also be assessed among infants through at least the first year of life. Annual interim reports will be submitted until FDA has acknowledged that sufficient data has been collected.

You will conduct this study according to the following timetable:

Protocol Submission: November 2008  
Study Start: May 2009  
Final Report: Within six months of FDA notification that sufficient data has been collected.

4. To conduct a milk only lactation study in the subset of women enrolled in the pregnancy registry who choose to breastfeed their infants. This study will be designed to detect the presence and concentration of romiplostim in breast milk and any effects on milk production and composition. The study will include a symptom diary for mothers to record any adverse effects in the breastfeeding infants. Annual interim reports will be submitted until FDA has acknowledged that sufficient data has been collected.

You will conduct this study according to the following timetable:

Protocol Submission: November 2008  
Study Start: May 2009  
Final Report: Within six months of FDA notification that sufficient data has been collected.

Thanks,  
Florence O. Moore, M.S.  
Acting Team Leader, Regulatory Project Management  
FDA/CDER/OODP/DMIHP  
hone: 301-796-2050  
Fax: 301-796-9849

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**Ali Ibrahim, Ebla**

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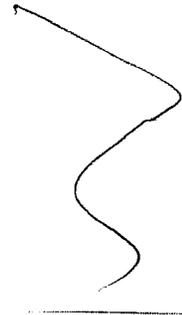
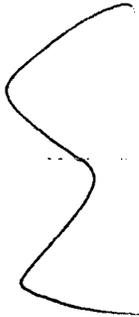
**From:** Moore, Florence O  
**Sent:** Tuesday, August 12, 2008 3:00 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Cc:** Ali Ibrahim, Ebla  
**Subject:** RE: REMS Submission  
**Follow Up Flag:** Follow up  
**Due By:** Thursday, August 14, 2008 12:00 PM  
**Flag Status:** Flagged

Dear Mei Ling:

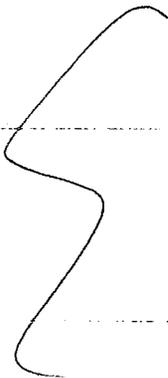
We have the following comments on the REMS materials submitted yesterday:

1. The REMS Supporting Document will not be attached to the action letter and will not be made public.
2. We apologize that we didn't catch the omission of the reauthorization component to the "safety registry" in the last round of comments. Please see below:

**"REMS Nplate NEXUS Patient Safety Registry" document:**



**"Nplate Risk Evaluation and Mitigation Strategy (REMS) Supporting Document:"**



Please revise the above documents (and any others that we did not catch concerning this issue). Please re-submit the entire REMS again as you did yesterday. If you agree with the changes, you do not need to attach an RTQ document.

Thanks,  
Florence

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**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Monday, August 11, 2008 4:00 PM  
**To:** Moore, Florence O  
**Subject:** REMS Submission

Dear Florence,

Please find attached the final submission of the REMS template, REMS Supporting Document and all the REMS material.

Thank you,

Mei Ling

In response to FDA comments received on 06 August 2008 via email regarding our REMS submission dated 01 August 2008 (Sequence No. 0039) and the Information Request Letter received via email on 25 July 2008, and in accordance with section 505-1 of the Federal Food, Drug and Cosmetic Act, Amgen is formally submitting our REMS template, REMS Supporting Document and all the REMS material. This submission is intended as a complete response to the above-mentioned comments received by FDA on 06 August 2008.

The submitted REMS include the following components: a Medication Guide, Communication Plan, Elements to Assure Safe Use, Implementation System, and a Timetable for Assessments. All relevant REMS materials, including enrollment forms, baseline data collection forms, safety monitoring and follow-up forms, and any educational materials are appended within the proposed REMS.

The REMS Supporting Document is based on previous versions of the risk management plan submissions. This document includes a complete and detailed description of the entire REMS and includes the Procedure for Prescriber Distribution, Procedure for Direct Shipment, Nplate™ NEXUS Program Call Center and details provided in previous RMP proposed documents.

8/13/2008

Amgen also provides in the submission a Response to Questions document which summarizes Amgen's responses to FDA points provided on 06 August 2008.

In accordance with previous advice Amgen recognizes that the REMS document and materials are considered product labeling. As such, any changes to these tools will be managed as changes being effected.

### Change Status for REMS Template and Supporting Documents

<b>REMS</b>	<b>Description of Changes</b>
Nplate™ Risk Evaluation and Mitigation Strategy (REMS template)	This document has been updated to reflect FDA comments dated Aug 6, 2008
Nplate REMS Supporting Document	This document has been updated to reflect FDA comments dated Aug 6, 2008
<b>REMS Materials</b>	
Medication Guide	No changes
Nplate™ NEXUS Program Healthcare Provider Introductory Letter	No changes
Nplate™ NEXUS Program Healthcare Provider Enrollment Form	No changes
Nplate™ NEXUS Program Brochure	This document has been updated to reflect FDA comments dated Aug 6, 2008
Nplate™ NEXUS Program Training Kit Folder	No changes
Nplate™ Dose Calculator	No changes
Nplate™ NEXUS Program Website	This document has been updated to reflect FDA comments dated Aug 6, 2008
Nplate™ NEXUS Call Center	This document has been updated to reflect FDA comments dated Aug 6, 2008
Procedure for Prescriber Distribution (HCPs/Hospitals/Institutions)	This document has been updated to reflect FDA comments dated Aug 6, 2008
Nplate™ NEXUS Program Institution Enrollment Form	This document has been updated to reflect FDA comments dated Aug 6, 2008
Procedures for Direct Shipment to Registered Healthcare Providers and Hospitals/Institutions	No changes
Nplate™ NEXUS Program Patient Enrollment Form	No changes
Patient/Caregiver Introductory Letter	No changes
What is Nplate™ NEXUS Program? A Brochure for Nplate™ Patients and Caregivers	This document has been updated to reflect FDA comments dated Aug 6, 2008
Patient Identification Card and Dosing Tracker	No changes

Nplate™ NEXUS Patient Safety Registry	New appended document to the REMS
Nplate™ NEXUS Program Patient Baseline Data Form	No changes
Nplate™ NEXUS Program Safety Questionnaire	This document has been updated to reflect FDA comments dated Aug 6, 2008
Nplate™ NEXUS Program Discontinuation/Post-Discontinuation Follow-Up Form	This document has been updated to reflect FDA comments dated Aug 6, 2008
Nplate™ NEXUS Program Thrombotic/Thromboembolic Complications	No changes
Nplate™ NEXUS Program Hematological Malignancy/MDS	No changes
Nplate™ NEXUS Program Medication Errors Associations and Serious Outcomes	This form has been updated to reflect FDA comments dated Aug 6, 2008
Nplate™ NEXUS Program Bone Marrow Reticulin/Bone Marrow Fibrosis	No changes
Nplate™ NEXUS Program Worsened Thrombocytopenia after Cession of Treatment with Nplate	This form has been updated to reflect FDA comments dated Aug 6, 2008
Monitoring and Compliance of Nplate™ NEXUS Program Elements	New appended document to the REMS
Nplate™ NEXUS Program: Training Kit Folder Mock-up	Per FDA email dated Aug 7, 2008, another mock-up of the folder, including copies of the REMS materials is not necessary
Flash Drive	This risk specific safety questionnaires have been added to the flash drive as requested in FDA comments dated Aug 6, 2008, but not resubmitted per FDA email dated Aug 7, 2008.

## Ali Ibrahim, Ebla

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**From:** Ali Ibrahim, Ebla  
**Sent:** Thursday, August 07, 2008 1:37 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: REMS Clarification

Mei-Ling,

All the REMS materials must be in final format in order to append to the action letter. If any of the forms/materials will be/have been changed, those forms need to be resubmitted in electronic format. We do not need another mock-up hard copy of the training kit again at this time; just all the materials in electronic format. Thank you.

Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Medical Imaging and 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

-----Original Message-----

From: Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
Sent: Thursday, August 07, 2008 10:40 AM  
To: Ali Ibrahim, Ebla  
Subject: REMS Clarification

Dear Ebla,

Thank you for the comments to the REMS yesterday. The team has reviewed and will provide the following documents in the next formal submission:

1. Response to Questions document
2. Revised REMS with all REMS materials appended.
3. REMS supporting document

Amgen does not plan to submit another mock up of the housing kit folder with copies of all forms/tools at this time. Please confirm that this is acceptable. Post approval, Amgen will submit a final housing kit folder with copies of all final forms/tools.

Thank you again,  
Mei Ling

**Ali Ibrahim, Ebla**

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**From:** Ali Ibrahim, Ebla  
**nt:** Wednesday, August 06, 2008 2:43 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** FDA Review of August 1, 2008 Nplate REMS submission

**Attachments:** FDA Nplate Comments 8.6.08.doc

Mei-Ling,

Please find attached the FDA Review of August 1, 2008 Nplate REMS submission.

Amgen (if you agree with all our comments), in the next submission you do not need to include any track changes, Word version, etc.... You should include the (revised) REMS Template, REMS Supporting Document, and all the REMS materials (intro letters, enrollment forms, safety forms, training kit folder, website, dosing calculator, d/c forms, PI, MG, etc...). Thank you.



FDA Nplate  
omments 8.6.08.doc

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Medical Imaging and 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*

10 Page(s) Withheld

       Trade Secret / Confidential

X Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative- 1



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

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**Memorandum**

Nplate (romiplostim) has Orphan Drug designation hence user fee does not apply. *FM*

STN 125268/0 Romiplostim (Nplate)



Our STN: BL 125268/0

**INFORMATION REQUEST LETTER**

Amgen, Inc.  
Attention: Mei-Ling Chang-Lok, Ph.D., RAC  
Director, Regulatory Affairs  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799

JUL 25 2008

Dear Dr. Chang-Lok:

Please refer to your October 23, 2007, Biologics Licensing Application (BLA) 125268, submitted under section 351(a) of the Public Health Service Act for Nplate (romiplostim) Subcutaneous Injection for the treatment of thrombocytopenia in patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins, or splenectomy.

We also refer to your February 7, March 24, April 30, June 4, and June 24, 2008 submissions.

**RISK EVALUATION AND MITIGATION STRATEGY (REMS) REQUIREMENTS**

Title IX, Subtitle A, Section 901 of the Food and Drug Administration Amendments Act of 2007 (FDAAA) amends the Federal Food, Drug, and Cosmetic Act (FDCA) to authorize FDA to require the submission of a Risk Evaluation and Mitigation Strategy (REMS) if the Secretary determines that such a strategy is necessary to ensure that the benefits of the drug outweigh the risks (section 505-1(a)(1)). This provision took effect on March 25, 2008.

In accordance with section 505-1 of the FDCA, we have determined that a REMS is necessary for Nplate (romiplostim) Subcutaneous Injection to ensure the benefits of the drug outweigh the risks of bone marrow reticulin formation and bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate, thromboembolic complications, an increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS), and serious complications due to medication errors. The REMS, once approved, will create enforceable obligations.

You submitted a proposed Nplate Risk Minimization Action Plan (RiskMAP) on February 7, 2008, and subsequent revised risk management plans on April 30, June 4, and June 24, 2008. Before this biologics licensing application may be approved, you must submit a proposed REMS and a REMS Supporting Document, which can be based on your prior risk management plan submissions. A suggested template for your REMS is included in Appendix A.

Your proposed REMS must include the following:

**Medication Guide:** As one element of a REMS, FDA may require the development of a Medication Guide as provided for under 21 CFR Part 208. Pursuant to 21 CFR Part 208, FDA has determined that Nplate poses a serious and significant public health concern requiring the distribution of a Medication Guide. The Medication Guide is necessary for patients' safe and effective use of Nplate. FDA has determined that Nplate is a product that has serious risks (relative to benefits) of which patients should be made aware because information concerning the risks could affect patients' decisions to use, or continue to use, Nplate. Under 21 CFR 208 and in accordance with 505-1, you are responsible for ensuring that the Medication Guide is available for distribution to patients who are dispensed Nplate.

You have submitted a Medication Guide as part of your BLA 125268. You should submit this Medication Guide as part of your REMS.

**Communication Plan:** We have determined that a communication plan to healthcare providers likely to prescribe, dispense, and administer your drug, such as hematologists, oncologists, and hospital pharmacists, will support implementation of the elements of your REMS. The communication plan must include the dissemination of information about the elements of the REMS, including the Medication Guide and the healthcare provider materials.

**Elements to Assure Safe Use:** We have determined that the following elements to assure safe use are necessary to mitigate specific serious risks listed in the labeling of the drug which include bone marrow reticulin formation and the risk of bone marrow fibrosis, worsened thrombocytopenia after cessation of Nplate, thromboembolic complications, an increased risk of hematological malignancies and progression of malignancy in patients with a pre-existing hematological malignancy or myelodysplastic syndrome (MDS), and serious complications due to medication errors.

- Nplate will only be prescribed by healthcare providers who are specially certified under 505-1(f)(3)(A).
- Nplate will only be dispensed by practitioners and healthcare settings (i.e., hospitals/institutions) that are specially certified under 505-1(f)(3)(B).
- Each patient treated with Nplate is enrolled in a program for documentation of safe-use conditions under 505-1(f)(3)(D).
- Each patient is subject to certain monitoring under 505-1(f)(3)(E).

**Implementation System:** We have determined that your REMS must have an implementation system to monitor and evaluate implementation of such elements by healthcare providers and work to improve implementation of such elements.

**Timetable for Assessments:** We have determined that your REMS must include a timetable for assessments that shall be no less frequent than every 6 months for the first 24 months following approval, then annually (from the approval date), thereafter.

Each assessment must include information to evaluate the extent to which the elements to assure safe use of Nplate are meeting the goals of the REMS and whether the goals or elements should

be modified. See Appendix B for additional description of the information that should be provided in an assessment.

Additionally, all relevant REMS materials including enrollment forms, baseline data collection forms, safety monitoring and follow-up forms, and any educational materials should be appended to the proposed REMS.

The REMS Supporting Document should be a document explaining the rationale for each of the elements of the REMS and should include the following sections:

1. Background Section
2. Goals Section
3. Rationale and Description of Proposed REMS Section
  - a. Additional Potential REMS Elements (Sec 505-1(e))
  - b. Elements to Assure Safe Use (Sec 505-1(f)(3))
  - c. Implementation System (Sec 505-1(f)(4))
  - d. Timetable for Assessment and information that will be used to assess the REMS (Sec 505-1(d))

Use the following designator to prominently label all submissions relating to this REMS:

**BLA 125268/0 PROPOSED REMS**

If you have any questions, call Florence Moore, M.S., Regulatory Project Manager, at (301) 796-2050.

Sincerely,



Rafael Dwaine Rieves, M.D.  
Director  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research

10 Page(s) Withheld

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X Draft Labeling

       Deliberative Process

Withheld Track Number: Administrative- 2

**Ali Ibrahim, Ebla**

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**From:** Ali Ibrahim, Ebla  
**Sent:** Wednesday, July 23, 2008 4:25 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** Nplate - Comments and Requests Per Our Tecon on July 22, 2008  
**Attachments:** Nplate Items 7.23.08.doc

Hello Mei-Ling,

Attached are our comments and requests, as mentioned on 7/22/08. We encourage you to submit revised draft documents (REMS materials) for our review. Indeed, if Amgen would like to submit all the draft forms, letters, questionnaires, and educational materials ahead of the anticipated IR letter, we will review these. If Amgen prefers to send everything in response to the IR Letter, of course that is fine, as well (as you had mentioned in a prior conversation, submission of the revised documents--in anticipation of the response to the IR letter--may facilitate the review of your response to the IR letter).



Nplate Items  
7.23.08.doc (54 K...

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research  
Food and Drug Administration  
0903 New Hampshire Avenue, Rm 2159  
Silver Spring, MD 20903*

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

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       Deliberative Process

Withheld Track Number: Administrative 3

Record of telephone conversation

BLA 125268/0

Today's date: July 22, 2008

Speakers: Dwaine Rieves for FDA

**FDA Attendees:** Karen Weiss, Dwaine Rieves, Glen Jones, Suzanne Berkman and Ebla Ali Ibrahim

**Amgen Attendees:** David Feigal, Susan Boynton, Mei Ling Chang-Lok, Monica Batra, Sarah Khalil, Paul Eisenberg

Amgen requested this telephone conference to discuss and get concurrence from the FDA, regarding a statement they plan to post on their website on July 23, 2008. Here is the statement:

*"The FDA notified Amgen that they will not issue a decision on Nplate by the PDUFA deadline of July 23, 2008"*

*Amgen is working with the FDA to assist in the completion of these*

*Σ*

*>*

FDA did not concur or object to the statement but explained to Amgen that the review process is still underway and that an agreement from both parties on the final REMS is an outstanding issue. FDA stated again that an action letter is not anticipated for July 23, 2008 because of the ongoing internal discussion around drafting the planned FDA Information Request (IR) Letter.

FDA informed Amgen that questions/comments on their July 2, 2008 submission would be emailed on July 23, 2008 before the IR letter is ready. FDA informed Amgen that to facilitate the ongoing review they may respond to these questions/comments prior to receiving the planned IR letter. FDA is hoping the continuing interactive review of all REMS documents (e.g. the educational material, questionnaire) will allow us to take an action quicker once the IR letter is issued and Amgen's response received.

Amgen was initially concerned about the circular process of review but after discussion indicated their intent to be as interactive as possible.

Record of telephone conversation

BLA 125268/0

Today's date: July 18, 2008

Speakers: Dwaine Rieves for FDA

**FDA Attendees:** Dwaine Rieves, Kathy Robie Suh, and Ebla Ali Ibrahim

**Amgen Attendees:** David Feigal, Susan Boynton, Mei Ling Chang-Lok, Monica Batra

FDA requested this telephone conference to discuss the status of the Information Request Letter to be sent to Amgen for Nplate.

FDA informed Amgen that we anticipate missing the PDUFA date, July 23, 2008 because of ongoing internal discussion and review of the Information Request Letter. FDA noted that multiple groups were involved in the review of this letter, including the division, the Office of Surveillance and Epidemiology and the Office of Chief Counsel (OCC). The letter would be forwarded to Amgen as soon as we get internal concurrence on it.

Amgen asked if they could send all the REMS documents before the letter, to aid with the process. FDA did not think it was a good idea but told Amgen that we would get back to them after we consult with the appropriate group. Amgen made it clear to the FDA that they would rather wait for an approval than to receive a Complete Response Letter.

**Appears This Way  
On Original**

**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Wednesday, June 25, 2008 9:31 AM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** Information Request (REMS)

**Attachments:** FDA CommentsNplate REMS 6.24.08.doc; FDA RevisedNplateMaterials 6.24.08.zip

Dear Mei Ling:

Please see attached FDA's comments in response to your June 3, 2008 draft "Nplate REMS"; "Corresponding Response to Questions" (RTQ) dated May 30, 2008, and subsequent June 20, 2008 RTQ.



FDA  
CommentsNplate REMS (

In addition, we have also included in this email the following revised (track changes) materials (in the zip file):

- **HCP Intro letter**
- **Patient/Caregiver Intro letter**
- **HCP Enrollment Form**
- **Patient Enrollment Form**
- **Institution Enrollment Form**
- **HCP NEXUS Brochure**
- **Patient NEXUS Brochure**



FDA  
RevisedNplateMaterials (

These documents will be the talking points for today's t-con. Please let me know know if you have any questions.

Thanks,

*Florence O. Moore, M.S.*  
*Acting Team Leader, Regulatory Project Management*  
FDA/CDER/OODP/DMIHP  
Phone: 301-796-2050  
Fax: 301-796-9849

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       Deliberative Process

Withheld Track Number: Administrative- 4

Record of telephone conversation

BLA 125268/0

Today's date: June 25, 2008

Speakers: Dwaine Rieves for FDA  
Paul Eiesenberger for Amgen

**FDA Attendees:** Dwaine Rieves, Suzanne Berkman, Claudia Karwoski, Kathy Robie Suh, Kassa Ayalew and Florence Moore

**Amgen Attendees:** Paul Eisenberg, George Dimitrov, Steven Cha, Lisa Erickson, Diego Wyszynski, Mei Ling Chang-Lok, Sarah Khalil, Anne Lauritzen, Max Colao, Susan Boynton, Mark Rutstein, Stewart Akahoshi, Dietmar Berger

FDA requested this telephone conference to discuss the revised Nplate , Corresponding Response to Questions (RTQ) REMS submitted by Amgen on May 30 and June 20, 2008. The following Nplate materials were also discussed.

- HCP Intro letter
- Patient/Caregiver Intro letter
- HCP Enrollment Form
- Patient Enrollment Form
- Institution Enrollment Form
- HCP NEXUS Brochure
- Patient NEXUS Brochure

FDA indicated that we will be sending Amgen a REMS information request letter. The letter is currently under review internally in the FDA and would be forwarded to Amgen as soon as we get internal concurrence on it. FDA advised Amgen to send all REMS documents before the letter is issued as we will not have enough time to review new materials that have not yet been submitted. FDA indicated that if Amgen agrees with the proposed REMS discussed at this t-con we will be able to send them the IR letter sooner than later.

## Moore, Florence O

---

**From:** Moore, Florence O  
**Sent:** Friday, June 20, 2008 3:32 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** STN 125268/0 Nplate information request

**Importance:** High

**Follow Up Flag:** Follow up  
**Due By:** Monday, June 23, 2008 3:30 PM  
**Flag Status:** Flagged

Hi Mei Ling:

Please provide a response to the comment below by COB Monday 6/23/08 or provide a timeline you can respond to this asap:

In section 3.5.1 of the REMS document, the Sponsor says they will conduct market research with HCPs and patients. The proposed REMS draft document (6.3.08) fails to detail how the Nplate educational materials will be evaluated. Submit for review all methodology and instruments used to evaluate the effectiveness of the education about the safe use of Nplate.

This should include, *but not be limited to*:

- Sample size and confidence associated with that sample size
- How the sample will be determined (selection criteria)
- The expected number of patients/physicians/pharmacists surveyed
- How the participants will be recruited
- How and how often the surveys will be administered
- Explain controls used to minimize bias
- Explain controls used to compensate for the limitations associated with their methodology

The Sponsor should submit all survey instruments (questionnaires and moderator's guide) for review.

Provide any background information on testing survey questions and the correlation to the educational materials, and explain what will be done with the resulting data from the surveys.

Thanks,

Florence O. Moore, M.S.  
Acting Team Leader, Regulatory Project Management  
FDA/CDER/OODP/DMIHP  
Phone: 301-796-2050  
Fax: 301-796-9849

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LICENSING ACTION RECOMMENDATION

Applicant: AMGEN INC. STN: 125268/0

Product: Romiplostim (Nplate)

Indication / manufacturer's change :  
Treatment of thrombocytopenia in adult patients with chronic immune (idiopathic)  
thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids,  
immunoglobulins or splenectomy

- Approval:
  - Summary Basis For Approval (SBA) included
  - Memo of SBA equivalent reviews included
- Refusal to File: Memo included
- Denial of application / supplement: Memo included

RECOMMENDATION BASIS

- Review of Documents listed on Licensed Action Recommendation Report
- Inspection of establishment  Inspection report included
- BiMo inspections completed  BiMo report included
- Review of protocols for lot no.(s) \_\_\_\_\_
- Test Results for lot no.(s) \_\_\_\_\_
- Review of Environmental Assessment  FONSI included  Categorical Exclusion
- Review of labeling Date completed \_\_\_\_\_  None needed

CLEARANCE - PRODUCT RELEASE BRANCH

- CBER Lot release not required
- Lot no.(s) in support - not for release \_\_\_\_\_
- Lot no.(s) for release \_\_\_\_\_
- Director, Product Release Branch \_\_\_\_\_

CLEARANCE - REVIEW

Review Committee Chairperson: \_\_\_\_\_ Date: \_\_\_\_\_

Product Office's Responsible Division Director(s)\*: \_\_\_\_\_

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

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

DMPQ Division Director\* : [Signature] Date: 6/19/08

\* If Product Office or DMPQ Review is conducted

CLEARANCE - APPLICATION DIVISION

- Compliance status checked  Acceptable  Hold Date: \_\_\_\_\_
- Cleared from Hold Date: \_\_\_\_\_

Regulatory Project Manager (RPM) \_\_\_\_\_ Date: \_\_\_\_\_

Responsible Division Director \_\_\_\_\_ Date: \_\_\_\_\_  
(where product is submitted, e.g., application division or DMPQ)

**Moore, Florence O**

**From:** Ali Ibrahim, Ebla  
**Sent:** Wednesday, June 18, 2008 4:51 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Cc:** Moore, Florence O  
**Subject:** Nplate REMS  
**Attachments:** 6-17-08 FDA Comments.doc

Mei Ling,

Please find attached comments and questions for the Nplate REMS. Thank you.

*Ebla Ali Ibrahim, MS  
Regulatory Health Project Manager  
Division of Medical Imaging and 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:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Wednesday, June 18, 2008 11:08 AM  
**To:** Ali Ibrahim, Ebla  
**Cc:** Moore, Florence O  
**Subject:** RE: FDA Attendees

Hi Ebla,  
Could you please email it to me? Thank you!

---

**From:** Ali Ibrahim, Ebla [mailto:Ebla.Ali-Ibrahim@fda.hhs.gov]  
**Sent:** Wednesday, June 18, 2008 7:00 AM  
**To:** Chang-Lok, Mei Ling  
**Cc:** Moore, Florence O  
**Subject:** RE: FDA Attendees

Mei Ling,

The reviewers for REMS have some comments and questions. How would you like me to forward it to you, via email or fax? Please advise. Thank you.

*Ebla Ali Ibrahim, MS*

6/19/2008

*Regulatory Health Project Manager  
Division of Medical Imaging and 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:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Tuesday, June 17, 2008 6:21 PM  
**To:** Ali Ibrahim, Ebla  
**Cc:** Moore, Florence O  
**Subject:** FDA Attendees

Hello Ebla,

Could you please send me the list of the FDA attendees for our t-con today?

From Amgen's side, we have:

Paul Eisenberg  
Susan Boynton  
Roy Baynes  
Mei Ling Chang-Lok  
Dietmar Berger  
Monica Batra  
Yow-Ming Wang  
Beth Hinkle

Thank you,

Mei Ling

June 17, 2008  
BLA 125268/0  
Nplate REMS

Listed below are some of the initial review findings regarding the REMS. We anticipate the need for additional clarifications as our review progresses. If some or all of these items can be readily addressed, please submit the items. Alternatively, you may wish to await and address all items with a single, composite submission.

- Procedures for hospitals/institutions:
  - Based on the proposed submission, it is not clear how the institution/hospital component will work (both inpatient and outpatient). Prescribing via institutions/hospitals to outpatients may account for a large proportion of prescribing (vs private practice) given that patients who are difficult to treat are often referred to large, academic institutions. Procedures for what is expected of the hospital/institution are essential to program effectiveness. Please provide a clear, detailed explanation of how this component will work.
- Educational materials for hospitals/institutions:
  - Amgen has not provided any education directed at hospitals/institutions to explain the requirements. Educational materials to explain the requirements, procedures, and expectations must be developed if hospitals/institutions are part of NEXUS.
- Procedures for inpatient to outpatient transition:
  - It is unclear how the NEXUS program will identify who is an inpatient vs an outpatient to help to facilitate transition. Continuity of care from inpatient to outpatient is difficult and including a prescriber's name/phone on the baseline data collection form (which does not need to be completed for the patient to receive Nplate and the patient could be discharged before it is completed) is not sufficient to ensure transition.
- Submit the patient roster monitoring form.
- Submit a mockup of "training kit" that will comprise all the materials.
- Submit all enrollment forms, safety questionnaires and educational materials in Word versions.
- Include the dosing calculator in the training kit, as stated in the RTQ on page 6.
- Please clarify how the risk-specific questionnaires will be utilized.

## MEMORANDUM OF TELECON

DATE: June 17, 2008

APPLICATION NUMBER: BLA 125268

BETWEEN:

Name:

Paul Eisenberg  
Susan Boynton  
Roy Baynes  
Mei Ling Chang-Lok  
Dietmar Berger  
Monica Batra  
Yow-Ming Wang  
Beth Hinkle

Representing: Amgen

AND

Name: DIVISION of Medical Imaging and Hematology Products, HFD-160

Rafel Rieves, M.D - Division Director  
Tushar Kokate, Ph.D. - Pharmacologist  
John Leighton, Ph.D. - Pharmacologist  
Yanli Ouyang, Ph.D. - Pharmacologist Team Leader covering for Adebayo  
Laniyonu (Team Leader- Pharmacologist)  
Ebla Ali Ibrahim, M.S. - Regulatory Health Project Manager covering for  
Florence Moore

SUBJECT: Pharm/Tox Clarification

Amgen requested to meet with FDA to clarify the three proposed changes to the pharmacology section of the labeling (PI).

Amgen explained the three proposed changes to the FDA. The FDA did not agree to the proposed changes and asked Amgen to revise the labeling back to the original labeling. Amgen agreed with the FDA to revise the labeling back to the original.  
Amgen said they would provide the FDA with the final labeling.

Ebla Ali Ibrahim, M.S.  
Regulatory Health Project Manger

LICENSING ACTION RECOMMENDATION

Applicant: AMGEN INC. STN: 125268/0

Product: Romiplostim (Nplate)

Indication / manufacturer's change: Treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy

- Approval:
  - Summary Basis For Approval (SBA) included
  - Memo of SBA equivalent reviews included
  - Refusal to File: Memo included
  - Denial of application / supplement: Memo included

RECOMMENDATION BASIS

- Review of Documents listed on Licensed Action Recommendation Report
- Inspection of establishment  Inspection report included
- BiMo inspections completed  BiMo report included
- Review of protocols for lot no.(s) \_\_\_\_\_
- Test Results for lot no.(s) \_\_\_\_\_
- Review of Environmental Assessment  FONSI included  Categorical Exclusion
- Review of labeling Date completed \_\_\_\_\_  None needed

CLEARANCE – PRODUCT RELEASE BRANCH

- CBER Lot release not required
- Lot no.(s) in support – not for release \_\_\_\_\_
- Lot no.(s) for release \_\_\_\_\_
- Director, Product Release Branch \_\_\_\_\_

CLEARANCE – REVIEW

Review Committee Chairperson: Eric M. Zindel Date: 05/12/2008

Product Office's Responsible Division Director(s)\*: Kathleen A. Clouse Date: 05/12/2008

DMPQ Division Director\* : \_\_\_\_\_ Date: \_\_\_\_\_

\* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

- Compliance status checked  Acceptable  Hold Date: 4/19/08
- Cleared from Hold Date: \_\_\_\_\_

Regulatory Project Manager (RPM) [Signature] Date: 5/15/08

Responsible Division Director (where product is submitted, e.g., application division or DMPQ) [Signature] Date: 6-13-08

**Moore, Florence O**

---

**From:** Moore, Florence O  
**Sent:** Tuesday, June 10, 2008 1:56 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** Revised Final Draft USPI  
**Attachments:** draft-labeling-text-plr-redline (06-10-2008) (2).doc

Dear Mei Ling:

Please see attached FDA's final draft of the Nplate USPI. Please double check for typos and resubmit for the final action letter by COB 6/13/08.



draft-labeling-text-  
plr-redlin...

Also note that we do not have any questions as at now regarding the REMS so we do not need a t-con this week. If you have any questions please do give me a call or email me.

Thanks,

Florence O. Moore, M.S.  
Acting Team Leader, Regulatory Project Management  
FDA/CDER/OODP/DMIHP  
Phone: 301-796-2050  
Fax: 301-796-9849

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Withheld Track Number: Administrative 5

**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Wednesday, June 04, 2008 11:55 AM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: New carton labels with the word "dilute" removed

Hi Mei-Ling:

regarding the carton and container labels you sent here are some of the comments we have:

Manufacturer's license number should be associated with (close to) the manufacturer's name and address (this was communicated to you earlier).

Placement of "DO NOT SHAKE reconstituted solution" and "Reconstituted with 0.72mL Sterile Water for Injection, USP" on two separate panels seems a bit off. It seems the latter is almost lost in the list of ingredients.

Thanks,  
Florence

---

**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Monday, June 02, 2008 1:30 PM  
**To:** Moore, Florence O  
**Subject:** New carton labels with the word "dilute" removed

Dear Florence,

Please find below the new carton labels with a minor change to align with US PI change per FDA request from May 16, 2008 to remove the word "dilute".  
Thank you,

Mei Ling

6/11/2008

Record of telephone conversation

BLA 125268/0

Today's date: May 28, 2008

Speakers: Dwaine Rieves for FDA  
Paul Eiesenberger for Amgen

**FDA Attendees:** Dwaine Rieves, Suzanne Berkman, Claudia Karwoski, Kathy Robie Suh, Kassa Ayalew and Florence Moore

**Amgen Attendees:** Eiesenberger, Mei Ling Chang-Lok, Monica Batra, Susan Boynton, Dietmar Berger, Mark Rustein, Reggie Kelly, Steven Cha, Dan Chirby, Christine Dale, Wende Davis, Beth Hinkle, Yow Ming Wang, Sarah Khalil, Lisa Erickson, Steven Cha, Matthew Guo, Roy Baynes, and Diego Wyszynski

Amgen requested this t-con to discuss their proposal and seek further clarification regarding the Risks Evaluation and Mitigation Strategy (REMS). Amgen noted that a key component of the REMS is complete capture of safety information for all patients, regardless of diagnosis. Data collection includes the indication/diagnosis code. Because of liability issues, Amgen has been advised by their legal team to track use data separately. Amgen explained that all safety components recommended by FDA will be included in the program and linked to product distribution however, Amgen will not be ~~\_\_\_\_\_~~ Data regarding diagnosis will be handled separately from the other safety data.

Amgen indicated that the NEXUS program will operate under a controlled access program. The program will not prevent patients from getting the medication, but would dis-enroll physicians who are not compliant. Amgen went through the product ordering requirements and audit systems that will ensure tracking of all patients in the Nplate registry to minimize diversion (see attached).

Amgen proposed the following timelines for submissions:

5/30/08- to provide response to FDA May 16, 2008 REMS recommendations

5/30/08- to provide all safety forms

Early week of 6/2/08- to provide REMS tools/ component related to products.

Record of telephone conversation

BLA 125268/0

Today's date: May 22, 2008

**Speakers:** Dwaine Rieves for FDA  
Paul Eiesenberger for Amgen

**FDA Attendees:** Dwaine Rieves, Faranak Jamali, Suzanne Berkmann, Claudia Karwoski, Hong Zhao, Angela Men, David Frucht and Florence Moore

**Amgen Attendees:** Monica Batra, Susan Boynton, Dietmar Berger, Mark Rustein, Reggie Kelly, Steven Cha, Dan Chirby, Christine Dale, Wende Davis, Beth Hinkle, Yow Ming Wang, Sarah Khalil, Lisa Erickson, Steven Cha, Matthew Guo, Roy Baynes, and Diego Wyszynski

This is the fourth of the scheduled weekly teleconferences requested by Amgen after the March 12, 2008 ODAC meeting to address the Agency's questions regarding Nplate and to help facilitate the review process. FDA and Amgen used this t-con to discuss and seek clarification on the attached FDA REMS sent to Amgen on May 16, 2008.

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       Deliberative Process

Withheld Track Number: Administrative- 6



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

---

Memorandum

**From:** Florence Moore *FM*  
**To:** STN 125268/0 File  
**Subject:** Safety Update Review  
**Sponsor:** Amgen, Inc.  
**Products:** Nplate (romiplostim)  
**Date:** May 20, 2008

Safety update review(s) see clinical review section 7.5



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

---

Memorandum

**From:** Florence O. Moore, M.S. *FM*  
**To:** STN 125268/0 File  
**Subject:** Sponsor Financial Disclosure Review  
**Sponsor:** Amgen, Inc.  
**Products:** Nplate (romiplostim)  
**Date:** May 20, 2008

Sponsor's financial disclosure review: see clinical review section 3.3

Record of telephone conversation

BLA 125268/0

Today's date: May 8, 2008

Speakers: Dwaine Rieves for FDA  
Susan Boynton for Amgen

**FDA Attendees:** Dwaine Rieves, Kathy Robie-Suh, Kassà Ayalew, Faranak Jamali, Suzanne Berkmann, Claudia Karwoski, Hong Zhao, Angela Men, David Frucht, Timothy Lape and Florence Moore

**Amgen Attendees:** Monica Batra, Susan Boynton, Dietmar Berger, Mark Rustein, Reggie Kelly, Steven Cha, Dan Chirby, Christine Dale, Wende Davis, Beth Hinkle, Yow Ming Wang, Sarah Khalil, Lisa Erickson, Steven Cha, Matthew Guo, Roy Baynes, and Diego Wyszynski

This is the third of the weekly scheduled teleconferences requested by Amgen after the March 12, 2008 ODAC meeting to address the Agency's questions regarding Nplate and to help facilitate the review process. FDA and Amgen used this t-con to discuss the following:

FDA informed Amgen that we did not have major changes to the last revised physician package inserted provided by Amgen on 4/25/08, but we made minor edits and are in the process of reviewing the Medication Guide with DSRCs. Regarding Amgen's REMS submitted on 4/29/08 and formally to the BLA on 4/30/08, FDA informed Amgen that it is still under review. However, the preliminary review shows that Amgen dropped the goals and objectives of the REMS and should put it back in the document. Amgen stated that this was not intentional and will provide FDA the goals via email and also put it back in the REMS documents. FDA informed Amgen that FDA will provide Amgen draft questionnaires for patient status and safety; patient discontinuation and patients' post-discontinuation follow up by 5/16/08 for Amgen's comments.

Regarding Post Marketing Commitments, FDA will modify Amgen's proposed draft PMCs submitted 5/1/08 for Amgen's final comments and to provide timelines for the PMCs. FDA explained that after consulting with the QTc experts regarding EKG/ECGS monitoring, given that romiplostim is a peptibody with molecular weight of 59 kDa, it is unlikely that romiplostim will have access to the hERG pore from the intracellular side. However, Amgen has not collected adequate ECGs during the development of romiplostim to rule out other off-target cardiac effects. FDA recommends that Amgen continues routine ECG monitoring in the post-marketing clinical studies to capture any important cardiac effects in the patient population following chronic dosing of romiplostim. ECGs should be collected after patients have received multiple doses of romiplostim.

Regarding the lactation study proposal and pregnancy registry, FDA stated that these are still under review and would provide comments to Amgen's proposed draft as soon as FDA get a chance to discuss them internally.

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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:** May 1, 2008

**From:** *Florence Moore, M.S. Regulatory Project Manager (OOPD/DMIHP)*

**Subject:** STN 125268/0: Labeling Meeting

---

Labeling Meeting to discuss Amgen's proposed package insert for romiplostim (Nplate) which is indicated for idiopathic thrombocytopenic purpura (ITP).

The team met to go over the physician package insert (PI) and Medication Guide received from Amgen April 25, 2008.

FD Attendees included:

Dwaine Rieves  
Kathy Robie Suh  
Kassa Ayalew  
Faranak Jamali  
Florence Moore  
Hong Zhao  
Angela Men  
David Frucht  
Suzanne Berkman



FDA recommended that Amgen consider developing a kit containing syringes that will be used with the product, and if Amgen does not go that route, Amgen should consider referring to a specific syringe to be used with the product to avoid medication errors. Amgen acknowledged FDA's recommendations and thoughts.

Amgen stated that based on the overall data as well as considering the molecular size and specificity of romiplostim Amgen believes that romiplostim does not prolong the QTc interval through either direct or indirect effects. Amgen indicated that romiplostim does not prolong the QTc interval and that a further evaluation of the impact of romiplostim on QTc interval is not warranted. Amgen also stated that a post marketing requirement for further evaluation is not necessary. FDA agreed that a detailed QTc study is not needed for this indication, however, FDA recommended that Amgen should perform evaluation of EKG at baseline and periodically and indicated that this is generally an expectation for both large and small molecule products. FDA noted that we will have an internal discussion with the QTc division and will provide Amgen feedback for the next steps regarding QTc evaluation.

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Memorandum

**Date:** April 22, 2008  
**From:** Florence O. Moore, M.S., DMIHP/OODP/CDER *FM*  
**Subject:** OSE Preapproval Safety Conference for STN 125268/0- Nplate

The Preapproval Safety Conference was held between the Division of Medical Imaging and Hematology Products (DMIHP) and the Office of Surveillance and Epidemiology (OSE) to discuss Amgen's Nplate™ (romiplostim) which is indicated for treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to corticosteroids, immunoglobulins or splenectomy.

**FDA Attendees included:**

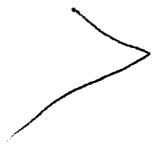
Florence Moore	Betsy Scroggs
Rafel Rieves	Susan Lu
Kathy Robie Suh	Suzanne Berkman
Faranak Jamali	Chardae Araojo
Angela Men	Ann Mahon
Hong Zhao	Sammie Beam
Kassa Ayalew	Ira Krefting
Min Ha Tran	Allen Brinker
Ebla Ali Ibrahim	
Jyoti Zalkikar	
Janet Anderson	

The OSE safety conference began with a presentation and overview of the application and the main safety concerns by DMIHP to OSE.

The team discussed the following:

Why a QTc study in ITP patients will not be required as a Post Marketing Commitment (PMC). The clinical pharmacology reviewers explained that the potential of Nplate treatment on QT interval has not been studied. Romiplostim is an Fc fusion protein (peptibody) with relatively smaller molecular weight (~59 KDa) than that of most other therapeutic proteins and monoclonal antibodies. However, the potential effect of romiplostim on the QT interval via on-target and/or off-target mechanisms cannot be ruled out. Given that the potential of Nplate treatment on QT interval was not evaluated during clinical studies in patients with chronic ITP and there are no additional clinical studies planned or ongoing for this proposed orphan indication, the sponsor should address the QT issue

OSE asked if there were any concerns regarding the population (age group) receiving the product. DMIHP indicated that there were no age related clinical concerns.



The group talked about a PMR to conduct a Randomized Controlled study in patients with ITP with different platelet count levels comparing platelet count response in relation to the rate of bleeding, but the team acknowledged this as well as collecting data for loss of efficacy and immunogenicity would be logistically challenged. If possible the sponsor should collect bleeding in the Risk Evaluation and Management Strategies (REMS) questionnaire.

The review team indicated that there is a high potential of off-label use. The restricted distribution program for the product is still under discussion with the sponsor. The off-label use will be handled through the REMS under discussions. Both physicians and patients will be required to enroll in the active surveillance program as part of the REMS.

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Memorandum

**Date:** April 21, 2008

**From:** *Florence Moore, M.S. Regulatory Project Manager (OOPD/DMIHP)*

**Subject:** STN 125268/0: Labeling Meeting

---

Labeling Meeting to discuss Amgen's proposed package insert for romiplostim (Nplate) which is indicated for idiopathic thrombocytopenic purpura (ITP).

The team met to go over the physician package insert (PI) received from Amgen April 17, 2008.

FD Attendees included:

Karen Weiss  
Dwayne Rieves  
Kathy Robie Suh  
Kassa Ayalew  
Faranak Jamali  
Florence Moore  
Hong Zhao  
Angela Men  
Richard Abate  
David Frucht  
Richardae Araojo  
Suzanne Berkman

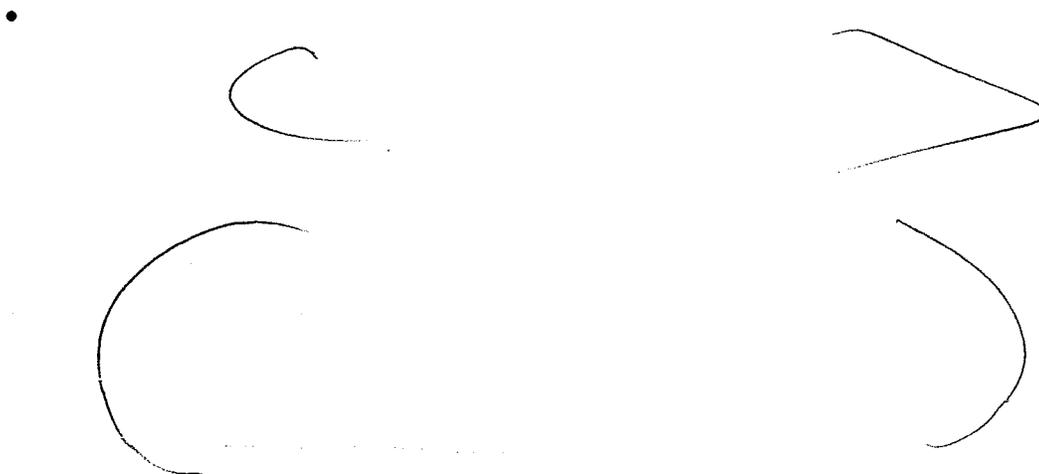
Amgen Telecon  
BLA 125268  
April 18, 2008  
2:00 p.m. – 2:30 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participant: David Frucht, Kathleen Clouse, Florence Moore  
Amgen participants: Lisa Erickson, Brent Kendrick and Camilla Santos

The following issues were discussed:

Amgen requested clarification regarding the following point:



FDA clarified that although we agree with Amgen's comments in principle when



In addition, the following points were discussed:

- FDA advised Amgen to be consistent in referring to the product as romiplostim and/or Nplate in future submissions, and not to refer to it as AMG-531 for consistency and to avoid confusion.
- FDA requested clarification on the concentration of the product listed in Table 1 of the package insert, because a simple calculation involving the mass of romiplostim and the volume of diluent to be added does not yield the indicated concentration (500 mcg/mL). Amgen will discuss internally and explain this discrepancy.
- FDA recommended that the proposed wording of the DS and DP stability protocols included in the BLA and intended for use subsequent to product approval be modified to clearly state that these studies are intended to extend expiry dating, if this is correct. Also, the wording indicating that Amgen would consider whether or not to place lots on stability studies following major manufacturing changes should be deleted, as this decision would be the purview of FDA.

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**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Tuesday, April 15, 2008 3:26 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: Question for FDA

Dear Mei Ling:

Patient #311131 (UK195490) developed myelofibrosis (positive trichrome stain for collagen) after completing study 105 and at the beginning of study 213. He started to have anemia (Hb: 7) and severe refractory thrombocytopenia early in study 213 (extension study). Bone marrow report prior to Romiplostim exposure was negative for myelofibrosis.

Thanks,  
Florence

---

**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Tuesday, April 15, 2008 1:10 PM  
**To:** Moore, Florence O  
**Subject:** Question for FDA

Dear Florence,

Amgen has tried to find the patient FDA referred to in the statement in section 5.1 of the label. FDA added "However, one patient in the extension study developed marrow fibrosis with cytopenias."

Could FDA please clarify the above in order for Amgen to discuss with the Agency?

Thanks,

Mei Ling

Amgen Telecon  
BLA 125268  
April 11, 2008  
1:00 p.m. – 1:30 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participant: David Frucht, Faranak Jamali, Florence Moore  
Amgen participants: Lisa Erickson, Bill Kendrick

Amgen requested this teleconference to update the agency on a few CMC and nonclinical items. Amgen indicated that there were a couple of new sites that were not included in the original BLA submission and were also not included in the pre approval inspection (PAI). According to Amgen materials tested in the new sites had no impact on final drug product; however, raw materials used for the drug substance formulation were tested at these sites. FDA asked Amgen to submit this new updates officially to the document room for FDA review as DMPQ input is needed to determine impact on the facility review.

The attached were discussed.

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       Deliberative Process

Withheld Track Number: Administrative-   7

**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Thursday, April 10, 2008 7:46 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** STN 125268/0 FDA Draft Labeling

**Follow Up Flag:** Follow up  
**Due By:** Thursday, April 17, 2008 3:30 PM  
**Flag Status:** Flagged

**Attachments:** FDA Version 2 Amgen Nplate 4.10.08 revised clean copy.doc

Dear Mei Ling,

Please see attached FDA's first draft proposal of the PI label with all the sections. Please respond by COB 4/17/08.



FDA Version 2  
Amgen Nplate 4.1...

Thank you.

**Florence O. Moore, M.S.**  
**Acting Team Leader, Regulatory Project Management**  
**FDA/CDER/OODP/DMIHP**  
**Phone: 301-796-2050**  
**Fax: 301-796-9849**

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Deliberative Process

Withheld Track Number: Administrative-

8



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:** April 10, 2008

**From:** *Florence Moore, M.S. Regulatory Project Manager (OOPD/DMIHP)*

**Subject:** STN 125268/0: Labeling Meeting

---

Labeling Meeting to discuss Amgen's proposed package insert for romiplostim (Nplate) which is indicated for idiopathic thrombocytopenic purpura (ITP).

The team met to go over the clinical sections of the physician package insert (PI).

FD Attendees included:

Dwaine Rieves  
Kathy Robie Suh  
Kassa Ayalew  
Faranak Jamali  
Florence Moore  
Hong Zhao  
Angela Men  
Richard Abate  
David Frucht  
Richardae Araojo  
Suzanne Berkman

**Moore, Florence O**

---

**From:** Moore, Florence O  
**Sent:** Tuesday, April 08, 2008 5:32 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** Agenda REMS for T-con

**Attachments:** FDA NPLATE tcon agenda 4.9.08 final (3).doc

Hi there Mei-Ling,

Please see attached the FDA REMS document that we will like to discuss with you tomorrow.



FDA NPLATE tcon  
agenda 4.9.08 ...

We look forward to the discussions tomorrow.

Best Regards,

*Florence O. Moore, M.S.  
Regulatory Health Project Manager  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation Research  
Food and Drug Administration  
0903 New Hampshire Avenue, Rm 2381  
Silver Spring MD 20903*

*Tel: 301-796-1423  
Fax: 301-796-9849*

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125268/0

Amgen, Inc.  
ATTENTION: Mei-Ling Chang-Lok, Ph.D., RAC  
Director, Regulatory Affairs  
One Amgen Center Drive  
Thousand Oaks, CA 91320-1799

APR 03 2008

Dear Dr. Chang-Lok:

Please refer to your biologics license application submitted under section 351 of the Public Health Service Act for Nplate.

We received your March 26, 2008, amendment to this application on March 27, 2008, and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to July 23, 2008, to provide time for a full review of the amendment.

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, Florence O. Moore, at (301) 796-2050.

Sincerely,

Rafel Dwaine Rieves, M.D.  
Acting Director  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation and Research



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:** April 3, 2008

**From:** *Florence Moore, M.S. Regulatory Project Manager (OOPD/DMIHP)*

**Subject:** STN 125268/0: Labeling Meeting

---

Labeling Meeting to discuss Amgen's proposed package insert for romiplostim (Nplate) which is indicated for idiopathic thrombocytopenic purpura (ITP).

The team met to go over the clinical sections of the physician package insert (PI). The team agreed another meeting is needed to discuss the PI before sending to the sponsor.

FD Attendees included:

Dwaine Rieves  
Faranak Jamali  
Florence Moore  
Hong Zhao  
Angela Men  
Richard Abate

**Moore, Florence O**

---

**From:** Moore, Florence O  
**Sent:** Wednesday, April 02, 2008 9:28 AM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: Information Request

Hi Mei Ling:

Regarding the carton and container labels, please note that the name, address and license number should be together. As it is right now the license number is not on the same panel as Amgen's name and address.

Thanks,  
Florence

---

**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Wednesday, March 26, 2008 8:01 PM  
**To:** Moore, Florence O  
**Subject:** FW: Information Request

Dear Florence,

Please find attached the revised container labels and carton labels. The name has been revised to one color per FDA's comment. The name is now all blue.

Thank you,

Mei Ling

---

**From:** Moore, Florence O [mailto:florence.moore@fda.hhs.gov]  
**Sent:** Tuesday, March 25, 2008 4:27 PM  
**To:** Chang-Lok, Mei Ling  
**Subject:** RE: Information Request

Dear Mei Ling:

In your response to our 2/26/08 information request letter (cover letter dated 3/11/08) and during the 3/3/08 t-con, you indicated that, "The 'N' in Nplate does not stand for anything," yet you continue to maintain the presentation of the proprietary name with the use

The Medication Error Staff questions the use of the letter 'N' in the name Nplate.

 In addition, the Medication Error Staff noted the difficult to read, and the product could be arranged in the refrigerator of a pharmacy under 'P' for 'Plate' rather than 'N' for 'Nplate'.

Best regards,  
Florence

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4/15/2008

**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Tuesday, March 25, 2008 3:49 PM  
**To:** Moore, Florence O  
**Subject:** FW: Information Request

Dear Florence,

Do you think we could get clarification with regards to the comment on the container labels and carton label?  
Thank you,

Mei Ling

The team would appreciate feedback from FDA as to the rationale for the change of the proprietary name to 1 color in order to better understand FDA's perspective for this product and future Amgen products. The name is currently trademarked with the  scheme and the team has noticed other products with  colors. The team hopes to resolve this as soon as possible in order to provide a response to FDA in a timely manner.

---

**From:** Moore, Florence O [mailto:florence.moore@fda.hhs.gov]  
**Sent:** Monday, March 24, 2008 9:37 AM  
**To:** Chang-Lok, Mei Ling  
**Subject:** Information Request:

Dear Mei Ling:

We refer you to your amendment submitted March 11, 2008 which provided responses to our advice/information request regarding the container and carton labels as well as our comments regarding the proprietary name. We have reviewed your responses and have the following comment:

Revise the container labels and carton labeling using one color in the presentation of the proprietary name.

Best regards,

*Florence O. Moore, M.S.  
Acting Team Leader, Regulatory Health Project Management  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2381  
Silver Spring MD 20903*

*Tel: 301-796-1423  
Fax: 301-796-9849*

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4/15/2008

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**MEMORANDUM**

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

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**CLINICAL INSPECTION SUMMARY**

DATE:

TO: Florence Moore, Regulatory Project Manager  
Faranak Jamali, M.D., Medical Officer  
Division of Medical Imaging and Hematology Products, HFD-160

THROUGH: Joseph P. Salewski  
Acting Branch Chief  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

FROM: Karen M. Storms, Consumer Safety Officer  
Good Clinical Practice Branch II, HFD-47  
Division of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 12-5268/0

NME: Yes

APPLICANT: Amgen, Inc.

DRUG: Romiplostin (Nplate™)

THERAPEUTIC CLASSIFICATION: Standard Review, Substantially Equivalent

INDICATION: Thrombocytopenia in subjects with idiopathic thrombocytopenic purpura (ITP)

CONSULTATION REQUEST DATE: November 9, 2007

DIVISION ACTION GOAL DATE: March 30, 2008

PDUFA DATE: April 23, 2008

**I. BACKGROUND:**

Immune (Idiopathic) thrombocytopenic purpura (ITP) is an autoimmune disorder that is usually characterized by platelet destruction caused by anti-platelet autoantibodies. AMG 531 is a recombinant protein that is expressed in *E coli*. AMG 531 stimulates platelet production by a mechanism similar to endogenous thrombopoietin concentrations (eTPO), but no sequence homology exists between AMG 531 and eTPO. Preclinical results demonstrate that AMG 531 increased platelet counts in rodents and nonhuman primates. A Phase I study in healthy volunteers showed that AMG 531 was effective in

increasing platelet counts above baseline values by more than 4-fold at the 10-µg/kg IV dose and by less than 2-µg/kg SC does. The safety results in all cohorts (.3, 1, and 10 µg/kg IV and 0.1, 0.3, 1, and 2-µg/kg SC) have been unremarkable. No deaths, serious adverse events, hospitalization, or unexpected laboratory findings were reported in the Phase 1 study.

The protocols covered during these inspections were:

- #20030105, “A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Refractory to Splenectomy”
- #20030212, “A Randomized, Placebo Controlled Study Evaluating the Efficacy and Safety of AMG 531 Treatment of Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura (ITP) Prior to Splenectomy”
- #20030213, “An Open-Label Study Evaluating the Safety Efficacy of Long-Term Dosing of AMG 531 in Thrombocytopenic Subjects with Immune (Idiopathic) Thrombocytopenic Purpura “

**II. RESULTS (by protocol/site):**

Name of CI	City, State*	Protocol #	Insp. Date	Final Classification
[REDACTED]	[REDACTED]	20030105/6	[REDACTED]	Pending
		20030212/8		
		20030213/17		
[REDACTED]	[REDACTED]	20030105/3	[REDACTED]	Pending
		20030212/4		
		20030211/7		
Edo Vellenga, M.D.	Groningen, Netherlands	20030105/4 20030213/4	2/4-6/08	VAI
Amgen Inc.	Thousand Oaks, CA	20030105 20030212 20030213	2/21-3/5/08	Pending

Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested= Deviations(s) from regulations. Data acceptable.

VAI-Response Requested = Deviation(s) form regulations. See specific comments below for data acceptability

OAI = Significant deviations for regulations. Data unreliable.

1.

**Protocols 20030105; 20030212; and 0030213**

a. **What was inspected:** Protocol 20030105 – 6 subjects screened, enrolled, and completed. Five serious adverse events (SAEs) were reported and considered not related to the study drug. Subject 301632 died of atypical pneumonia on [REDACTED] the subject’s End of Study visit was February 9, 2006. Protocol 20030212 – 10 subjects screened (2 screen failures), 8 enrolled and 7 completed (Subject 301655 withdrew consent due to probability of spontaneous remission of ITP and inability to come for weekly clinic visits [completed week 23 visit June 27, 2006]. Two SAEs were reported and considered not related to the study drug. Protocol 20030213 – 19 subjects screened and enrolled, 13 ongoing, 6 ended study (Subject 1624 transferred to [REDACTED], Subject 301601 ended study due to possible ITP remission, Subject 301633 and 301637 withdrew consent, Subject 301651 died on [REDACTED] of cardiac arrest [AMG 531 last administered March 2, 2006] and Subject 301630 died on [REDACTED] of pneumonia [AMG 531 last administered December 31, 2007]. Twenty-two SAEs were reported and one (Subject 301658 myocardial infarction) was considered related to the study drug. Informed consent for the bone marrow biopsy was included in the ICF. **There were no bone marrow biopsies performed at Site 016.**

The following study-related records were reviewed: original source data, informed consent forms (ICF), case report forms (CRF), test article accountability, and correspondence with the sponsor and institutional review board (IRB). Study records for all subjects were reviewed for eligibility, protocol adherence, primary efficacy endpoint, and adverse event reporting. Protocol specified blinding/randomization procedures were followed; however for Protocol 20030105, Subject 301630 received/administered a vial assigned to Subject 301637. Subject 301630 was randomized to the AMG 531 Treatment Group whereas Subject 301637 was randomized to the Placebo Treatment Group. The data appeared to be accurately reported and there was no evidence of underreporting of adverse events (AEs).

b. **General observations/commentary:** A Form FDA 483 Inspectional Observations was issued at the conclusion of the inspection citing: An Investigation was not conducted in accordance with the signed statement of investigator and investigational plan; specifically, failure to follow dosing adjustments according to the protocols; randomized subject received the wrong vial of study drug; SAEs were not reported according to the protocol requirements; and subject failed to meet eligibility criteria. Failure to report promptly to the IRB all unanticipated problems involving risk to human subjects or others; specifically, numerous IND Safety Reports and the Investigator's Brochure Version 5.0, which included safety data, were not promptly submitted to the IRB.

c. **Assessment of data integrity:** Based on preliminary review of email correspondence from the field, data from this site appear acceptable.

2.

**Protocols 20030105; 20030212; and 2003021**

a. **What was inspected:** Records for all subject were reviewed for all three protocols. Field investigator stated that all subjects meet inclusion criteria and all subjects received informed consent prior to any study procedures.

b. **General observations/commentary:** There was no Form FDA 483 issued at the conclusion of the inspection. Based on email communication with the field investigator, the inspection is classified as NAI. Should review of the final inspection report reveal information that would change the classification of the inspection, the review division will informed.

c. **Assessment of data integrity:** Based on preliminary review of email correspondence for the filed, data from his site appear acceptable.

3. **Edo Vellenga, M.D., Universitair Medisch centrum Groniingen, Netherlands –  
Protocols 20030105 and 20030213**

a. **What was inspected:** At this site, 6 subjects were screened; 4 subjects completed the study. There were new AE/s reported for 2007 and 2008 that did not appear on the line listing. Subject 310830 experienced hematuria, chest pain, back pain; subject 310831 experienced tinnitus, myalgia, pyrosis; and subject 310833 experienced non-insulin dependent diabetes mellitus.

b. **General observations/commentary:** A Form FDA-483 was issued at the conclusion of the inspection with the following violation noted. For Protocol 20030105 1) subjects 10830, 10831, 10832, and 10833 received study medication beyond the 24 week protocol schedule; 2) numerous instances of all 4 subjects' doses of test article incorrectly increased or incorrectly maintained at the previous dose; 3) 3 of the 4 subjects had test article doses calculated using the wrong weights throughout the study instead of using the protocol required screening weight. Dr. Vellenga adequately responded to the inspectional findings in a letter dated 2/14/08.

I spoke with the review division Medical Officer, Faranak Jamali and Team Leader, Dwaine Rieves regarding the problems with dose adjustments and dose calculations as well as the 4 subjects receiving two additional doses of study drug prior to the wash-out period required by the protocol in order to enter the open label portion of the study. Dr. Rieves was aware of these types of problems with this study drug. He also acknowledged that there are significant problems with the calculations and titrations of this drug. Dr. Rieves said he would be more concerned if the problems noted above did not happen, unfortunately, it is the nature of romiplostim.

c. **Assessment of data integrity:** Data from this site appear acceptable.

**4. Amgen, Inc., Thousand Oaks, CA 91320  
Protocols 20030105; 20030212; and 0030213**

a. **What was inspected:** Total number of subjects screened, enrolled and completing the study at the 3 sites:

Study 20030105: Screened	Enrolled	Completed	Discontinued
Site 001	4	3	0
Site 016	6	6	0
Site 108	6	4	0

Study 20030212			
Site 001	5	4	4
Site 016	8	8	7
Site 108	0	0	0

Study 20030213 (On-going)			
Site 001	21	17	0
Site 016	18	17	0
Site 108	4	4	0

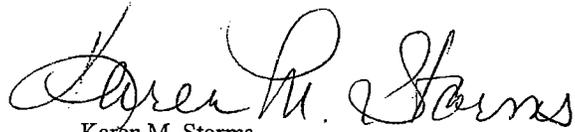
Number of subject records reviewed during the inspection: Study 20030105: 20; Study 20030212: 31; Study 20030213: 39. There was not any evidence of under-reporting of AE. The primary efficacy endpoint data were verified. There were isolated data entry errors observed on CRFs, but the firm did not notice the errors during the review of the CRFs. For example: dose volume and "Mean Platelet Volume" and one of the reviewed monitoring report was not submitted within the firm's 10 day timeframe.

b. **General observations/commentary:** There was no Form FDA 483 issued at the conclusion of the inspection.

c. **Assessment of data integrity:** Based on preliminary review of email correspondence from the field, data from this site appear acceptable.

**III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS**

With the limited information provided for four above mentioned sites, no major deficiencies were noted that could compromise the integrity of the data. Thus, the data reviewed is acceptable. Should the inspection report contain information that would affect the application, it will be forwarded to the Review Division.



Karen M. Storms  
Consumer Safety Officer  
Good Clinical Practice Branch II  
Division of Scientific Investigations

CONCURRENCE:

Supervisory comments



Joseph P. Salewski  
Acting Branch Chief  
Good Clinical Practice Branch II  
Division of Scientific Investigations



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:** March 25, 2008  
**From:** *Florence Moore, M.S. Regulatory Project Manager (OOPD/DMIHP)*  
**Subject:** STN 125268/0: Labeling Meeting

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First Labeling Meeting to discuss Amgen's proposed package insert for romiplostim (Nplate) which is indicated for idiopathic thrombocytopenic purpura (ITP).

The team met to go over the CMC, Non-Clinical, Clinical Pharmacology, Maternal and Pregnancy sections of the physician package insert.

FD Attendees included:

Kathy Robie Suh  
Dwayne Rieves  
Florence Moore  
Tushar Kokate  
Adebayo Laniyonu  
Richard Abate  
David Frucht  
Vivian Wang



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:** March 24, 2008

**From:** *Florence Moore, M.S. Regulatory Project Manager (OOPD/DMIHP)*

**Subject:** STN 125268/0: Labeling Meeting

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Labeling Meeting to discuss Amgen's proposed package insert for romiplostim indicated for ITP.

The review team met to discuss the indication for the product and other significant risk management evaluation strategies for labeling. The team agreed to have another labeling meeting to discuss comments that were raised at the meeting.

FD Attendees included:

Florence Moore  
Kathy Robie Suh  
Dwaine Rieves  
Faranak Jamali  
Susan Berkmann  
Claudia Karwaski  
Hong Zhao  
Angela Men

**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Monday, March 24, 2008 12:37 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** Information Request

Dear Mei Ling:

We refer you to your amendment submitted March 11, 2008 which provided responses to our advice/information request regarding the container and carton labels as well as our comments regarding the proprietary name. We have reviewed your responses and have the following comment:

Revise the container labels and carton labeling using one color in the presentation of the proprietary name.

Best regards,

*Florence O. Moore, M.S.  
Acting Team Leader, Regulatory Health Project Management  
Division of Medical Imaging and Hematology Products  
Office of Oncology Drug Products  
Center for Drug Evaluation Research  
Food and Drug Administration  
10903 New Hampshire Avenue, Rm 2381  
Silver Spring MD 20903*

*Tel: 301-796-1423  
Fax: 301-796-9849*

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**Hughes, Patricia**

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**From:** Ferguson, Shimette D  
**Sent:** Wednesday, March 19, 2008 12:40 PM  
**To:** Hughes, Patricia; CDER-TB-EER  
**Subject:** RE:

**Follow Up Flag:** Follow up  
**Flag Status:** Red

The Manufacturing Assessment and Preapproval Compliance Branch has completed its review and evaluation of the compliance below. There are no ongoing or pending compliance actions that would prevent approval of STN 125268 at this time. The inspectional data listed below has not yet been entered into FACTS. According to FACTS, the last inspection conducted for Amgen was 5/1-5/9/2007, VAI, TRP and \_\_\_\_\_ was 1/9-1/3/2006, VAI, SVL.

Shimette

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**From:** Hughes, Patricia  
**Sent:** Monday, March 17, 2008 1:15 PM  
**To:** CDER-TB-EER  
**Cc:** Randazzo, Giuseppe; Laska, Susan F  
**Subject:**

Please conduct an establishment evaluation of the following facilities in support of the BLA 125268 from Amgen for Nplate (romiplostim) The drug substance is manufactured at: Amgen, Boulder Co. FEI 3003072024 and Amgen Longmont, CO FEI 1724812 and these facilities were last inspected on 1/28-2/1/2008 by S. Laska, Paul Li-Hong Yeh, David Frucht.

The drug product is manufactured at:

\_\_\_\_\_

The action date for the BLA is April 23, 2008, but all reviews need to be completed by March 22, 2008 for internal processing of the BLA action package.

Thank you.

Patricia

RECORD OF TELEPHONE CONVERSATION

BLA 125268 (Romiplostim)

Today's date: March 14, 2008

Speakers: For FDA: Florence Moore, Faranak Jamali, Dwaine Rieves, Angela Men,  
Hong Zhao

For Amgen: Paul Eisenberg, Dietmar Berger, Susan Boynton, Monica  
Batra, Meil Ling Chang-Lok, Steven Cha, George Dimitrov, Mark Rustein

FDA called the sponsor and the following points were conveyed:

1. Amgen will submit datasets to clarify the immunogenicity data.
2. Amgen notes that they do not have endogenous TPO levels available for the 5 patients FDA requested.
3. FDA requested that Amgen justify more thoroughly the choice of 10 mcg/kg/week as a maximum dose. FDA noted that median doses in the phase 3 studies were much lower than 10 mcg/kg/week.
4. Amgen stated they would supply the information by next Wednesday March 19, 2008).

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Record of telephone conversation

BLA 125268

Today's date: March 14, 2008

Speakers: Kaye Kang, Florence Moore and Dwaine Rieves for FDA  
Amgen representatives/Dr. Johnson

FDA called Amgen to obtain the target date for submission of the risk management plan. Amgen initially stated April 1, 2008 was the target date for submission, but the Amgen team talked among themselves and then conclude that March 26 would be the date to submit the entire risk management plan.

FDA stated Amgen would be contacted if additional information was needed.

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**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Friday, March 14, 2008 2:18 PM  
**To:** Moore, Florence O; 'Chang-Lok, Mei Ling'  
**Subject:** RE: T-con Request

Hi Mei Ling:

As discussed today (March 14, 2008), FDA requests additional analyses and documentation to justify the maximum proposed dose of 10 mcg/kg/week, especially in light of the considerably lower median doses observed in the phase 3 studies. Please provide this justification as soon as possible. FDA anticipates this consideration as an important part of the labeling development.

Thanks,  
Florence

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**From:** Moore, Florence O  
**Sent:** Friday, March 14, 2008 11:01 AM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: T-con Request  
**Importance:** High

Good morning Mei Ling:

Here are the other questions the clinical team had:

1. Within the subset of phase 3 study (active group) patients who developed binding antibodies, please summarize the proportion of patients who attained
  - a) a durable platelet response
  - b) any platelet response.

Please perform the analysis uniquely for antibody development to a) TPO; to b) AMG; and to c) both TPO and AMG.

2. Please develop figures that summarizes the weekly platelet levels within the subset of phase 3 (active group) patients who developed binding antibodies to:
  - a) TPO
  - b) AMG
  - c) both TPO and AMG
3. Please develop a figure that summarizes the weekly (as data available) platelet levels within the long term extension study for patients who develop binding antibodies to:
  - a) TPO
  - b) AMG
4. Please provide information about change in eTPO level (before and after cessation of Romiplostim) in patients who developed thrombocytopenia after cessation of Romiplostim: these patients include the following:
  - a) Within the early phase clinical studies, 4 of the 57 patients and in the phase 3 controlled studies, one patient with intracranial hemorrhage

Thanks,  
Florence

3/14/2008

**From:** Moore, Florence O  
**Sent:** Thursday, March 13, 2008 6:48 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: T-con Request

Thanks Mei Ling. See below a table that needs clarification. There seems to be some discrepancies that needs to be resolved (our reviewers numbers are not matching yours).

Incidence of Immunogenicity: the highlights in red is the reviewer's calculation using the data (ABRESULT in ab.xpf) in 120-day Safety Submission

Study	Placebo					Romiplostim				
	N	Abs to Romiplostim at pre-dose	Abs to Romiplostim at post-dose	Abs to TPO at pre-dose	Abs to TPO at postdose	N	Pre-existing Abs to Romiplostim	Developing Abs to Romiplostim	Pre-existing Abs to TPO	Developing Abs to TPO
20000137A						24	2 (8.3)	0	0	0
20000137B	4	0	0			17	0	0	0	0
20010218						16	0	0	1 (6.3)	0
20050162						12	0	0	0	0
20040209						28	1 (3.6) 2 (7.1)	3 (10.7)	1 (3.6) 0	2 (7.1) 0
20060131						10	1 (10)	1 (10) 2 (20)	0	1 (10) 0
20030213						34 (107) 143 (N=107 A; N=36 P)	9 (6.4) 11 (7.7) New 2	15 (10.6) 21 (14.7)	6 (4.3) 0	8 (5.7) 0
20030105	21	2 (9.5) 3 (14.3)	1 (4.9)	2 (9.5) 0	0	42	4 (9.5) 7 (16.7)	1 (2.4)	3 (7.1) 1 (2.4)	0
20030212	20	2 (10) 4 (20)	2 (10)	4 (20) 0	0	42	1 (2.4) 3 (7.1)	3 (7.1) 5 (11.9)	2 (4.8) 0	2 (4.8) 0
Total	45	4 (8.9%) 7 (15.6)	3 (6.7)	6 (13.3%) 0	0	225 191	17 (7.5%) 17 (8.9)	23 (10.2) 32 (16.8)	12 (5.3) 1 (0.5)	13 (5.8%) 0

Thanks,  
 Florence

**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Thursday, March 13, 2008 6:27 PM  
**To:** Moore, Florence O  
**Subject:** RE: T-con Request

Thank you Florence!

We will do whatever is more convenient for you. I was trying to make the t-con as productive as possible but I am not sure how to do that since we don't have the actual request from the clin pharm reviewers yet.

Thank you again,

Mei Ling

Regulatory Project Manager  
 FDA/CDER/OODP/DMIHP  
 Phone: 301-796-2050  
 Fax: 301-796-9849

3/14/2008

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Record of Telephone Conversation

Today's date: March 7, 2008

FDA: Dwaine Rieves, Faranak Jamali, Florence Moore, Kathy Robie Suh

Amgen: Dietmar Berger, Susan Boynton, Monica Batra, Meil Ling Chang-Lok, Steven Cha, George Dimitrov, Mark Rustein

- 1) FDA briefly outlined the planned presentation and talked about the limitations of having only recently received the revised riskmap outline
- 2) Amgen provided the following feedback regarding FDA requests:
  - a) regarding the item number 5, the MI outcomes occurred in 2 patients (one patient also had a DVT and the occurrence of the DVT "trumped" the MI categorization for this patient; the other categorization would have left 1 patient identified as having only an MI
  - b) Regarding the number of patients developing binding antibodies/the number should be 12 not 13; the 13 in the report was an error; hence the accurate report would be 12 (5%)
  - c) Regarding the number of patients with neoplasms in the phase 3 studies, the total number for the placebo group should be 5/and should include occurrence of a "fibroma" in a placebo patient.

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Amgen Telecon  
BLA 125268  
March 5, 2008  
2:00 p.m. – 2:45 p.m. EDT

Conference toll-free phone number: 1-888-804-6796  
Conference Code: 8054472146

FDA participants: David Frucht (DMA), Patricia Hughes (BMT)

Amgen participants: Lisa Erickson (Regulatory Affairs), Bill Garden (Regulatory Affairs), Linda Narhi (Scientific Director, Process Sciences, spoke on extractables), Yasser Nashed-Samuel (Scientist, Process Sciences, spoke on extractables), Gary Hutchinson (Director of Transportation), Darrin Cowley (Product Quality Leader, Colorado), Clea Talley (Drug Product Team Leader), Sharon McGuire (Drug Product Validation Engineer)

The following issues were discussed:

1. FDA: Dr. Frucht requested further information regarding the additional extractable testing that had been performed on the DS container. A summary of this information was provided via email in advance of the meeting. Dr. Frucht commented that he had reviewed the submission and had several questions as follows:

FDA: Amgen reports that an extractable compound was obtained from the bottle system using r \_\_\_\_\_, Was this compound extracted using other \_\_\_\_\_

Amgen: \_\_\_\_\_

FDA: What are Amgen's future plans to characterize this extractable compound?

Amgen: \_\_\_\_\_

FDA: Dr. Frucht noted Amgen's response and indicated that this point would be discussed with his supervisors. If additional information were to be required, these inquiries would be communicated to Amgen.

Amgen: Amgen committed to providing the additional extractable testing data as an amendment to the BLA by the end of this working week.

2. FDA: Dr. Frucht requested further information regarding the validation of oceanic shipping. A summary of this requested information was provided via email in advance of the meeting.

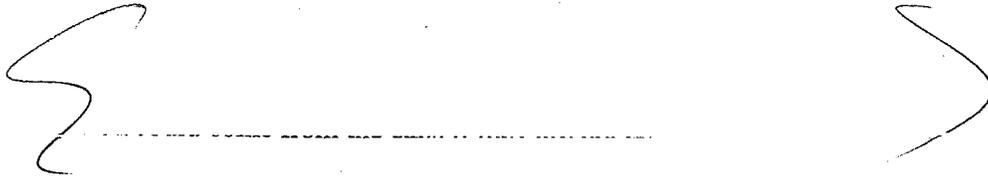
FDA: Dr. Frucht first inquired if oceanic shipping would be performed for DS, DP, or both.

Amgen: Amgen clarified that oceanic shipping would be performed only for DP. Amgen then discussed validation data involving the proposed Transport Packaging Configuration for romiplostim DP. These data indicate that oceanic shipping is less hazardous than ground shipping with regard to transient shock events, normal package handling shock events, continuous vibration and duration, and pressure changes. In addition, ocean transport is conducted in mechanically controlled refrigerated ocean containers and is monitored for the duration of shipment with temperature logging devices.

FDA: Dr. Frucht indicated these data would be sufficient to support oceanic shipping, provided these data were submitted as a formal amendment to the BLA, and it was clearly indicated that validation was performed using the Transport Packaging Configuration to be used for romiplostim DP shipment (it was not clearly indicated in the emailed pre-meeting response).

Amgen: Amgen committed to providing the amended oceanic shipping validation report by the end of this working week.

3. FDA: Dr. Hughes inquired about the use of \_\_\_\_\_ caps \_\_\_\_\_



Amgen:



FDA: Dr. Hughes stated that further discussions on this are needed internally as to requirements and further discussions on the handling of caps would occur with Amgen.

4. FDA: Dr. Hughes discussed the sterilization validation of the



## Record of Telephone Conversation

Today's date: March 3, 2008

FDA: Dwaine Rieves, Faranak Jamali, Florence Moore, Kathy Robie Suh; Susan Berkman, David Frucht, Steve Lemery, Hong Zhao, Richard Pazdur, Claudia Karwoski

Amgen: Paul Eisenberg, Dietmar Berger, Susan Boynton, Monica Batra, Meil Ling Chang-Lok, Steven Cha, George Dimitrov, Mark Rustein

Amgen requested this t-con and the following were discussed:

- 1) FDA requests for information of 26 February 2008 in regards to the two identified cases in point #5 of the FDA information request. Amgen sought FDA's guidance on the approach/extent of discussion of these cases and what FDA would like to see in Amgen's ODAC presentation.
- 2) Amgen updated FDA of their proposals following consideration of FDA's briefing book feedback on the RMP/RiskMAP proposal. Amgen indicated they had thoughtfully considered FDA's feedback and as a result had taken steps to address these comments in an updated RMP/RiskMAP proposal. Amgen stated they would like to ensure full transparency as to the revised proposal and would want to discuss the proposal as well as share their draft slides they intended to present at ODAC on this topic. Amgen stated that they are currently preparing an amendment to outline the RMP/RiskMAP proposal to be forwarded to FDA promptly. Detailed RiskMAP materials are currently in development and will also be forwarded to the FDA promptly.
- 3) Amgen briefly reviewed the outcome of a Bone Marrow Panel evaluation recently held. Amgen indicated they intend to briefly mention the outcome of the review panel assessment in their ODAC presentation. Amgen stated that they are compiling a brief paper of the information for FDA to be provided promptly.
- 4) FDA asked Amgen what the "N" in Nplate stands for and expressed concern that it seems the N could imply "normal" platelet levels. Amgen assured FDA that they will not use "Nplate" to represent or imply any such claims. Amgen indicated that in researching a trade name that could be used globally, Amgen was looking for a name that would have a good chance of securing a trade mark worldwide, would be distinct from other products, and minimize medication errors. Amgen reiterated that the "N" in Nplate does not stand for anything and the "Npl" pre-fix is so unusual that they have successfully secured this trade mark globally. Amgen stated that given the complexity of generating unique trade names globally and wanting to minimize "sound alike or look alike" concerns with other products, Amgen believes that it is important that they be able to market romiplostim using the trade name "Nplate," as FDA preliminarily approved this trade name earlier.

**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Friday, February 29, 2008 2:37 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** Re: FDA statistician's request.

Hi Mei Ling,

this is the clinical request. Please provide us the doses of Romiplostim at the time of thrombotic events in the "comprehensive ITP safety set".

thanks again,  
Florence

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**From:** Moore, Florence O  
**Sent:** Friday, February 29, 2008 1:58 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Subject:** RE: FDA statistician's request.

You are welcome. I just got another email we might need more information requested by Dr Jamali. I am seeking clarification that.

Thanks,  
Florence

---

**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Friday, February 29, 2008 1:56 PM  
**To:** Moore, Florence O  
**Subject:** RE: FDA statistician's request.

Thank you so much Florence!

---

**From:** Moore, Florence O [mailto:florence.moore@fda.hhs.gov]  
**Sent:** Friday, February 29, 2008 10:50 AM  
**To:** Chang-Lok, Mei Ling  
**Subject:** RE: FDA statistician's request.

Hi Mei Ling,

We have edited what you had with some additions.

data listings of bleeding as well as thrombosis events from study 105, 212 and 213 with platelet and dosing information prior to the events. FDA also requested separate listings for serious bleeding events and serious thrombosis events by coming Monday.

**Florence O. Moore, M.S.**  
**Regulatory Project Manager**  
**FDA/CDER/OODP/DMIHP**  
**Phone: 301-796-2050**

3/3/2008

Fax: 301-796-9849

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**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Friday, February 29, 2008 10:23 AM  
**To:** Moore, Florence O  
**Subject:** FW: FDA statistician's request.

Dear Florence,  
How are you? Happy Friday!!

I have been informed that the FDA biostatistcian had requested from our statistician data listings of bleeding events from study 105, 212 and 213 with platelet and dosing information prior to the events. FDA also requested separate listings for serious bleeding events by coming Monday. FDA biostatistician also mentioned that he will go through you for a formal request.

Florence, is this the complete request?

Thank you,

Mei Ling

3/3/2008

**Moore, Florence O**

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**From:** Moore, Florence O  
**Sent:** Friday, February 29, 2008 2:42 PM  
**To:** 'Chang-Lok, Mei Ling'  
**Cc:** 'Erickson, Lisa'  
**Subject:** RE: question about carton and label comments  
**Attachments:** Clarification of points 1a and 1c.doc

Dear Mei Ling,

please see attached clarification on questions 1a and 1c.

Thanks,  
Florence

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**From:** Chang-Lok, Mei Ling [mailto:meilingc@amgen.com]  
**Sent:** Wednesday, February 27, 2008 1:50 PM  
**To:** Moore, Florence O  
**Subject:** FW: question about carton and label comments

Dear Florence,

Could we get clarification with regards to question 1a and 1c?  
Thank you Florence,

Mei Ling

---

**From:** Erickson, Lisa [mailto:lisae@amgen.com]  
**Sent:** Tuesday, February 26, 2008 9:10 PM  
**To:** Frucht, David  
**Subject:** question about carton and label comments

Hi David,

Today we received the following comments from the clinical team on the label and I wanted to check with you regarding a couple of points that are related to CMC.

1. **Container Labels and Carton Labeling:**

- a. The strength of the product shown on the vial and carton labels should indicated in mcg units \_\_\_\_\_
- b. We recommend using \_\_\_\_\_ in the name of the product for clarity on the labels and labeling.
- c. If space allows on the container label, we recommend that you attempt distinguish the expression of strength beneath the proper name rather than a supplementary strength expression.