

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

BLA 125268

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies, NIH Bldg 29B, HFD-123
29B Lincoln Drive, Bethesda, MD 20892

The Quality Team Leader's Executive Summary

From: Kathleen A. Clouse, Ph.D., Director
Division of Monoclonal Antibodies (DMA)

Through: Patrick Swann, Ph.D., Deputy Director, DMA

BLA Number: 125268
Product: Nplate™ (Romiplostim)
Sponsor : Amgen, Inc.

Date of Review : April 30, 2008

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of Nplate™ (romiplostim) is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents sufficient to meet the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use (under conditions specified in the package insert).

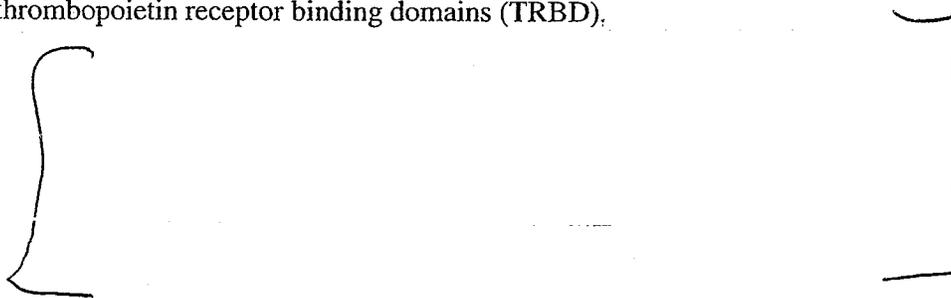
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

There are no CMC-related Phase 4 (post-marketing) commitments

II. Summary of Quality Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

- Nplate™ (romiplostim) is a 59,085 Da recombinant, ~~monoclonal antibody~~, thrombopoietic protein composed of a human immunoglobulin IgG₁ Fc domain, with each single chain subunit covalently linked at the C-terminus to a peptide chain containing two thrombopoietin receptor binding domains (TRBD).



- This type of recombinant protein is referred to by Amgen, Inc., as a “peptibody”, since it contains an active peptide region and an antibody (immunoglobulin) Fc region.
 - The mechanism of action for romiplostim is to increase platelet production via interaction of the specific peptide sequences of the molecule with the thrombopoietin receptor (referred to as Mpl) on megakaryocytes, which activates intracellular transcriptional pathways and thereby stimulates platelet production. Mpl is the product of the oncogene, c-mpl. Romiplostim has no sequence homology to thrombopoietin,
-

- Nplate™ (romiplostim) Drug Product (DP) is supplied as a sterile, preservative-free, lyophilized white powder for reconstitution in sterile water for injection (WFI). It is intended for single use and is supplied in 5 cc Type I glass vials containing 375 or 625 µg of romiplostim, 250 or 500 µg deliverable drug product when reconstituted with _____ nL of preservative-free WFI, respectively. When reconstituted with the appropriate volume of sterile water for injection (WFI), romiplostim is at a final concentration of _____ mM histidine, _____ (w/v) mannitol, _____ (w/v) sucrose, and _____ (w/v) polysorbate 20 at a pH of 5.0. The reconstituted product is a clear colorless solution practically free of particles. The container closure system consists of a Type I glass vial, _____ stopper, and aluminum seal with flip-off cap.
- Nplate™ (romiplostim) has been found to have _____ in bacteriostatic WFI, which contains benzyl alcohol as a preservative. For this reason, the package insert specifically states that bacteriostatic WFI should not be used for reconstitution of Nplate™ (romiplostim). Only preservative-free WFI should be used for reconstitution of Nplate™ (romiplostim), _____
- The excipients used in the formulation of romiplostim as noted above are L-histidine, mannitol, sucrose, and polysorbate 20; pH _____ hydrochloric acid. L-histidine is used to maintain pH control at 5.0. A pH of 5 was determined to be optimal for romiplostim, since HPLC revealed the best overall stability, and HPLC showed that _____ were minimized at this pH. Mannitol is included as a _____ and sucrose is added as a _____. The _____ Polysorbate 20 _____ is minimized in the current lyophilized formulation, and does not increase over long-term storage at 2° to 8° C. Sterile preservative-free WFI is used to reconstitute the lyophilized cake.
- Each vial of Nplate™/romiplostim is packaged in an individual carton. The diluent, preservative-free sterile water for injection (sWFI), as well as the syringes, needles and alcohol swabs, will be provided by the dispensing pharmacy or health care provider.
- The stability of Nplate™ lyophilized drug product has been confirmed for up to 24 months at 2°-8° C (36°-46° F) in multiple lots used for validation. In addition, data available from manufacturing experience with a similar process (P1 process), along with calculations of confidence intervals generated from data from primary validation

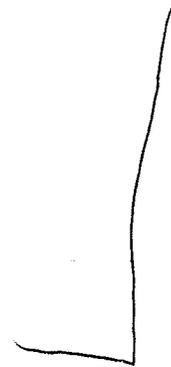
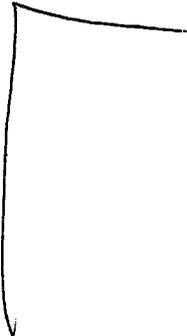
lots (current P2 process) support the requested expiration dating of 36 months. Lyophilized romiplostim product is to be stored refrigerated (2°-8° C) inside the original carton to protect it from light, since photostability studies have shown that it degrades when exposed to light under the conditions tested.

- Reconstituted romiplostim can be maintained at room temperature (25° C/77° F) or refrigerated (2°-8° C) for up to 24 hours prior to administration. Stability data are provided in the BLA in support of this statement. Romiplostim does not contain preservatives, so any unused portion must be discarded.

- Romiplostim is expressed in *Escherichia coli*



- Romiplostim Drug Substance (DS) is produced



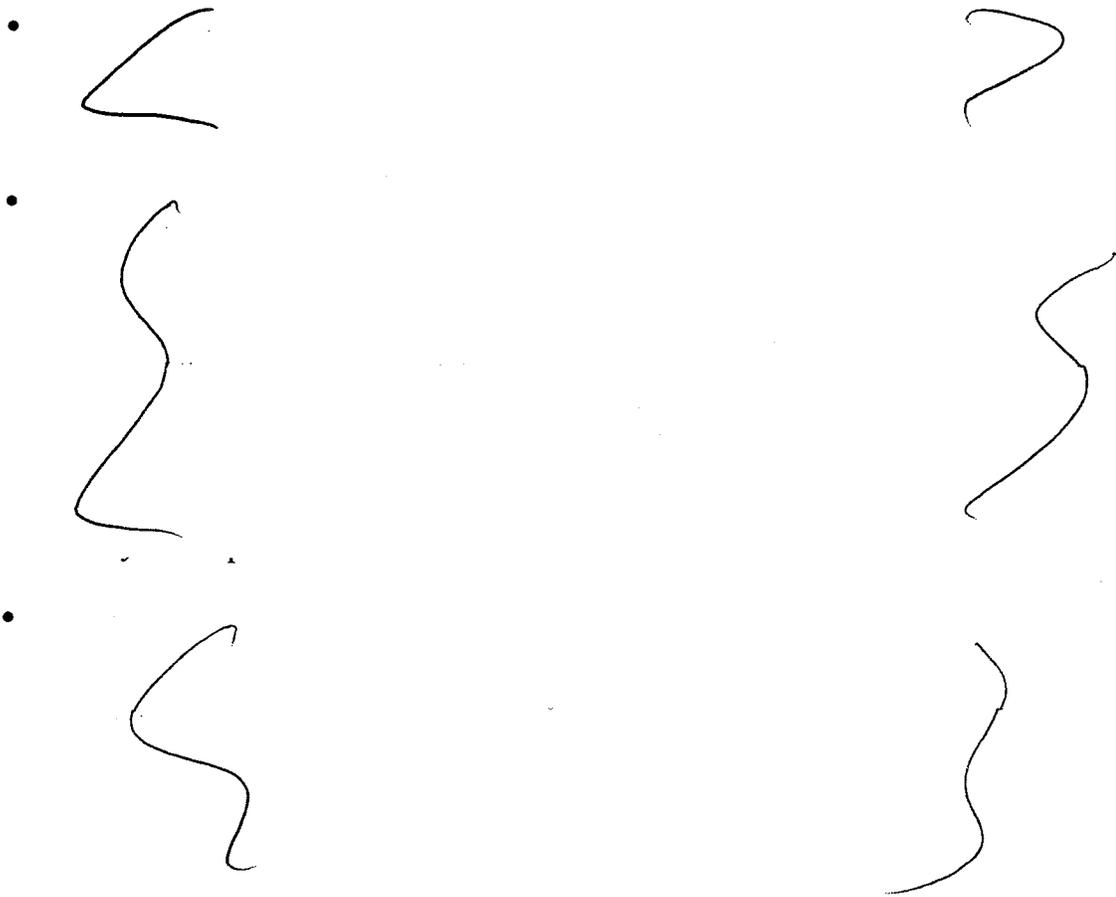
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B. Description of How the Drug Product is Intended to be Used

- Nplate™/romiplostim is indicated for the treatment of thrombocytopenia in adult patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP) who have had an insufficient response to either splenectomy or corticosteroids and/or immunoglobulins. Nplate™ should be used only in patients with ITP whose degree of thrombocytopenia is associated with an increased risk for bleeding.
- Nplate™ is available only through a special restricted distribution program called NEXUS (Network of Experts Understanding and Supporting Nplate and Patients program). Under NEXUS, only prescribers and patients registered with the program are able to prescribe, administer, and/or receive product.
- Nplate™/romiplostim drug product is supplied in single-use, 5-mL glass vials as a sterile, preservative-free, lyophilized powder that should be stored under refrigeration at 2° C to 8° C in the original carton to protect it from light. It must be reconstituted in sterile preservative-free WFI as follows:

<u>Vial</u>	<u>Romiplostim Total content</u>	<u>Vol. WFI</u>	<u>Deliverable Product</u>	<u>Final Conc</u>
250 mcg	375 mcg	0.72 mL	250 mcg in 0.5 mL	500 mcg/mL
500 mcg	625 mcg	1.20 mL	500 mcg in 1.0 mL	500 mcg/mL

Dissolution of Nplate™ generally takes less than 2 minutes and is best reconstituted using gentle swirling. Reconstituted product should not be shaken and should be administered using a syringe with 0.01 mL gradations. No diluent (preservative-free SWFI) or syringes are provided with the product. Following reconstitution of the lyophilized drug product, the product is to be administered subcutaneously by a health care provider.

- The package insert states that the reconstituted romiplostim can be maintained at room temperature (25° C/77° F) or refrigerated (2-8° C) for up to 24 hours prior to administration, but must be protected from light. Stability data are provided in the BLA in support of this statement. Romiplostim does not contain preservatives, so any unused portion should be discarded.
- The recommended dosage regimen for Nplate™/romiplostim in adults is an initial dose of 1 mcg/kg once weekly via subcutaneous injection, followed by weekly doses adjusted at increments of 1 mcg/kg to minimize the risk of bleeding by achieving a platelet count $\geq 50 \times 10^9/L$. The maximum weekly dose of 10 mcg/kg should not be exceeded, and should be held if excessive platelet counts are attained. Romiplostim should be discontinued if the platelet count does not increase after 4 weeks at the maximum dose.

C. Basis for Approvability or Not-Approval Recommendation

Romiplostim is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Romiplostim is manufactured consistently, leads to a safe and effective product, and approval is recommended for the proposed indication.

Quality unit Assessment

I. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 3.2: BODY OF DATA

The review of module 3.2 is attached as a separate document that also includes a review of the product immunogenicity.

II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q) MODULE 1

A. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL EXCLUSION

Amgen claims categorical exclusion from the requirements of environmental assessment (BLA section 1.12.14) based on 21 CFR 5.15(d) and 21 CFR 25.31(c). Given that romiplostim is composed of a sequence of amino acids and a protein, Amgen contends that it meets the criteria for compounds that may be exempted from testing because of their chemical structure and constituents (amino acids and proteins), which should either degrade into their amino acid or constitutive elements in the environment.

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

There are no CMC-related deficiencies precluding approval of this BLA.

IV. ADMINISTRATIVE

A. Reviewer's Signature

Product Quality Reviewer: David Frucht, M.D. 

B. Endorsement Block

Product Division Team Leader: Kathleen A. Clouse, Ph.D. 

Product Division Deputy Director: Patrick Swann, Ph.D. 

Product Division Director: Kathleen A. Clouse, Ph.D. 

C. CC Block

OBP Office Director: Steven Kozlowski, M.D.

Clinical Deputy Division Director: Libero Marzella, M.D.

Clinical Division Director: Dwaine Rieves, M.D.

Division of Monoclonal Antibodies File: BLA STN 125268

BLA #125268

Romiplostim

Amgen Inc.

David M. Frucht, M.D
Division of Monoclonal Antibodies

Product Quality Review Data Sheet

1. **BLA:** STN 125268

2. **REVIEW #:** 1

3. **REVIEW DATE:** 25-April-2008

4. **REVIEWER:** David M. Frucht, M.D.

5. **COMMUNICATIONS AND PREVIOUS DOCUMENTS:**

<u>Previous Documents</u>	<u>Document Date</u>
Clinical Pre-BLA meeting	22-MAY-2007
CMC Pre-BLA meeting	24-MAY-2007
Telecon	01-NOV-2007
Telecon	07-NOV-2007
Application orientation meeting	20-NOV-2007
Telecon	29-NOV-2007
Telecon	12-DEC-2007
Telecon	08-JAN-2008
Telecon	15-JAN-2008
Telecon	16-JAN-2008
Telecon	22-JAN-2008
Telecon	06-FEB-2008
Telecon	28-FEB-2008
Telecon	11-APR-2008
Telecon	18-APR-2008

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
0000 (original submission)	23-OCT-2007
0001 (amendment)	29-OCT-2007
0002 (meeting package)	14-NOV-2007
0003 (amendment)	16-NOV-2007
0004 (amendment)	23-JAN-2008
0005 (amendment)	31-JAN-2008
0009 (amendment)	8-FEB-2008
0010 (amendment)	14-FEB-2008
0012 (amendment)	22-FEB-2008
0013 (amendment)	11-MAR-2008
0014 (amendment)	17-MAR-2008
0015 (amendment)	17-MAR-2008
0024 (amendment)	21-APR-2008
0025 (amendment)	24-APR-2008

7. NAME & ADDRESS OF APPLICANT:

Name:	Amgen Inc.
Address:	One Amgen Drive Thousand Oaks, CA 91320-1799
Representative:	Mei Ling Chang-Lok, Ph.D, RAC
Telephone:	(805) 447-0299

8. DRUG PRODUCT NAME/TYPE:

- a) Proprietary Name: Nplate
- b) Non-Proprietary Name (USAN): Romiplostim
- c) Other names: AMG 531, AMP2
- d) Submission Priority: P

9. PHARMAC. CATEGORY: Thrombopoietin receptor agonist-Fc fusion protein

10. DOSAGE FORM: lyophilized white, solid cake

11. STRENGTH/POTENCY: Romiplostim is provided in two dosage formats: 250 mcg and 500 mcg deliverable.

Table 1. Quantitative and Qualitative Composition of AMG 531

Component	Grade	Function	Deliverable amount per vial 250 µg	Deliverable amount per vial 500 µg
romiplostim (10 mg/mL)	In house ^a		375 µg	625 µg
Mannitol	USP/Ph. Eur./JP		30 mg	50 mg
Sucrose	NF/Ph. Eur./JP		15 mg	25 mg
L-Histidine	USP/Ph. Eur.		1.2 mg	1.9 mg
hydrochloric acid	NF/Ph. Eur.		As required ^b	As required ^b
Polysorbate 20	NF/Ph. Eur.		0.03 mg	0.05 mg

12. ROUTE OF ADMINISTRATION: SQ

13. ANIMAL- AND HUMAN-DERIVED RAW MATERIALS





14. PRIMARY STRUCTURE, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURES:

Romiplostim is a recombinant _____ 59 kDa thrombopoietic protein produced in *E coli*. It is a fusion protein which Amgen has termed a peptibody. The peptibody molecule is composed of a human immunoglobulin IgG₁ Fc domain, with each single chain subunit covalently linked at the C-terminus to a peptide chain containing two thrombopoietin receptor binding domains (TRBD). Romiplostim stimulates platelet production by a mechanism similar to that of endogenous thrombopoietin (eTPO); however there is no sequence homology between romiplostim and eTPO.

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ROMIPLOSTIM BLA PRODUCT QUALITY REVIEW

15. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	STATUS ²	DATE REVIEW COMPLETED	COMMENTS
—	DMF	N/A	—	4	N/A	N/A	No review required as relevant information related to the DP — was present in the BLA

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

16. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	Approve		
Carton and Vial Labeling	Approve	14-MAY-2008	David Frucht, Sheila Rawls, Vivian Wang, Richard Abate
Environmental Assessment	Approve	17-MAR-2008	David Frucht
BMT-Lake Centre DS facility review	EIR Pending		Susan Laska (lead), Frucht, Lankford, Yeh
BMT-Longmont DS	EIR Pending		Susan Laska (lead), Frucht,

ROMIPLOSTIM BLA PRODUCT QUALITY REVIEW

testing facility review			Lankford, Yeh
BMT-F facility review	EIR Pending		Susan Laska (lead)
Trade name review	Approve		

17. CMC Inspectional Activities:

The pre-approval inspection of the Drug Substance manufacturing and testing facilities at Lake Centre (Boulder, CO) and the Longmont facility (Longmont, CO) occurred January 28-31, 2008. The inspection team consisted of Susan Laska (BMT, lead), Li-Hong Yeh (BMT), Carla Lankford (DMA), and David Frucht (DMA). Two GMP-related 483 issues were noted during the inspection, but neither of these two deficiencies raised sufficient safety concerns to deny approval of the facility. **The final inspection report is pending.**

The pre-approval inspection of the Drug Product manufacturing facility at _____ was conducted by BMT (DMA did not participate). **The final inspection report is pending.**

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BLA 125268 Chemistry Assessment [Romiplostim (Nplate™), Amgen]
CTD Module 3.2 and immunogenicity assays

Reviewed by:**David M. Frucht, M.D., Product Quality Reviewer, Division of Monoclonal Antibodies****Team Leader:****Kathleen A. Clouse, Ph.D., Director, Division of Monoclonal Antibodies**

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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Avenue
Silver Spring, MD 20993

Date: April 9, 2008
To: Administrative File, STN 125268/0
From: Patricia F. Hughes, Ph.D., CDER/OC/DMPQ/BMT
Endorsement: Edwin Rivera, Branch Chief, CDER/OC/DMPQ/MAPCB
Michelle Clark-Stuart, M.S., Peer Reviewer, CDER/OC/DMPQ/BMT
Subject: New BLA
US License: # 1080
Applicant: Amgen, Inc.
Mfg Facility: Amgen, Inc. Longmont CO 80503 (FEI 1724812)
Amgen, Inc. Boulder, CO 80301 (FEI 1724627)

DPH 411-108
E. Rivera
04/15/08
myll 4/15/08

Product: Nplate (romiplostim, AMG 531)
Dosage: Lyophilized, white, solid cake for reconstitution and SC injection, 250 mcg (5mL vial), 500 mcg (5mL vial)
Indication: Treatment of thrombocytopenia in adult patients with immune thrombocytopenia purpura
Due Date: 23 April 2008

Recommendation for Approvability: The BLA, as amended, is recommended for approval from a microbial control, sterility assurance perspective and microbiology product quality perspective.

SUMMARY:

Amgen, Inc. submitted BLA 125268 to obtain licensure to market Nplate (romiplostim, AMG 531), a peptibody that is intended to treat thrombocytopenia in patients with Immune Thrombocytopenic Purpura (ITP). The peptibody increases platelet production.

An orphan drug designation for AMG 531 was issued on 27 March 2003 and a Fast Track designation was granted 23 November 2004 for AMG 531 in the treatment of ITP for use in serious thrombocytopenic refractory to existing therapies.

The drug product is a sterile lyophilized solid white cake containing 250 mcg or 500 mcg in a 5 mL single dose vial for reconstitution for solution for injection. The drug product is reconstituted with sterile water for injection, USP.

This review covers the drug substance and drug product manufacturing process from a microbial control, sterility assurance and microbiology product quality perspective.

STN: 125268, Amgen, Inc.

The BLA was amended in response to CMC questions on the _____ of the drug product. The review includes an assessment of the responses to Amendments 007 and 0015.

The following facilities were inspected:

- Amgen, Boulder Co. FEI 3003072024 and Amgen Longmont, CO FEI 1724812 were inspected on 1/28-2/1/2008 by S. Laska, P. Li-Hong Yeh, and D. Frucht for drug substance manufacturing.

ASSESSMENT:

3.2. S DRUG SUBSTANCE

3.2. S.1 GENERAL INFORMATION

AMG 531 is a recombinant non-glycosylated 59 kDa thrombopoietic protein produced in *E. coli*. The protein is a peptibody consisting of a Fc IgG1 domain. Each Fc unit is linked at the C-terminus to a peptide chain containing two thrombopoietin receptor binding domains (TRBD). AMG531 stimulates platelet production as does endogenous thrombopoietin (eTPO); however there is no sequence homology between AMG531 and eTPO.

3.2. S.1.1 Nomenclature

This section is reviewed by OBP and is not reviewed here.

3.2. S.1.2 Structure

This section is reviewed by OBP and is not reviewed here.

3.2. S.1.3 General Properties

This section is reviewed by OBP and is not reviewed here.

3.2. S.2 MANUFACTURE

3.2. S.2.1 Manufacture(s)

The name and address of each manufacturer involved in manufacture, storage and testing of drug substance as presented in the BLA is as follows:

Table 1. Drug Substance Facility Responsibilities:

Company Name and Address	Activity
Amgen Inc. (ACO) LakeCentre Facility (LC) 5550 Airport Boulevard Boulder, CO 80301 USA Registration Number 1724627	Raw materials/components storage and testing Working cell bank storage Drug substance manufacturing Drug substance storage Drug substance release testing Drug substance stability testing

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Regulatory Filing Review Memo for BLAs and Supplements

The filing review should seek to identify all omissions of clearly necessary information such as information required under the statute or regulations or omissions or inadequacies so severe that a meaningful review cannot be accomplished. CBER may refuse to file (RTF) an application or supplement as provided by 21 CFR 601.2, and 21 CFR 314.101, including those reasons consistent with the published RTF policy (<http://www.fda.gov/cber/regsopp/8404.htm>). An RTF decision may also be appropriate if the agency cannot complete review of the application without significant delay while major repair or augmentation of data is being done. To be a basis for RTF, the omissions or inadequacies should be obvious, at least once identified, and not a matter of interpretation or judgement about the meaning of data submitted. Decisions based on judgments of the scientific or medical merits of the application would not generally serve as bases for RTF unless the underlying deficiencies were identified and clearly communicated to the applicant prior to submitting a license application, e.g., during the review of the IND or during pre-BLA communications. The attached worksheets, which are intended to facilitate the filing review, are largely based upon the published RTF policy and guidance documents on the ICH Common Technical Document (CTD) (see <http://www.fda.gov/cber/ich/ichguid.htm>).

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

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

STN: 125268 Product: Mplate Applicant: Amgen, Inc.
(romiplostin)

Final Review Designation (circle one): Standard Priority

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

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 12/22/07 Committee Recommendation (circle one): File RTF

RPM: _____
(signature/date)

Attachments:

- Discipline worksheets (identify the number of lists attached for each part and fill-in the name of the reviewer responsible for each attached list):
 - ____ Part A – RPM
 - Part B – Product/CMC/Facility Reviewer(s): Hughes
 - ____ Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s): _____
 - ____ Part D – Clinical (including Pharmacology, Efficacy, Safety, and Statistical) Reviewers _____
- Memo of Filing Meeting

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