

**CENTER FOR DRUG EVALUATION AND RESEARCH**

**Approval Package for:**

***APPLICATION NUMBER:***

**125118/S107**

***Trade Name:*** Orencia®

***Generic Name:*** abatacept

***Sponsor:*** Bristol Myers Squibb

***Approval Date:*** 6/23/2011

# CENTER FOR DRUG EVALUATION AND RESEARCH

**APPLICATION NUMBER:  
125118/S107**

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**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125118/S107**

**APPROVAL LETTER**



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Biotechnology Products

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** June 23, 2011

<b>To:</b> Linda Gustavson	<b>From:</b> Melinda Bauerlien, M.S. for Colette Jackson Project Manager
<b>Company:</b> Bristol-Myers Squibb	Office of Biotechnology Products
<b>Fax number:</b> 609-252-6000	<b>Fax number:</b> (301) 796-9743
<b>Phone number:</b> 609-252-3688	<b>Phone number:</b> (301) 796-0906
<b>Subject:</b> STN 125118/107	

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**Total no. of pages including cover:** 3

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Comments: Please find following the action letter for the above supplement for Orenica.

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**Document to be mailed:**                       YES                       NO

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125118/107

Bristol-Myers Squibb Company  
P.O. Box 4000  
Princeton, New Jersey 08543-4000

June 23, 2011

Attention: Ashley Pereira, Pharm.D.  
Global Regulatory Science, U.S. Regulatory Liaison

Dear Dr. Pereira:

This letter is in regard to the supplement to your biologics license application (BLA), dated October 26, 2009, received October 26, 2009, submitted under section 351 of the Public Health Service Act, Orenicia (abatacept).

We acknowledge receipt of your amendments dated January 22, March 25, and April 9, 2010, and February 22, 2011. The February 22, 2011 submission constituted a complete response to our April 23, 2010, action letter.

This supplement to your biologics license application for Orenicia proposes to replace the use of the currently approved formulation of the abatacept chemically defined (CD)- [REDACTED] (b) (4) with the use of a new CD- [REDACTED] (b) (4)

We have completed our review of this supplemental biologics license application, as amended. This supplement is approved.

This information will be included in your biologics license application file.

If you have any questions, please contact Colette Jackson, Senior Regulatory Health Project Manager at (301) 796-1230.

Sincerely,

A handwritten signature in black ink, appearing to read "Amy Rosenberg". The signature is fluid and cursive, with a large initial "A" and "R".

Amy Rosenberg, M.D.  
Director  
Division of Therapeutic Proteins  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125118/S107**

**OTHER ACTION LETTER(S)**



**COMPLETE RESPONSE**

Our STN: BL 125118/107

April 23, 2010

Bristol-Myers Squibb Company  
Attention: Anand Achanta, Ph.D.  
Associate Director  
Global Regulatory Sciences  
P.O. Box 5400  
Princeton, NJ 08543

Dear Dr. Achanta:

This letter is in regard to the supplement to your biologics license application, dated October 26, 2009, received October 26, 2009, submitted under section 351 of the Public Health Service Act for Orencia® (abatacept).

This supplement proposes the use of a new formulation of the abatacept chemically defined (CD)- [REDACTED] (b) (4)

We acknowledge receipt of your amendment dated January 22, 2010. We also acknowledge receipt of your amendment dated March 25, 2010, and of your amendment dated April 21, 2010, which could not be reviewed in its entirety, specifically sections 3.2.S.2.6.6 and 3.2.S.2.6.7.

We have completed the review of your supplement and have determined that we cannot approve this supplement in its present form. We have described below our reasons for this action and, where possible, our recommendations to address these issues.

Comparability of Drug Substance

Comparability of drug substance manufacturing may be established through physico-chemical and biological analyses provided that such analyses are sufficiently comprehensive and the results convincingly provide assurance that clinical safety and efficacy have not been altered. Release testing is generally not sufficient to establish the comparability of Drug Substance (DS) lots and additional product characterization, commensurate with the risk to product quality, is required. Beyond the differences in N-linked Carbohydrate analysis noted by Bristol-Myers Squibb (BMS), the extended DS characterization and trended data that have been submitted exhibit numerous minor differences in Critical Quality Attributes (CQA), the multitude of which raise serious concerns about whether DS produced post manufacturing change, in both measured and unmeasured attributes, is equivalent to the currently approved DS.

In addition, multiple differences observed in the trended DS attributes, as detected (b) (4)

[Redacted]

In your resubmission, please fully address these comments and those below and/or provide *in vivo* data to support the comparability of pre- and post- (b) (4) change DS produced at (b) (4)

[Redacted]

1. With regard to alterations in protein charge, please address the following issues:

(b) (4) [Redacted]

[Redacted] beyond the quantitative changes you have reported in the mean % difference for Domains I, III, and IV, which are seen in the trended data, the side-by-side comparison of DS produced (b) (4) profile that are not captured by the reporting method (see examples below). Please provide data that assess the significance of these changes and revise your reporting method to capture these changes as warranted.

(b) (4) [Redacted]

(b) (4) [Redacted]

[Redacted] content of DS produced (b) (4)



(b) (4)

[Redacted text block]

(b) (4)

[Redacted text block]

**Additional Comments**

1. Please update your submission to reflect that only (b) (4)
2. (b) (4)  
in abatacept manufacturing (b) (4) perform compatibility studies to demonstrate that the (b) (4) have not had an impact on leachables, extractables, or column life span.
3. Please provide a side-by-side comparison of DS produced (b) (4) under accelerated stability conditions to assure that they have comparable degradation profiles.

Within one year after the date of this letter, you are required to resubmit or withdraw the application. If you do not take any of these actions, we will consider your lack of response a

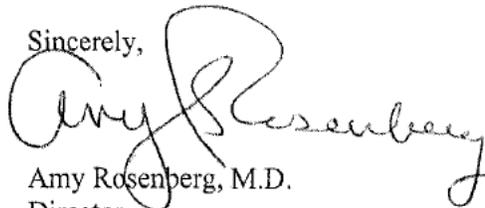
request to withdraw the application under 21 CFR 601.3(c). A resubmission must fully address all the deficiencies listed, and will start a new review cycle. A partial response to this letter may not be reviewed and will not start a new review cycle.

You may request a meeting or teleconference with us to discuss the steps necessary for approval. If you wish to have such a meeting, submit your meeting request as described in the FDA Guidance for Industry on *Formal Meetings Between FDA and Sponsors or Applicants*, February, 2009 at

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf>

If you have any questions, please contact the Regulatory Project Manager, Melinda Bauerlien, at (301) 796-0906.

Sincerely,

A handwritten signature in cursive script that reads "Amy Rosenberg". The signature is written in black ink and is positioned to the right of the word "Sincerely,".

Amy Rosenberg, M.D.

Director

Division of Therapeutic Proteins

Office of Biotechnology Products

Office of Pharmaceutical Science

Center for Drug Evaluation and Research

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125118/S107**

**CHEMISTRY REVIEW(S)**

**Part B – Product/CMC/Facility Reviewer(s)**



**DEPARTMENT OF HEALTH AND HUMAN SERVICES  
Public Health Service  
Food and Drug Administration**  

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**Memorandum of Filing Review**

STN:	125118/107
Applicant:	Bristol-Myers Squibb
Product:	Orencia® (abatacept)
Short Summary:	proposes the use of a new formulation of the abatacept CD- (b) (4) (b) (4)
Reviewer:	Jack Ragheb
Office/Division:	OBP/DTP

I have conducted a filing review of the above referenced BLA supplement to determine whether it is sufficiently complete to permit a complete review.

Brief description of the change: *see short summary above*

The following was submitted in support of the change (check all that apply):

<input checked="" type="checkbox"/>	A detailed description of the proposed change
<input checked="" type="checkbox"/>	Identification of the product(s) involved
<input checked="" type="checkbox"/>	A description of the manufacturing site(s) or area(s) affected
<input checked="" type="checkbox"/>	A description of the methods used and studies performed to evaluate the effect of the change on the identity, strength, quality, purity, or potency of the product as they may relate to the safety or effectiveness of the product
<input checked="" type="checkbox"/>	The data derived from such studies
<input checked="" type="checkbox"/>	Relevant validation protocols and data
<input type="checkbox"/>	A reference list of relevant standard operating procedures (SOP's)

The following deficiencies were identified (identify those that are potential filing issues):

Recommendation:

<input checked="" type="checkbox"/>	I recommend that this supplement be filed.
<input type="checkbox"/>	I recommend that this supplement be refused for filing for the reasons stated above.

Reviewer: *[Signature]* *4/26/10* Type (circle one): Product (Chair) Facility (DMPQ)  
(signature / date)

Concurrence:

Branch/Lab Chief: \_\_\_\_\_  
(signature / date)

Division Director: \_\_\_\_\_  
(signature / date)

## Jackson, Colette

---

**From:** Pohlhaus, Timothy  
**Sent:** Tuesday, May 24, 2011 4:49 PM  
**To:** Jackson, Colette  
**Cc:** Pohlhaus, Timothy; CDER-TB-EER  
**Subject:** RE: sBLA 125118/107 TBP EER

**Attachments:** TB-EER response - STN 125118-107.doc; 125118 s107 TBP EER.pdf

The New and Generic Drug Manufacturing Team in the Division of Manufacturing and Product Quality has completed its review and evaluation of the TB-EER for STN 125118/107. Please see the attached form for individual site compliance statuses. There are no pending or ongoing compliance actions that prevent approval of this supplement.



TB-EER response -  
STN 125118-1...

**Timothy J. Pohlhaus, Ph.D.**  
Interdisciplinary Scientist, Chemist  
Food and Drug Administration  
CDER/OC/DMPQ  
10903 New Hampshire Avenue  
Building 51, Room 1333  
Silver Spring, MD 20993  
Phone - (301) 796-5224

---

**From:** Jackson, Colette  
**Sent:** Friday, April 29, 2011 1:33 PM  
**To:** CDER-TB-EER  
**Subject:** sBLA 125118/107 TBP EER

To TBP EER,

Attached is the TBP EER for sBLA 125118 s107. This is a prior approval supplement which proposes the use of an alternate formulation of the CD- (b) (4) for abatacept. The PDUFA date is June 24, 2011. This is a resubmission, with a CR letter issued April 23, 2011.

I will make sure that I send another request 15 to 30 days prior to the action date (@ May 25, 2011).

Thank you for your assistance with this application. Please let me know if you need additional information.

FYI- I will be sending a second request for the same BLA, but for an (b) (4). The manufacturing sites are the same for both for drug substance and drug product, but the (b) (4)



125118 s107 TBP  
EER.pdf (126 K...

*Colette Jackson*

# Therapeutic Biological Establishment Evaluation Request (TB-EER) Form

Version 1.0

## Instructions:

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

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

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

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## APPLICATION INFORMATION

PDUFA Action Date: June 24, 2011

Applicant Name: Bristol-Myers Squibb

U.S. License #: 1713

STN(s): 125118/107

Product(s): Orenzia (abatacept)

Short summary of application: This is a prior approval supplement to allow the use of an alternate formulation of the [REDACTED] (b) (4) for abatacept.

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## FACILITY INFORMATION

[REDACTED] (b) (4)

Short summary of manufacturing activities performed: *Drug Substance Manufacturing and Release*

Inspected [REDACTED] (b) (4) by [REDACTED] (b) (4) DO and classified VAI. The CBI profile was updated and is acceptable. This site was also inspected [REDACTED] (b) (4) to cover issues related to equipment maintenance. That inspection was also classified VAI.

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

Establishment number: (b) (4)

Short summary of manufacturing activities performed: (b) (4)

No evaluation of this site is required for this site based on the responsibility listed.

(b) (4)

(b) (4)

(b) (4)

(b) (4)

Establishment number: N/A

Short summary of manufacturing activities performed: (b) (4)

(b) (4)

No evaluation of this site is required for this site based on the responsibility listed.

Bristol-Myers Squibb Holdings Pharma, LTD.

P.O. Box 301000

Road 686, KM. 2.3

Manati, Puerto Rico 00674-3000

Establishment Number: 2650089

Short summary of manufacturing activities performed: *Manufacturing, Microbiological Control Testing, Packaging, Labeling, Release, and Quality Control Testing and Stability Testing as part of the Routine Market Stability Program*

Inspected by SJN-DO (b) (4) and classified VAI. This was a GMP inspection to verify corrective actions following the Warning Letter issued on (b) (4)

(b) (4) The CTL, SVS, SVL, and TRP profiles were updated and are acceptable.

Bristol-Myers Squibb Company

6000 Thompson Road

East Syracuse, New York 13057

Establishment number: 1317461

Short summary of manufacturing activities performed: *Quality Control Testing and Stability Testing as part of the Routine Market Stability Program*

Inspected by NYK-DO (b) (4) and classified NAI. The CTL profile was updated and is acceptable.

**CENTER FOR DRUG EVALUATION AND  
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*APPLICATION NUMBER:*

**125118/S107**

**PHARMACOLOGY REVIEW(S)**

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

**PHARMACOLOGY/TOXICOLOGY BLA REVIEW AND EVALUATION**

Application number: **125118**  
Supporting document/s: **Seq 131, S107**  
Applicant's letter date: Feb 22, 2011; Oct 26, 2009  
CDER stamp date: Feb 22, 2011; Oct 26, 2009  
Product: Orencia<sup>®</sup> (abatacept)  
Indication: Reducing signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis.  
Applicant: Bristol-Myers Squibb Co.  
Review Division: Division of Pulmonary, Allergy, and Rheumatology Products  
Reviewer: L. Steven Leshin, D.V.M., Ph.D.  
Supervisor: Molly E. Topper, Ph.D.  
Division Director: Badrul Chowdhury, M.D., Ph.D.  
Project Manager: Colette Jackson

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Except as specifically identified, all data and information discussed below and necessary for approval of BLA 125118 are owned by Bristol-Myers Squibb Co. or are data for which Bristol-Myers Squibb Co. has obtained a written right of reference. Any information or data necessary for approval of BLA 125118 that Bristol-Myers Squibb Co. does not own or have a written right to reference constitutes one of the following: (1) published literature, or (2) a prior FDA finding of safety or effectiveness for a listed drug, as described in the drug's approved labeling. Any data or information described or referenced below from a previously approved application that Bristol-Myers Squibb Co. does not own (or from FDA reviews or summaries of a previously approved application) is for descriptive purposes only and is not relied upon for approval of BLA 125118.

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Figure 2: Individual Serum Concentration versus Time Profile of Abatacept Following a  
Single Intravenous Dose of 10 mg/kg Abatacept (b) (4)  
(b) (4) to Male Monkeys ..... 15

# 1 Executive Summary

## 1.1 Recommendations

### 1.1.1 Approvability

From the pharmacology-toxicology perspective, the Application may be approved.

### 1.1.2 Additional Non Clinical Recommendations

There are no additional nonclinical recommendations.

### 1.1.3 Labeling

There are no nonclinical changes to the label.

## 1.2 Brief Discussion of Nonclinical Findings

This supplement is to allow a change in the manufacture of abatacept that incorporated the (b) (4) enhances the (b) (4) of abatacept produced. In previous discussions with the Applicant following an initial CR decision for this supplement, the Applicant was request to conduct a nonclinical study to demonstrate pharmacokinetic similarity between abatacept from the approved manufacturing method and abatacept from the manufacturing method (b) (4)

This supplement contained 1 nonclinical pharmacokinetic study that provided support for the proposed manufacturing change. This was a pharmacokinetic comparison between abatacept prepared from manufacture (b) (4) Administered as a single intravenous infusion of 10 mg/kg to cynomolgus monkeys, there were no differences in pharmacokinetic parameters between batches of abatacept produced with the different (b) (4) There were also no differences in the incidence and relative time for the development of anti-abatacept antibodies between abatacept manufacturing processes. There was no mortality and no differences between the 2 abatacept batches in clinical signs, body weight, food consumption, or clinical pathology values.

A toxicological analysis was also conducted by the Applicant of the (b) (4) within an approved dose a dose of abatacept. At the maximal dose of 1000 mg, the levels of (b) (4) were much lower than regulatory levels of permitted daily exposures. Thus, the levels of (b) (4) in the approved maximal dose present no toxicological concern for the indicated clinical population.

## 2 Drug Information

### 2.1 Drug

**2.1.1 CAS Registry Number** 332348-12-6

**2.1.2 Generic Name** Abatacept (Orencia, proprietary name)

**2.1.3 Code Name** BMS-188667

**2.1.4 Chemical Name** (b)(4)-oncostatin M (human precursor) fusion protein with CTLA-4 (antigen) (human) fusion protein with immunoglobulin G1 (human)

**2.1.5 Molecular Weight** ~92300 Daltons

**2.1.6 Structure** Recombinant, fusion protein consisting of extracellular domain of human CTLA-4 and a fragment ("hinge"-CH2 (b)(4) domains) of the Fc domain of human IgG1

**2.1.7 Pharmacologic class** Fusion protein immunosuppressant

### 2.2 Relevant IND/s, NDA/s, and DMF/s

BLA 125118 (Orencia<sup>®</sup>, abatacept, approved Dec 2005)

IND 9391 (abatacept)

### 2.3 Clinical Formulation

ORENCIA<sup>®</sup> (Abatacept for Injection, 250 mg/Vial). The abatacept drug substance consists of approximately (b)(4) mg/mL abatacept in (b)(4) containing (b)(4) mM sodium chloride at pH (b)(4). The composition is listed in Table 1.

**Table 1: Composition of Abatacept Injection, 125 mg/mL**

Component	Quality Standard	Function	Amount per Syringe (mg) <sup>a</sup>
Abatacept	BMS <sup>b</sup> Specification	Active Ingredient	(b) (4)
(b) (4)	NF/Ph.Eur.	[Redacted]	(b) (4)
(b) (4)	NF/ Ph.Eur/BP		
Sodium Phosphate Monobasic,	USP/BP		
(b) (4)	USP/Ph.Eur.		
(b) (4)			
(b) (4)			
Water for Injection	USP/Ph.Eur./JP		
(b) (4)	NF/JP		

**2.3.2 Comments on Novel Excipients**

There are no novel excipients.

**2.3.3 Comments on Impurities/Degradants of Concern**

There are no new impurities or degradants of toxicological concern. Refer to the Product Quality Review for previous product quality issues that resulted in an initial CR action for this supplement and for additional information on how these issues were addressed.

**2.4 Proposed Clinical Population and Dosing Regimen**

**Clinical Population**

- Adult Rheumatoid Arthritis (RA), patients with moderately to severely active RA in adults.
- Juvenile Idiopathic Arthritis, pediatric patients 6 years of age and older with moderately to severely active polyarticular juvenile idiopathic arthritis.

## Dosing Regimen

### Adult RA, Intravenous Administration

<u>Body Weight of Patient</u>	<u>Dose</u>
<60 kg	500 mg
60 to 100 kg	750 mg
>100 kg	1000 mg

- Administer as a 30-minute intravenous infusion.
- Following initial dose, give at 2 and 4 weeks, then every 4 weeks
- Prepare ORENCIA using only the silicone-free disposable syringe

### Juvenile Idiopathic Arthritis

<u>Body Weight of Patient</u>	<u>Dose</u>
< 75 kg	10 mg/kg based on the patient's body weight
> 75 kg	follow the adult dosing regimen, not to exceed a maximum dose of 1000 mg

## Dosage Forms and Strengths

Intravenous infusion,

- 250 mg single-use vial

## 2.5 Regulatory Background

The BLA for abatacept (Orencia<sup>®</sup>) for the treatment of rheumatoid arthritis was approved in Dec 2005.

This submission is in response to a CR letter (April 23, 2010) for the Applicants Prior Supplement 107 submitted October 26, 2009. That supplement was to allow use of an alternate formulation of the CD- (b) (4) for abatacept. This new (b) (4)

Subsequent to the CR decision, the Applicant had two meetings with FDA, July 12, 2010 and October 28, 2010, to understand the Agency's concerns and to develop a path forward for Supplement approval. In this response to the CR Amendment, the following new information is provided:

- Responses to all FDA questions from the CR letter and subsequent meetings with the Agency
- Modified acceptable range limits for (b) (4)
- An end-of-production cell bank prepared from cells grown with CD- (b) (4)
- A report (including individual animal data) from a non-human primate (monkey) PK study comparing abatacept drug products using the currently approved (b) (4) and the CD (b) (4) (b) (4)
- A report and datasets analyzing data from human PK studies comparing abatacept drug products with (b) (4).

The Agency agreed to a four month review cycle for this Amendment.

### 3 Studies Submitted

#### 3.1 Studies Reviewed

Study number / Submission Location	Title
(b) (4) Mod 4.2.2.7	Abatacept (BMS188667) Single Dose Intravenous Comparability Study in monkeys

#### 3.2 Studies Not Reviewed

All studies were reviewed.

#### 3.3 Previous Reviews Referenced

BLA 125118 S0000, Pharmacology-Toxicology Review of July 2005

## 4 Pharmacology

### 4.1 Mechanism of Action

Abatacept, a selective costimulation modulator, inhibits T cell (T lymphocyte) activation by binding to CD80 and CD86 on antigen presenting cells, thereby blocking interaction with CD28 on T-cells. This interaction provides a costimulatory signal necessary for full activation of T lymphocytes. Activated T lymphocytes are implicated in the pathogenesis of RA and are found in the synovium of patients with RA. *In vitro*, abatacept decreases T cell proliferation and inhibits the production of the cytokines TNF alpha (TNF $\alpha$ ), interferon- $\gamma$ , and interleukin-2. In a rat collagen-induced arthritis model, abatacept suppresses inflammation, decreases anti-collagen antibody production, and reduces antigen specific production of interferon- $\gamma$ . The relationship of these biological response markers to the mechanisms by which abatacept exerts its effects in RA is unknown.

### 4.2 Pharmacodynamics

In clinical trials with Orencia at doses approximating 10 mg/kg, decreases were observed in serum levels of soluble interleukin-2 receptor (sIL-2R), interleukin-6 (IL-6), rheumatoid factor (RF), C-reactive protein (CRP), matrix metalloproteinase-3 (MMP3), and TNF $\alpha$ . The relationship of these biological response markers to the mechanisms by which Orencia exerts its effects in RA is unknown.

## 5 Pharmacokinetics/ADME/Toxicokinetics

A comparative single dose pharmacokinetic study was conducted in cynomolgus monkeys and reviewed in Section 6.1. Refer to Tables 3 and 4 for a summary of pharmacokinetic parameters

For comparison of the monkey data with human pharmacokinetic parameters from healthy adults single 10 mg/kg intravenous infusion and in RA patients after multiple 10 mg/kg intravenous infusions, the human data from the Orencia label is presented in Table 2, below.

**Table 2: Human Pharmacokinetic Parameters (Mean, Range) After 10 mg/kg Intravenous Infusion(s)**

PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses <sup>a</sup> ) n=14
Peak Concentration (C <sub>max</sub> ) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life (t <sub>1/2</sub> ) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (V <sub>ss</sub> ) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

<sup>a</sup> Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter.

## 6 General Toxicology

### 6.1 Single-Dose Toxicity

**Study title: Abatacept (BMS188667) Single Dose Intravenous Comparability Study in monkeys**

<b>Study no.:</b>	(b) (4)
<b>Study report location:</b>	Module 4.2.2.7
<b>Conducting laboratory and location:</b>	Bristol-Myers Squibb Pharmaceutical Research Institute Departments of Toxicology and Pathology Syracuse, New York USA
<b>Date of study initiation:</b>	Initiation date not provided (Protocol dated March 5, 2009 and Final Report dated Dec 7, 2009)
<b>GLP compliance:</b>	Yes
<b>QA statement:</b>	Yes
<b>Drug, lot #, and % purity:</b>	Abatacept Lot 9B45689 (b) (4) Purity 98.7% monomer

	Lot 9B45690 (b) (4) (b) (4) (b) (4) Purity 99.1% monomer
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**Key Study Findings**

There was no difference in the single-dose intravenous pharmacokinetics of abatacept manufactured from (b) (4)

The two batches of abatacept were identified as:

- (b) (4) using (b) (4)
- (b) (4) using (b) (4)

There was no mortality and no differences between the 2 abatacept batches in clinical signs, body weight, food consumption, or clinical pathology values.

A positive abatacept-specific antibody response was detected on or after Day 22 in 8 of 12 monkeys treated with (b) (4) or 7 of 12 monkeys treated with (b) (4) (b) (4)

When anti-abatacept antibodies were detected, the observed abatacept concentrations were generally lower in serum samples detected with high anti-abatacept antibody titers compared to samples with low or no anti-abatacept antibody titers at similar time points.

<b>Methods</b>	
Doses:	10 mg/kg
Frequency of dosing:	single dose
Route of administration:	intravenous
Dose volume:	1 mL/kg
Formulation/Vehicle:	0.9% Sodium Chloride
Species/Strain:	Cynomolgus monkeys, ( <i>M. fascicularis</i> ), males only, protein naive
Number/Sex/Group:	12 males/ group
Age:	2-4 years of age
Weight:	2.7 and 3.5 kg
Satellite groups:	none
Unique study design:	There was no control non-abatacept group. Comparisons for abatacept effects were made with predose levels or observations. Between batches comparisons at similar time points were made to determine batch effects.

Group Number	Abatacept Manufacturing Process/Description <sup>a</sup>	Abatacept Dose (mg/kg)	Dose Volume (mL/kg)	Concentration Abatacept (mg/mL)	Number of Animals
1	(b) (4)	10	1	10	12
2	(b) (4)	10	1	10	12

<sup>a</sup> Lot numbers were recorded in the study records.

Deviation from study protocol:	There were no deviations that affected the interpretation and conclusions of the study.
--------------------------------	---

## Observations and Results

**Mortality** checked once daily

There were no mortalities.

**Clinical Signs** included physical and neurologic examinations, body temperatures, heart rates, respiratory rate and evaluation of lung sounds and mucous membrane color. On the day of dosing, each animal was observed prior to dosing and at approximately 1 and 4 hours post-dose. During the recovery period the animals were observed once daily for changes in condition and behavior.

Red discoloration at the injection site was noted in both treatment groups. There were no toxicologically significant differences between treatment groups for any of the clinical observations, physical exams including neurological examination and respiratory sounds, or quantitative measurements (body temperature, heart rate, respiratory rate).

One animal administered (b) (4) 11 days earlier, was examined due to an injury of lacerations to the right toes. These were treated with topical antibiotics. One animal administered (b) (4) 36 days earlier was examined due to a prolapsed rectum and liquid feces. The prolapse was manually reduced and the animal was treated with antibiotics. The rectal prolapse was considered secondary to the liquid feces and the chairing for blood withdrawal.

**Body Weights** Each animal was weighed pretest, prior to dosing, and once each week thereafter.

There were no effects and no differences between batches on body weight.

**Feed Consumption** Qualitative assessment of food consumption was determined daily

There were no effects and no differences between batches on feed consumption.

**Ophthalmoscopy** not assessed  
**ECG** not assessed

**Hematology** Blood samples from the femoral vein were obtained from anesthetized animals twice in the pretest phase and on day 49. The following parameters were monitored:

**Hematology**

erythrocyte count	red cell distribution width
hemoglobin	platelet count
hematocrit	mean platelet volume
mean corpuscular volume	absolute total and differential
mean corpuscular hemoglobin	leukocyte counts
mean corpuscular hemoglobin concentration	evaluation of cell morphology
absolute reticulocyte count	

**Coagulation**

prothrombin time  
 activated partial thromboplastin time  
 plasma fibrinogen

There were no effects and no differences between batches on hematology or coagulation parameters.

**Clinical Chemistry** Blood samples from the femoral vein were obtained from anesthetized animals twice in the pretest phase and on day 49. The following parameters were monitored

**Serum Chemistry**

aspartate aminotransferase	triglycerides
alanine aminotransferase	glucose
gamma glutamyltransferase	urea nitrogen
alkaline phosphatase	creatinine
total bilirubin	calcium
total protein	phosphorus
albumin	sodium
globulins	potassium
albumin/globulin ratio	chloride
total cholesterol	

There were no effects and no differences between batches on hematology or coagulation parameters.

**Urinalysis** A urinalysis was performed on urine collected overnight into a chilled container twice at pretest and on Day 49. The following parameters were monitored

**Urinalysis**

volume  
color and clarity  
pH  
specific gravity  
glucose - qualitative determination  
ketones - qualitative determination  
bilirubin - qualitative determination  
occult blood - qualitative determination  
urobilinogen - qualitative determination  
urine total protein - quantitative determination  
urine total protein output - quantitative determination  
microscopic evaluation of urinary sediment

There were no effects and no differences between batches on urinalysis

**Gross Pathology** collected cutaneous and subcutaneous tissues from the injection site  
**Organ Weights** not assessed  
**Histopathology** not assessed

**Toxicokinetics** Serum concentrations of abatacept were determined from blood samples collected from the femoral vein of unanesthetized monkeys after dosing at 3 minutes, and 0.5, 1, 2, 4, 8, 24, and 48 hrs post-dose, and on Days 4, 8, 11, 15, 22, 29, 36 and 43. Abatacept in the study samples were determined using a validated ELISA.

The pharmacokinetic parameters were similar between abatacept batches manufactured (b) (4) (Tables 3 and 4, below). Also individual serum abatacept concentrations versus time profiles are presented in Figures 1 and 2.

**Table 3: Pharmacokinetic Summary**

Parameter	Abatacept (10 mg/kg)	
	(b) (4)	(b) (4)
C <sub>3min</sub> (µg/mL)	227	209
AUC(0-1008 h) (µg•h/mL)	16500	16600
AUC(INF) (µg•h/mL)	16600	16800
T-HALF <sup>b</sup> (h)	140	120
T-HALF <sup>c</sup> (h)	190	150
MRT (h)	170	170
CLT (mL/h/kg)	0.617	0.606
V <sub>ss</sub> (L/kg)	0.102	0.100

<sup>a</sup>All pharmacokinetic parameters are reported as mean values

<sup>b</sup>T-HALF during post dose phase was calculated with the samples detected with anti-abatacept antibodies.

<sup>c</sup>T-HALF during post dose phase was calculated without the samples detected with anti-abatacept antibodies.

**Table 4: Statistical Summary of Pharmacokinetic Parameters**

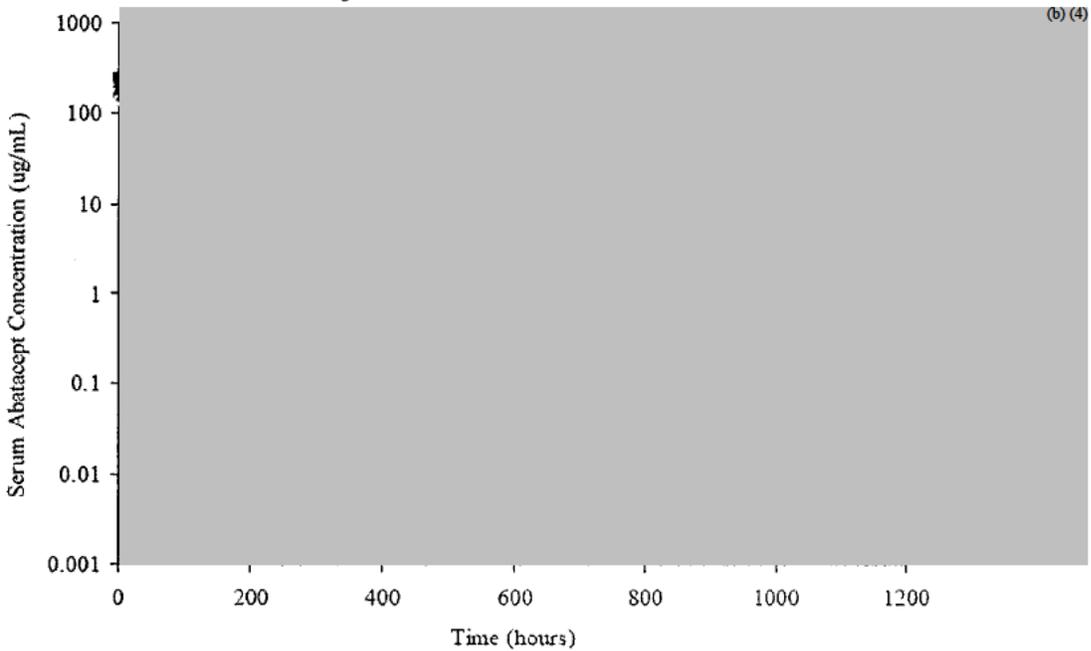
Parameter (n=12/group)	Geometric Mean		Ratio of Geometric Means (Test/Reference)	90% CL
	(b) (4) (Reference)	(b) (4) (b) (4) (Test)		
C <sub>3min</sub> <sup>b</sup> (µg/mL)	226	207 <sup>b</sup>	0.92	(0.84, 1.01)
AUC(0-1008h) (µg•h/mL)	16247	16519	1.02	(0.92, 1.13)
AUC(INF) (µg•h/mL)	16419	16616	1.01	(0.91, 1.13)

CL: Confidence Limit for difference.

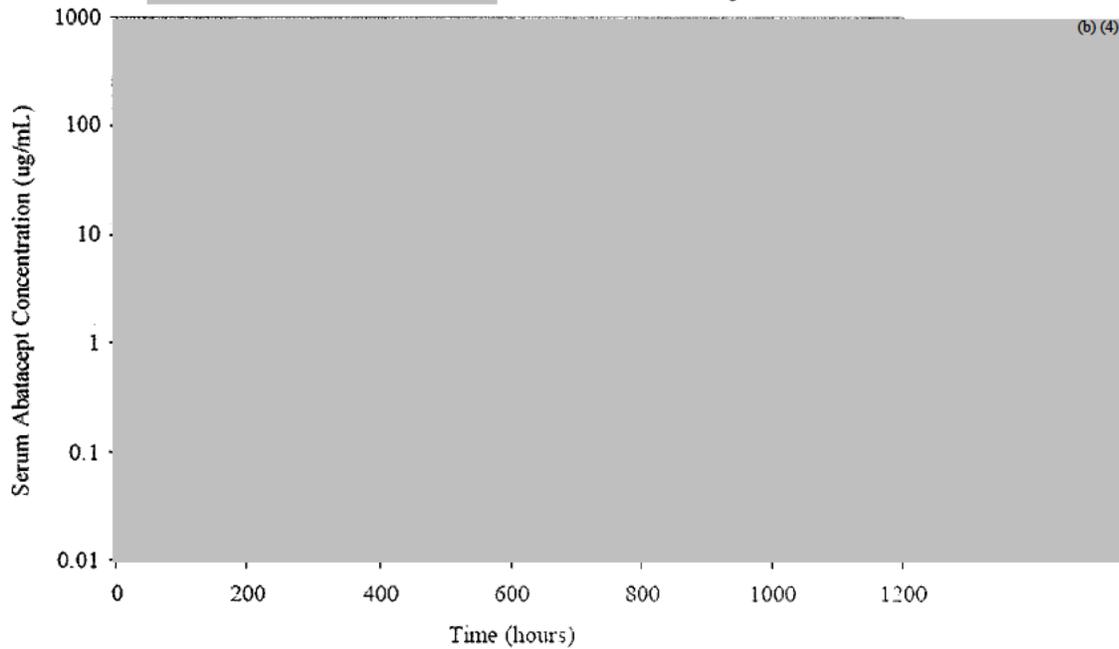
<sup>a</sup>Analyses were based on log-transformed pharmacokinetic parameters.

<sup>b</sup>C<sub>3min</sub> for Animal 2107 (Group 2, (b) (4)) was not determined.

**Figure 1: Individual Serum Concentration versus Time Profile of Abatacept Following a Single Intravenous Dose of 10 mg/kg Abatacept** (b) (4) **to Male Monkeys**



**Figure 2: Individual Serum Concentration versus Time Profile of Abatacept Following a Single Intravenous Dose of 10 mg/kg Abatacept** (b) (4) **to Male Monkeys**



The abatacept concentrations in serum samples detected with anti-abatacept antibodies are denoted with endpoint titer values.

**Immunogenicity** Assessment abatacept-specific antibodies using a validated electrochemiluminescent (ECL) method on an aliquot of serum obtained from TK samples on pretest and on Days 8, 15, 22, 29, 36, and 43.

There were no substantial differences in immunogenicity between the 2 lots of abatacept. Abatacept-specific antibodies of comparable magnitude occurred in 8 of 12 monkeys and 7 of 12 monkeys treated with (b) (4) (b) (4) respectively. Abatacept-specific antibodies were detected as early as Days 22 to 29 postdose with both processes and then in in additional monkeys through Day 43 (Table 5).

**Table 5: Incidence of Monkeys with Anti-Abatacept Antibody Titers**

Day	(total N = 12)	(b) (4) (b) (4) (total N = 12)
22	1	0
29	2	2
36	8	6
43	8 (67%)	6 (50%)

In general, when anti-abatacept antibodies were detected, the observed abatacept concentrations were lower in serum samples detected with high anti-abatacept antibody titers compared to samples with low or no anti-abatacept antibody titers at similar time points (Figures 1 and 2). Peak antibody titers were similar for the two treatment groups, ranging from 117 to 4305 and 105 to 4873 in those monkeys infused with abatacept manufactured from (b) (4).

**Stability and Homogeneity**

For content verification, all samples met acceptance criteria (individual concentrations were within 10% of each other and the mean concentration was within 10% of the intended concentration).

## 10 Special Toxicology Studies

(b) (4)

The Applicant addressed the Agency's concern (b) (4) of the formulation and potential toxicity associated with dosing. The question raised in the CR letter of April 23, 2010:

(b) (4)

*to be assured of the reproducibility of the clearance process, the level of these (b) (4) should be assessed in  $\geq 3$  DS lots from (b) (4) that span the history of the intended (CD- (b) (4) manufacturing process*

The Applicant responded with Table 6 indicating the level of these (b) (4) from five drug substance lots from (b) (4) that span the history of the intended (CD (b) (4) (b) (4) manufacturing process. The amount of (b) (4) per abatacept dose was calculated based on 750 mg dose/patient using the following equation:

Amount of (b) (4) per Abatacept Dose = (b) (4) Concentration in drug substance ( $\mu\text{g}/\text{mL}$ )/50 (mg abatacept/mL) \* 0.75 g per Dose, (where 50 refers to the abatacept protein concentration in the drug substance, 50 mg abatacept/mL).

However, since the maximal dose is 1000 mg, the reviewer added another set of rows below Table 6 indicating the intake values for this dose compared to the EMEA limits (used by the Applicant) as well as the current USP limits (USP Ad Hoc Advisory Panel on (b) (4) substantially below those specification limits generally recognized to ensure safety. Thus, based on these results, the levels of (b) (4) in the approved maximal dose present no toxicological concern for the indicated clinical population.

(b) (4)

## 11 Integrated Summary and Safety Evaluation

This supplement is to allow a change in the manufacture of abatacept that incorporated the (b) (4)

(b) (4)  
of abatacept produced. In previous discussions with the Applicant following an initial CR decision for this supplement, the Applicant was requested to conduct a nonclinical study to demonstrate pharmacokinetic similarity between abatacept from the approved manufacturing method and abatacept from the manufacturing method (b) (4)

This supplement contained one nonclinical pharmacokinetic study that provided support for the proposed manufacturing change. This was a pharmacokinetic comparison

between abatacept prepared from manufacture in a (b) (4) Administered as a single intravenous infusion of 10 mg/kg to cynomolgus monkeys, there were no differences in pharmacokinetic parameters between batches of abatacept produced with the (b) (4). There were also no differences in the incidence and relative time for the development of anti-abatacept antibodies between abatacept manufacturing processes. There was no mortality and no differences between the 2 abatacept batches in clinical signs, body weight, food consumption, or clinical pathology values.

A toxicological analysis was also conducted by the Applicant of the amount of added (b) (4) within an approved dose a dose of abatacept. At the maximal dose of 1000 mg, the levels of (b) (4) were much lower than regulatory levels of permitted daily exposures. Thus, the levels of (b) (4) in the approved maximal dose present no toxicological concern for the indicated clinical population.

Reviewer Signature L. Steven Leshin Date 5/5/11

Supervisor Signature Molly E. Topp Date 5/5/11

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125118/S107**

**CLINICAL PHARMACOLOGY REVIEW(S)**

## CLINICAL PHARMACOLOGY REVIEW

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BLA 125118/107  
Submission Date: 02/22/2011  
Brand Name Orenzia®  
Submission Type Prior Approval Supplement  
Generic Name Abatacept (BMS188667)  
OCP Reviewer Liang Zhao, Ph.D.  
Team Leader (Acting) Suresh Doddapaneni, Ph.D.  
OCP Division Clinical Pharmacology 2 (DCP2)  
OND Division Pulmonary, Allergy and Rheumatology Products (DPARP)  
Sponsor Bristol Myers Squibb  
Formulation; Strength(s); Administration Route 250 mg single-use vial; 30-minute intravenous infusion

Approved Indication Moderately to severely active RA in adults;  
Moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older

Purpose of this Efficacy Supplement To demonstrate that (b) (4) do not affect the PK of abatacept drug product when the drug substance is manufactured (b) (4) in the CD- (b) (4)

Approved Dosage Regimen

**Adult RA (2.1)**

Body Weight of Patient	Dose	Number of Vials
<60 kg	500 mg	2
60 to 100 kg	750 mg	3
>100 kg	1000 mg	4

**Juvenile Idiopathic Arthritis (2.2)**

- Pediatric patients weighing less than 75 kg receive 10 mg/kg based on the patient's body weight. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult dosing regimen, not to exceed a maximum dose of 1000 mg (2.2).

Following initial dose, give at 2 and 4 weeks, then every 4 weeks

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# 1 Executive Summary

## 1.1 Recommendation

From a Clinical Pharmacology perspective, supplement 107 is acceptable.

## 1.2 Phase IV Commitments

None.

## 1.3 Summary of Clinical Pharmacology Findings

Human PK data obtained from abatacept batches derived from CD- [REDACTED] (b) (4) [REDACTED] was submitted in this complete response to show that abatacept manufactured [REDACTED] (b) (4) in the CD [REDACTED] (b) (4) [REDACTED] results in comparable PK exposure in human subjects. The primary data for the PK analysis was derived from clinical studies IM101167 and IM101174. Study IM101167 was a Phase IIIB, multicenter, randomized, withdrawal study to evaluate the immunogenicity and safety of subcutaneously administered Abatacept in subjects with active rheumatoid arthritis. The purpose of this study was to investigate immunogenicity and safety after withdrawal and reintroduction of SC abatacept in a total of 270 enrolled subjects with RA on background MTX therapy who had responded to an initial 12 weeks of SC abatacept treatment. Study IM101174 was a phase IIIB multicenter, randomized, double-blind, double-dummy, study to compare the efficacy and safety of abatacept administered subcutaneously and intravenously in subjects with rheumatoid arthritis receiving background methotrexate and experiencing an inadequate response to methotrexate. In both studies, pre-dose blood samples were collected on several days throughout the course of the study. In study IM101167, blood samples were collected on days 1, 57, 78, 85, 113, 141, 169, 197, 225, and 253. In study IM101174, all subjects underwent pre-dose blood sampling on days 1, 85, 169 with a subset of patients undergoing additional sampling on other select days. The primary focus of the PK assessment of comparability is the trough serum concentration of abatacept after IV treatment at steady state ( $C_{minss}$ ) with the assumption that  $C_{minss}$  is the key driver for efficacy. Association of  $C_{minss}$  with efficacy has been investigated in both the IV and SC development programs for abatacept. Data for  $C_{max}$  and AUC were also

provided for completeness and informational purposes. Tables below show Cmin data between (b) (4) groups.

Table. Abatacept Cminss on Day 85 for high- and low- titer groups (Study IM101174).

Pharmacokinetic Variable	Adjusted Geometric Mean		Ratio of Geometric Means		
	Drug Product titer Group	Geometric Mean	Ratio	Point Estimate	90% CI
Cmin (µg/mL)	High (n=80)	19.383	High vs. Low	1.110	(0.977, 1.263)
	Low (n=319)	17.455			

Source: IM101174 wwbdm/clin/proj/im/101/174/dev/stats/ (b) (4)Cmin\_MIX.sas

Table. Combined Abatacept Cminss across Days 85, 113, 141, and 169 for high- and low- titer groups (Study IM101174).

Pharmacokinetic Variable	Adjusted Geometric Mean		Ratio of Geometric Means		
	Drug Product titer Group	Geometric Mean	Ratio	Point Estimate	90% CI
Cmin (µg/mL)	High (n=173)	19.639	High vs. Low	1.135	(1.021, 1.262)
	Low (n=717)	17.302			

Source: wwbdm/clin/proj/im/101/174/val/stats (b) (4)/parallel\_mix\_all.sas

These data show that the distribution of Cmin was comparable between subjects who had received high titer abatacept and low titer abatacept. The upper bound of the 90% confidence interval fell slightly outside the upper limit. These data combined with acceptable drug substance release and biochemical characterization testing and preclinical PK data suggests that drug manufactured (b) (4) are comparable.

## 2 Question-Based Review (QBR)

### 2.1 General Attributes

#### 2.1.1. What are the highlights of the chemistry and physico-chemical properties of the drug substance, and the formulation of the drug product?

**Chemistry and Physico-Chemical Properties:** Abatacept (ORENCIATM, BMS-188667, CTLA4Ig) is a recombinant, soluble, fusion protein consisting of the extracellular domain of human CTLA-4 and a fragment (hinge– CH2–CH3 domains) of the Fc domain of human IgG1. The molecular weight obtained by MALDI-TOF is 92,300 Daltons. It is a biological inhibitor of T-cell activation and was developed as the first generation of biological antirheumatics for rheumatoid arthritis (RA). Abatacept drug substance is produced as a secreted protein in large-scale cell culture using a (b) (4) (b) (4) steps.

**Formulation:** The intravenous (IV) formulation (ORENCIA®) is currently marketed by Bristol-Myers Squibb (BMS) as a lyophilized powder for intravenous infusion (250mg/vial).

#### 2.1.2. What is the approved therapeutic indication, dosage and route of administration?

**Indication:**

Moderately to severely active RA in adults; Moderately to severely active polyarticular juvenile idiopathic arthritis in pediatric patients 6 years of age and older.

**Dosage and Route of Administration:**

**Adult RA (2.1)**

Body Weight of Patient	Dose	Number of Vials
<60 kg	500 mg	2
60 to 100 kg	750 mg	3
>100 kg	1000 mg	4

**Juvenile Idiopathic Arthritis (2.2)**

- Pediatric patients weighing less than 75 kg receive 10 mg/kg based on the patient's body weight. Pediatric patients weighing 75 kg or more should be administered ORENCIA following the adult dosing regimen, not to exceed a maximum dose of 1000 mg (2.2).

### 2.2 Regulatory History

Abatacept was originally approved in December of 2005. On 26 October 2009, BMS submitted a Prior Approval Supplement (PAS) (reference STN BL 125118/107) to allow for the use of a new formulation of the CD- [REDACTED] (b) (4) for abatacept. On 23 April 2010, BMS received a Complete Response (CR) letter from FDA. On 12 July 2010, BMS and FDA held a Type A meeting to discuss the comments in the CR letter and to determine a path forward for resubmission of the 107 PAS. On 28 October 2010, BMS and FDA held a Type C meeting to further discuss required human data to demonstrate comparability for manufacturing process change.

Related to the demonstration of comparability aspect in the 28 October 2010 meeting, FDA's response to establish PK comparability after manufacturing process changes was as follows: "You (BMS) provided new human PK study results obtained from abatacept batches derived from a CD- [REDACTED] (b) (4) and compared the PK parameters from [REDACTED] (b) (4) with the already approved product [REDACTED] (b) (4). Combined with other studies you have provided, these findings appear adequate to support the complete response of the CD- [REDACTED] (b) (4) PAS. However, whether these results support the conclusion that the process change produces a comparable product will be a review issue. We (FDA) recommend that you submit the full study report in your submission".

## **2.3 General Clinical Pharmacology**

### **2.3.1. What are the clinical pharmacology and clinical trials used to support the proposed claims?**

#### **IM101167**

IM101167 was a Phase IIIB, multicenter, randomized, withdrawal study to evaluate the immunogenicity and safety of subcutaneously administered Abatacept in adults with active rheumatoid arthritis. The purpose of this study was to investigate immunogenicity and safety after withdrawal and reintroduction of SC abatacept in a total of 270 enrolled subjects with RA on background MTX therapy who had responded to an initial 12 weeks of SC abatacept treatment. The study consisted of a short-term (ST) period and an open label long-term extension (LTE) period. The ST period also included three distinct periods (ie, Periods, I, II, and III). Patients who completed Period III of the ST period could enter the open-label LTE on Day 253

where they continued to receive weekly SC abatacept. Period I non-responders who directly enrolled into the LTE at the Day 85 visit continued to receive weekly SC abatacept. If a clinical response was not achieved at the end of 12 weeks in the LTE, the subject was to be discontinued at that time. This study planned to randomize (1:1) at least 105 subjects to SC abatacept or placebo during Period II.

In Period I, all subjects received open-label SC abatacept 125 mg weekly 30' after a single IV loading dose of abatacept in this 12-week lead in period. In Period II, only the responders from the end of Period I entered the 12-week double blind placebo controlled period (SC abatacept or placebo). Only the responders from Period I were randomized in Period II. This was a 12-week double-blind placebo-controlled period in which subjects were randomized in a 2:1 ratio to SC placebo or SC abatacept. In Period III, subjects who received SC abatacept in Period II received an IV loading dose of placebo on Day 169. Subjects who received SC placebo in Period II were re-randomized to receive either a single IV loading dose of abatacept or placebo on Day 169. Following the IV loading dose on Day 169, all randomized subjects resumed weekly open-label SC abatacept, which continued through into Period III to Day 253. Venous blood samples were collected from all subjects prior to the IV infusion of abatacept and approximately 30 minutes after start of infusion on Days 1 and 169. Predose blood samples were collected on Days 57, 78, and 85 in Period I; Days 113, 141, and 169 in Period II; and Days 197, 225, and 253 in Period III. Blood samples were processed and shipped according to the instructions provided in the study protocol for IM101167.

#### **IM101174**

IM101174 was a phase IIIB multicenter, randomized, double-blind, double-dummy, study to compare the efficacy and safety of abatacept administered subcutaneously and intravenously in subjects with rheumatoid arthritis receiving background methotrexate and experiencing an inadequate response to methotrexate. The primary objective of the ST period was to demonstrate the non-inferiority of SC abatacept versus IV abatacept. This study was referred to as the "MTX-IR" (methotrexate-inadequate responder) study, consisting of a randomized, double-blind, double-dummy placebo-controlled 6-month short-term (ST) treatment period and an open-label, long-term (LT) period. The ST portion of the study consisted of a screening period of

variable length and a 6-month double-blind treatment period. The LT period will continue until the SC formulation becomes commercially available on a country basis or if the study is terminated.

During the double-blind ST period, subjects with RA who had an inadequate response to MTX were randomly assigned in a 1:1 ratio to treatment with SC abatacept or IV abatacept, with stratification by body weight (< 60 kg, 60 to 100 kg, > 100 kg, corresponding to body-weight-tiered doses of abatacept 500 mg, 750 mg, and 1000 mg, respectively) as 30 minute infusions on Days 1, 15, 29, and every 28 days thereafter. Subjects assigned to the SC abatacept group received 125 mg weekly, administered after the initial IV loading dose. The first 20 subjects stratified into each weight group had blood samples drawn according to the following schedule for determination of pre-dose abatacept serum concentrations: Days 1 (end of IV infusion sample also obtained), 57, 85, 113 (end of IV infusion sample also obtained), 115, 116, 117, 118, 120, 127, 134, 141, and 169. All other subjects underwent PK blood sampling such that predose samples were drawn on Days 1, 85, and 169.

### 2.3.2. What is the dataset used by sponsor?

Since IM101174 and IM101167 were the only studies that had PK measurements following IV doses of abatacept both with [REDACTED] (b) (4) PK data from these two studies have been analyzed retrospectively. In both trials, adult RA patients who received abatacept produced either from the current approved [REDACTED] (b) (4)

[REDACTED] IV abatacept was also administered either as a loading dose or as a comparator treatment in each study. In this submission (CD [REDACTED] (b) (4) PAS),

[REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]. For the trough concentration (C<sub>min</sub>) data, only the trough concentrations measured on Day 85 onward following IV treatment from the IM101174 IV arm were included in the analysis. For the peak concentration data, Day 1 and Day 113 peak concentrations of

IM101174 and Day 1 peak concentrations of IM101167 after IV treatment were included in the analysis.

(b) (4) patients treated with abatacept produced from two batches (Batch numbers: 7L22581 and 7M17902). These two batches were identified as lots that were manufactured from drug substance produced with (b) (4) in these two lots were summarized in Table 1.

Table 1. (b) (4) lots of abatacept used in clinical studies.

Drug Product Lot	Drug Substance Lot	(b) (4)
7L22581 (IV) <sup>a</sup>	47819 <sup>b</sup>	(b) (4)
7M17902 (IV) <sup>a</sup>	48415	(b) (4)

(b) (4)

(b) (4)

The number of subjects used in PK data analysis is summarized in Table 2.

Table 2: Number of subjects contributing PK data associated with batches of abatacept drug product with high and low titer (IM101174 and IM101167)

PK Parameter	High Titer <sup>(b) (4)</sup>	Low Titer
C <sub>min</sub> (µg/mL) <sup>a</sup>	75	502
C <sub>max</sub> (µg/mL) (single dose)	69	66
C <sub>max</sub> (µg/mL) (multiple dose)	28	7
AUC(TAU) µg•h/mL	31	7

Source: \Clinical\_Discovery\Clin Disc Group - Onc-Immu\Immunology Programs\BMS-188667(CTLA4Ig)\188667\ <sup>(b) (4)</sup>Regulatory Report\IM101174 <sup>(b) (4)</sup>JNB, and global/pkms/data/IM/101/C04/prd/sz/pk/sp/scripts/process. <sup>(b) (4)</sup>ssc

<sup>a</sup> An additional 14 subjects have abatacept concentration data associated with both high and low titer batches.

The subject numbers from study IM101174 shown in Table 2 can be further broken down based on study Days to the following numbers shown in Table 3.

Table 3. Number of subjects contributing C<sub>min</sub> data associated with batches of abatacept drug product manufactured with high and low titer (IM101174)

Study Day	Pure High Titer	Pure Low Titer	Mixed High Titer <sup>a</sup>	Mixed Low Titer <sup>a</sup>	Total (n)
85	66	319	14	0	399
113	24	6	1	0	31
141	25	4	0	0	29
169	43	374	0	14	431
Total (n)	75	502	14	14	591

Source: \Clinical\_Discovery\Clin Disc Group - Onc-Immu\Immunology Programs\BMS-188667(CTLA4Ig)\188667\ <sup>(b) (4)</sup>Regulatory Report\IM101174 <sup>(b) (4)</sup>JNB, and global/pkms/data/IM/101/C04/prd/sz/pk/sp/scripts/process. <sup>(b) (4)</sup>ssc

<sup>a</sup> During the course of the study, 14 subjects had PK trough observations associated with both high titer and low titer abatacept depending on the study day and referred to as a "mixed" population. If they did not receive 2 consecutive doses of either High titer or Low titer abatacept, their observations were not counted on that study day.

A slightly modified dataset was used for a sensitivity analysis for C<sub>min</sub>, where the high titer dataset remained intact as shown in Table 3 but the low titer dataset was modified by including data that was associated with lots manufactured only at the currently approved <sup>(b) (4)</sup> site, as

well as removing data associated with manufacturing in the (b) (4) vessels. The number of subjects included in the Cmin sensitivity analysis after such modification is shown in Table 4.

Table 4. Number of subjects contributing Cmin data associated with batches of abatacept drug product manufactured with high and low titer (Sensitivity Analysis)

Study Day	(b) (4)	(b) (4)	Total (n)
85	80	11	91
113	25	0	25
141	25	0	25
169	43	3	46
Total (n)	89	12	101



**2.3.3. What is the statistical analysis used by sponsor?**

PK parameters (i.e., Cmin (µg/mL), Cmax (µg/mL), and AUC(TAU) (µg•h/mL)) were derived by non-compartmental analysis. The primary goal of the submitted PK analysis was to assess the comparability in the trough serum concentration of abatacept after IV treatment at steady state (Cminss). This was based on the identification of Cminss as the key efficacy driver based on a previously submitted modeling and simulation report (IM101: Population Pharmacokinetics and Exposure-Response of Subcutaneously Administered Abatacept (BMS-188667) in Patients with Rheumatoid Arthritis). Data for peak serum concentration (Cmax) with single and multiple doses of abatacept and for area under the concentration time curve (AUC) were also provided, mainly for completeness and informational purposes.

Scatter plots and boxplots of the exposure parameters (Cmin, Cmax, and AUC(TAU)) against abatacept drug product, manufactured from drug substance derived using CD- (b) (4)

(b) (4)

(b) (4) were used to evaluate differences in their distributions. Cmin values across study Days 85

through 169 from study IM101174 were combined to evaluate C<sub>min</sub>, because abatacept C<sub>min</sub> concentrations have been shown to be stable once steady-state is achieved.

One way analysis of variance on log-transformed C<sub>min</sub> was conducted on the C<sub>min</sub> data from Day 85 of Study IM101174, representing the largest amount of data on a single study day at steady-state. Point estimate and the 90% CI for treatment difference on the log scale was exponentiated to obtain estimate for ratio of geometric mean on the original scale. Assuming C<sub>min</sub> is stable once steady state is achieved, sponsor also has run a mixed linear model on log-transformed C<sub>min</sub> data combined from Days 85, 113, 141, and 169 of Study IM101174, with treatment group and study day as fixed effects, and within subject measurements as repeated measured. Point estimate and 90% CI for treatment difference on the log scale was exponentiated to obtain estimate for ratio of geometric mean on the original scale.

**2.3.4. Were the active moieties in the plasma appropriately identified and measured to assess pharmacokinetic parameters?**

Yes. Abatacept serum concentrations were determined by a validated method by enzyme linked immunosorbent assay (ELISA). A monoclonal antibody against CTLA4Ig was used to capture abatacept. Abatacept was then detected with a (b) (4) antibody against CTLA4Ig, followed by detection with streptavidin- (b) (4)

**2.3.5. What are the PK characteristics of abatacept in patients?**

The pharmacokinetics characteristics of abatacept in both healthy volunteers and RA patients following IV administration have been reviewed by Dr. Anil Rajpal in the original BLA submission. The pharmacokinetics of abatacept in RA patients and healthy subjects appeared to be comparable. The half lives (T<sub>1/2</sub>) based on non-compartmental analyses were found to be approximately 16.7 and 13.1 days for healthy subjects and RA patients, respectively. Comparison of the non-compartmental PK results suggests that there was no clinically relevant impact on abatacept PK by concomitantly administering methotrexate or etanercept. Table 4 was the summary of the PK parameters in the original submission. The bioavailability of abatacept was identified to be 78.6% from trial IM101174.

Table 4. Pharmacokinetic parameters (mean, range) in healthy subjects and RA patients after 10 mg/kg intravenous infusion(s)

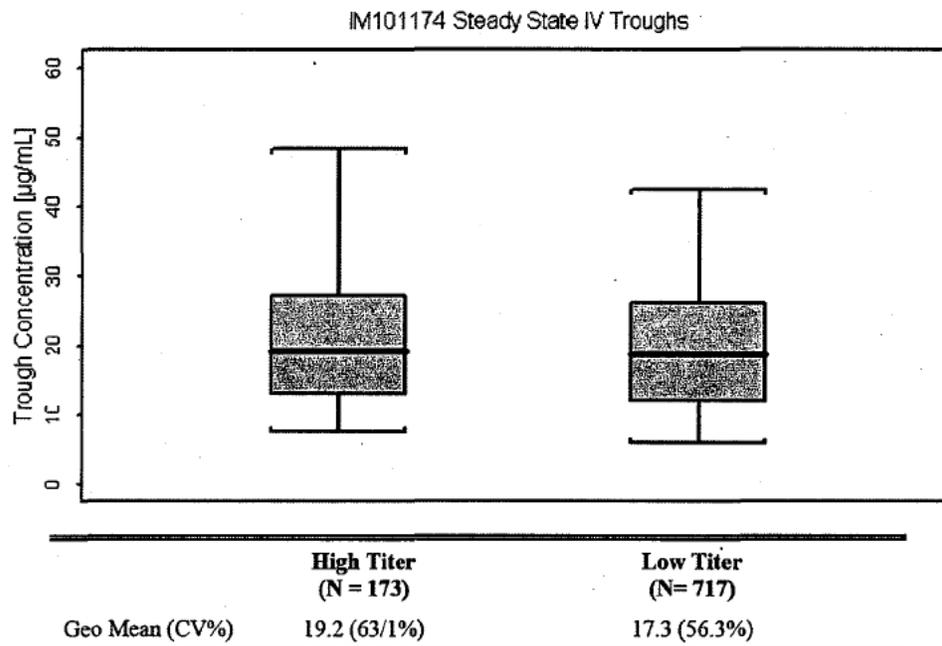
PK Parameter	Healthy Subjects (After 10 mg/kg Single Dose) n=13	RA Patients (After 10 mg/kg Multiple Doses*) n=14
Peak Concentration (C <sub>max</sub> ) [mcg/mL]	292 (175-427)	295 (171-398)
Terminal half-life (t <sub>1/2</sub> ) [days]	16.7 (12-23)	13.1 (8-25)
Systemic clearance (CL) [mL/h/kg]	0.23 (0.16-0.30)	0.22 (0.13-0.47)
Volume of distribution (V <sub>ss</sub> ) [L/kg]	0.09 (0.06-0.13)	0.07 (0.02-0.13)

\* Multiple intravenous infusions were administered at days 1, 15, 30, and monthly thereafter.

### 2.3.6. What are the key results from the statistical analysis?

The observed steady-state abatacept C<sub>min</sub> data from study IM101174 for (b) (4) are shown in Figure 1. The corresponding statistical analyses for C<sub>min</sub> comparability are shown in Tables 5 & 6, where Table 5 summarizes the result for C<sub>min</sub> on Day 85 only and Table 6 summarizes the result for C<sub>min</sub> across study Days 85, 113, 141, and 169.

Figure 1. Box plot of abatacept C<sub>min</sub> for high (Study IM101174)



Source: global/pkms/data/IM/101/C04/prd/sz/pk/sp/scripts/process (b) (4).ssc

Note: The trough concentration data were combined from study Days 85 to 169 and "N" represents the number of observations. The thick line in the middle of the box is the median, the lower and upper ends of the boxes represent the 25th and 75th percentiles, and the whiskers are the 5th and 95th percentiles.

Table 5. Abatacept Cminss on Day 85 for high- and low- titer groups (Study IM101174).

Pharmacokinetic Variable	Adjusted Geometric Mean		Ratio of Geometric Means		
	Drug Product titer Group	Geometric Mean	Ratio	Point Estimate	90% CI
Cmin (µg/mL)	High (n=80)	19.383	High vs. Low	1.110	(0.977, 1.263)
	Low (n=319)	17.455			

Source: IM101174 wwbdm/clin/proj/im/101/174/dev/stats <sup>(b) (4)</sup>/Cmin\_MIX.sas

Table 6. Combined Abatacept Cminss across Days 85, 113, 141, and 169 for high- and low- titer groups (Study IM101174).

Pharmacokinetic Variable	Adjusted Geometric Mean		Ratio of Geometric Means		
	Drug Product titer Group	Geometric Mean	Ratio	Point Estimate	90% CI
Cmin (µg/mL)	High (n=173)	19.639	High vs. Low	1.135	(1.021, 1.262)
	Low (n=717)	17.302			

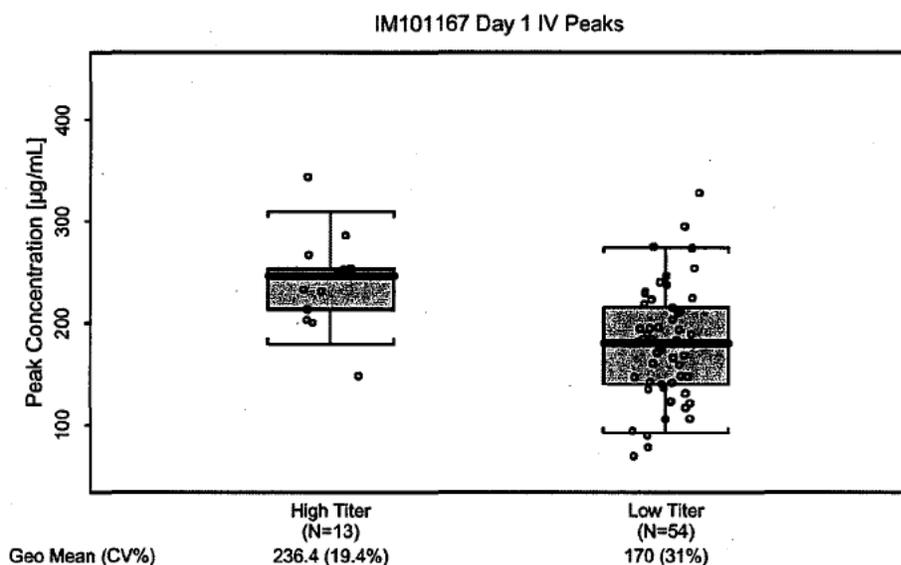
Source: wwbdm/clin/proj/im/101/174/val/stats <sup>(b) (4)</sup>parallel\_mix\_all.sas

As shown in Table 5, the point estimate for the adjusted geometric mean ratio of Cmin for high-titer to low-titer groups on Day 85 was 1.11. The upper bound of the associated 90% confidence interval (97.7%-126.3%) exceeded the bioequivalence bound by a marginal 1.3%.

Other PK parameters (i.e., Cmax and AUC (TAU) at steady state) for study IM101174 were also evaluated. The geometric mean (%CV) estimates for abatacept Cmaxss for high- and low-titer groups are 221.5 µg/mL (32%) (n=28) and 271.9 µg/mL (66%) (n=7), respectively. The geometric mean (%CV) estimates for abatacept AUC(TAU) for high- and low-titer groups are 38870 µg•h/mL (38%) (n=31) and 37614 µg•h/mL (33%) (n=7), respectively.

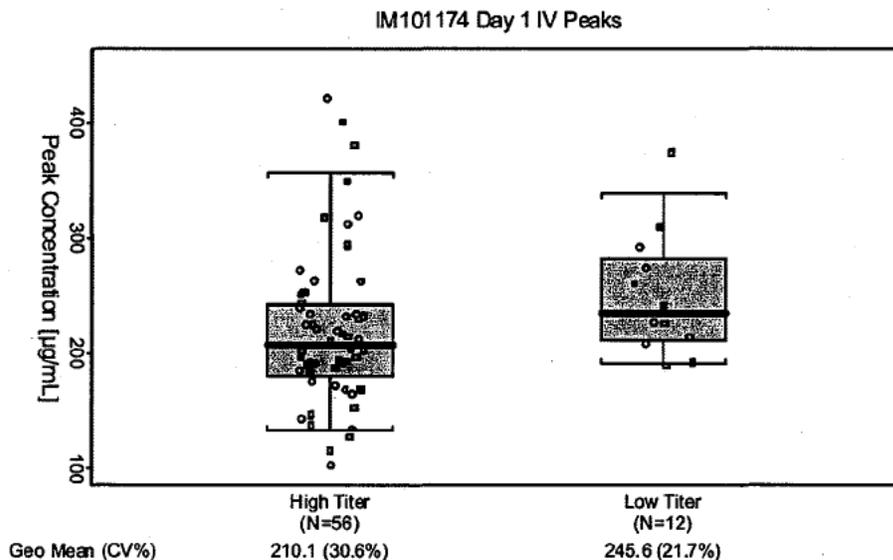
Figures 2 & 3 show the observed Cmax data following IV administration on Day 1 from Studies IM101167 and IM101174, respectively.

Figure 2. Abatacept Cmax on Day 1 for high- and low-titer groups (Study IM101167)



The thick line in the middle of the box, the lower and upper ends of the boxes, and the whiskers represent the median, the 25<sup>th</sup> and the 75<sup>th</sup> percentiles, and the 5<sup>th</sup> and 95<sup>th</sup> percentiles, respectively. Open circles represent the individual observed values.

Figure 3. Abatacept Cmax on Day 1 for high- and low-titer groups (Study IM101174)



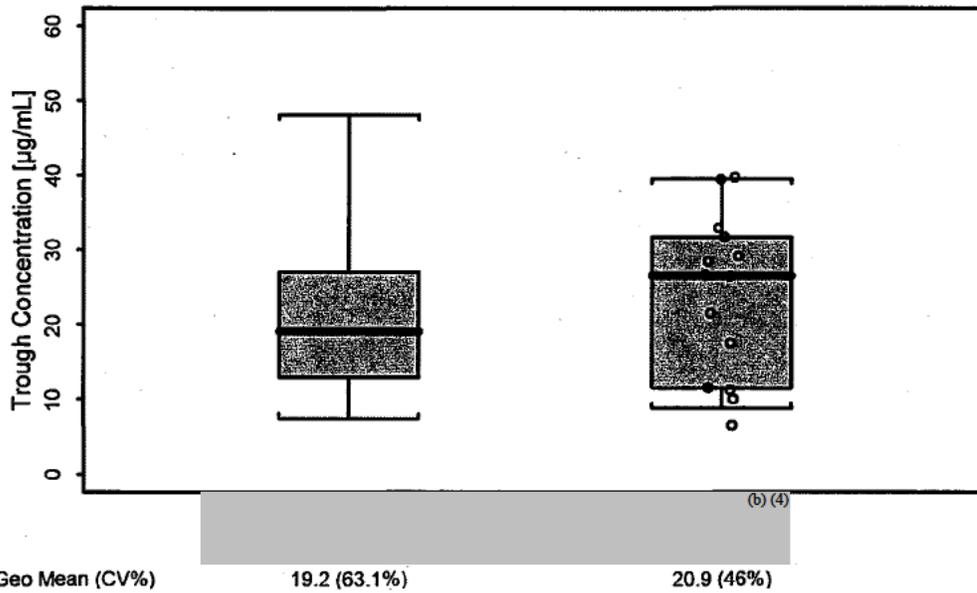
Again, the thick line in the middle of the box, the lower and upper ends of the boxes, and the whiskers represent the median, the 25<sup>th</sup> and the 75<sup>th</sup> percentiles, and the 5<sup>th</sup> and 95<sup>th</sup> percentiles, respectively. Open circles represent the individual observed values.

The geometric mean (%CV) estimates for abatacept C<sub>max</sub> on Day 1 for high- and low-titer groups in Study IM101167 are 236.4 µg/mL (19.4%) (n=13) and 170 µg/mL (31%) (n=54), respectively. The geometric mean (%CV) estimates for abatacept C<sub>max</sub> on Day 1 for high- and low-titer groups in Study IM101174 are 210.1 µg/mL (30.6%) (n=56) and 245.6 µg/mL (21.7%) (n=12), respectively.

A sensitivity analysis was based on a slightly modified dataset for C<sub>minss</sub>, where the high titer dataset remained intact but the low titer dataset was modified by including data that was associated with lots manufactured only at the currently approved (b)(4) site, as well as removing data associated with manufacturing in the (b)(4) vessels. The number of subjects after data modification is shown in Table 4. Figure 4 presents the sensitivity analysis results based on the modified dataset. It shows that the geometric mean (%CV) estimates for abatacept C<sub>minss</sub> for high- and low-titer groups in Study IM101174 were 19.2 µg/mL (63.1%) (n=173) and 20.9 µg/mL (46%) (n=14), respectively.

Figure 4. Sensitivity analysis for abatacept C<sub>minss</sub> for high- and low-titer groups (Study IM101174)

### IM101174 Steady State IV Troughs



Source: global/pkms/data/IM/101/C04/prd/sz/pk/sp/scripts/process.batch.ssc

Note: The trough concentration data were combined from study Days 85 to 169 and "N" represents the number of observations. The thick line in the middle of the box is the median, the lower and upper ends of the boxes represent the 25th and 75th percentiles, and the whiskers are the 5th and 95th percentiles. Open circles represent individual observations.

## 2.4 Intrinsic Factors

### 2.4.1. What was the impact of demographic covariates on abatacept exposure?

Only body weight has been identified as a covariate that results in clinical relevant exposure variation. The impact of all other covariates such as age, gender, race, renal function (measured by CGFR), hepatic function (measured by albumin and total bilirubin), and concomitant medication of methotrexate, corticosteroid, or NSAIDs, were all considered as clinically non-relevant.

### 2.4.2. What were the immunogenicity findings for abatacept? What was the impact of immunogenicity on exposure and/or safety?

Immunogenicity rates were low following IV treatment. The titers of antibodies against abatacept were low and non-persistent. The presence of antibodies against abatacept had no identified impact on safety, efficacy, or PK. The immunogenicity response did not appear to correlate with baseline body weight following IV abatacept treatment.

In the review of original supplement (107) submission conducted by Dr. Zhihong Li, it reads “In our communication with the product team, the CMC reviewer recognizes that based on *in vitro* comparability data, ‘there are small changes to the glycoforms which may impact PK. There are no changes that we can see that are likely to impact PD or immunogenicity.’” Therefore, it is agreed that a PK comparability study will be warranted for this CMC change. The product team also communicated with the Medical Officer to consult if any other studies will be required in addition to the PK study. The Medical officer’s opinion is: ‘Unless the PK characteristics are significantly different in the human study then I don't think we would need any other studies, especially since the new formulation is not expected to impact the PD or immunogenicity’”.

### 3 Conclusion

Based on this retrospective analysis report using sponsor-supplied human PK data obtained from abatacept batches derived from CD- (b) (4) (b) (4) it is concluded that abatacept manufactured (b) (4) in the CD- (b) (4) resulted in comparable PK exposure in human subjects..

**Signatures**

**Liang Zhao, Ph.D.**

**Clinical Pharmacology Reviewer**



6/10/2011

**Suresh Doddapaneni, Ph.D.**

**Clinical Pharmacology Acting TL**



6/10/2011

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125118/S107**

**OTHER REVIEW(S)**



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

Memorandum

**Review Date:** April 13, 2010  
**From:** Jack A. Ragheb M.D., Ph.D.  
**To:** The File, STN 125118/107

*Jack A. Ragheb 4/20/10*  
*Susan Kirshner 4-20-10*  
*Barry Chorney 4-20-10*

**Through:** Barry Chorney, Deputy Director, Division of Therapeutic Proteins  
Susan Kirshner, Associate Chief, Laboratory of Immunology, DTP  
**Subject:** STN 125118/107. Prior Approval Supplement to allow for the use of a new formulation of the abatacept CD- [REDACTED] (b) (4)

**Sponsor:** Bristol Myers Squibb

**Mfg Facility:** [REDACTED] (b) (4)

**Product:** Abatacept

**Indication:** Moderate to severe active rheumatoid arthritis in adult patients who have had an inadequate response to one or more Disease Modifying Anti-Rheumatoid Drugs (DMARDs), such as methotrexate or TNF antagonists; Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists.

**Deadlines:** April 23, 2010

**Submissions:** The supplement was originally submitted in eCTD format (#0094) on October 26, 2009. The firm amended its supplement on January 25, 2010 (125118/107/1, eCTD #0098) and a major amendment letter was issued on February 1, 2010. The supplement was amended again on March 25, 2010 (125118/107/2, eCTD #104).

**Recommendation:**

I recommend that a complete response letter be sent based on the findings described below.

**Review**

Background

The sponsor had observed variability in production [REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

[REDACTED]

[REDACTED] (b) (4)

Investigations (see below) determined the cause for the production [REDACTED] (b) (4)

[REDACTED]

[Redacted text block]

(b) (4)

**Preliminary investigations of the production**

(b) (4)

[Redacted text block]

(b) (4)

Based on this manufacturing history and the investigations outlined above, BMS now proposes to [Redacted]

(b) (4)

[Redacted text block]

formulation are presented in Table 2.3.T01 below. There are no other changes in the (b) (4)

[Redacted]

[Redacted] (b) (4)

To support this (b) (4) change, BMS conducted a comparability exercise consisting of PV studies of the (b) (4)

[Redacted]

the approved (b) (4)

[Redacted] (b) (4)

In order to establish comparability of the DS manufactured before and after the (b) (4) change, the Agency requested several additional pieces of information not included in the original submission.

BMS study results are reviewed below.

30 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page



*Comment: Based on the real time and accelerated stability data provided, I would concur with the sponsor's assessment that DS produced (b) (4) has a comparable stability profile. However, no side-by-side comparison was provided. Such a comparison under accelerated conditions would be useful to further interrogate the comparability of DS produced by the two processes.*



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

**Date:** 03 Feb 2010  
**To:** Administrative File, STN 125118/107  
**From:** Mary E. Farbman, Ph.D., CDER/OC/DMPQ/MAPCB/BMT. *mef 03/26/10*  
**Endorsement:** Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *P 2/4/10*  
**Subject:** Review memo: Prior Approval Supplement (PAS): Alternative cell culture  
(b) (4) component, comparability to existing (b) (4) and revised process parameters  
**US License:** # 1713  
**Applicant:** Bristol-Myers Squibb  
**Mfg Facility:** (b) (4)  
**Product:** Orenzia® (abatacept)  
**Dosage:** Lyophilized powder for injectable solution (250 mg/vial)  
**Indication:** Treatment of rheumatoid arthritis: reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease Modifying Anti-Rheumatoid Drugs (DMARDs), such as methotrexate or TNF antagonists; Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists  
**Due Date:** 25 Feb 2010

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**Recommendation for Approvability:** The changes in the (b) (4) described in this supplement have been evaluated from a microbiology and product quality perspective and were found to be acceptable. The submission is recommended for approval.

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**Summary**

BMS has submitted a PAS to request changes in the (b) (4) formulation (b) (4) formulation contains (b) (4) concentrations of (b) (4). This formulation was determined to allow (b) (4). To support these changes, the firm submitted process validation studies for the new (b) (4) formulation (b) (4) manufacturing sites. These studies allowed a comparison of data for drug substance made with the current and proposed (b) (4) formulations.



BMS's [REDACTED] (b) (4)

Satisfactory

**§3.2.S.2.5 PROCESS VALIDATION**

Validation of Abatacept Manufacturing Process Using CD (b) (4) [REDACTED] (b) (4)

[REDACTED]

[REDACTED]

[REDACTED]

*Review comments: use of the new (b) (4) formulation [REDACTED] (b) (4)*

[REDACTED]  
[REDACTED]  
[REDACTED] are comparable to levels reported for the original process.

Satisfactory

(b) (4) (b) (4) (b) (4)  
[Redacted text block]

[Redacted text block]

*Review comments: use of the new (b) (4) formulation (b) (4)*

[Redacted text block]

Satisfactory

**§3.2.S.2.6 MANUFACTURING PROCESS DEVELOPMENT**

This section will be reviewed by OBP.

**§3.2.S.2.7 STABILITY**

Three batches of abatacept drug substance manufactured (b) (4) have been placed on stability studies. Stability data is available for the initial three months. Bioburden data of bulk drug substance, which is stored at (b) (4) is within the specification (b) (4)

Satisfactory

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**Environmental Assessment**

The supplement did not involve the introduction of a new unlicensed molecular entity or an increase in the use of the active moiety; therefore, Environmental Assessment information is not required.

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**cGMP Status**

The Manufacturing Assessment and Pre-Approval Compliance Branch has completed its review and evaluation of the TB-EER for Bristol-Myers Squibb's STN 125118/107. Please see the attached response to find the individual compliance status of each facility. There are no pending or ongoing compliance actions to prevent approval of STN 125118/107 at this time.

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**Conclusion**

- I. The changes in the [REDACTED] <sup>(b) (4)</sup> described in this supplement have been evaluated from a microbiology and product quality perspective and were found to be acceptable. The submission is recommended for approval.
- II. CMC drug substance and drug product specific information and data should be reviewed by an OBP reviewer.
- III. There are no follow-up inspection items associated with this supplement.

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Cc: RPM: Shiber  
Committee Chair: Ragheb  
BMT Reviewer: Farbman

Archived File: S:\archive\BLAs\103764\103764.5086.rev.mem.PAS.02-03-10.doc

**Therapeutic Biological Establishment Evaluation  
Request (TB-EER) Form**  
Version 1.0

**Instructions:**

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

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

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

---

**APPLICATION INFORMATION**

PDUFA Action Date: 2/25/10

Applicant Name: Bristol-Myers Squibb

U.S. License #:

STN(s): 125118/107

Product(s): Abatacept

Short summary of application: [REDACTED] (b) (4)

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**FACILITY INFORMATION**

Firm Name: [REDACTED] (b) (4)

Short summary of manufacturing activities performed: drug substance manufacturing

Inspected by CDER-DMPQ in 2008 as a Pre-Approval Inspection for Abatacept DS manufacturing. This site was found to be acceptable. Abatacept DS manufacturing at this [REDACTED] (b) (4) using the requested changes will be released upon approval of this PAS.

Firm Name: [REDACTED] (b) (4)

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

Address: [REDACTED] (b) (4)

Short summary of manufacturing activities performed: drug substance manufacturing

Inspected [REDACTED] (b) (4) and classified VAI. The [REDACTED] (b) (4) profile was covered and is considered acceptable.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research

Mary E. Farbman, Ph.D.  
Building 51, Room 4214  
10903 New Hampshire Avenue  
Silver Spring, MD 20993  
Phone 301-796-4171

**Date:** 07 December 2009  
**To:** File STN 125118/107  
**FDA Participants:** Mary E. Farbman  
**BMS Participants:** Kwame Obeng, Ph.D., Director, World Wide Quality and Compliance  
Gary Lazarus, Ph.D., Associate Director, World Wide Quality and Compliance  
**Subject:** Teleconference Memo: Status of (b) (4)

On 02 Dec 2009, I called Dr. Obeng at Bristol-Myers Squibb to inquire about the status of the (b) (4) site in (b) (4). He was unavailable at the time of call but promptly returned the phone call; due to scheduling conflicts on FDA's side, the conversation could not be scheduled until Monday, 07 Dec 2009.

During the phone call, I stated that Patricia Hughes had been informed by BMS representatives that the (b) (4) site would be phased out for abatacept manufacturing. Because several changes at the (b) (4) site are listed in the PAS under review (STN 125118/107), I wanted to verify the manufacturing status of the site. Drs. Obeng and Lazarus stated that it is correct that the (b) (4) site has been phased out and that the last abatacept batches prepared there were manufactured in ~Sept-Oct 2009. They stated that they plan to formally file for deletion of the site in their February 2010 annual report. The requested changes discussed in the PAS were already made at the (b) (4) site for several batches which have not yet been released.

At the end of the conversation, BMS asked whether I had any information about a teleconference the firm had requested with Jack Ragheb, the CMC reviewer for the PAS. I was unaware of their request and suggested they contact the RPM for the supplement, Melinda Bauerlien.

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125118/S107**

**ADMINISTRATIVE and CORRESPONDENCE  
DOCUMENTS**

**From:** Joao Pedras-Vasconcelos./Ph.D. *Joao A Pedras* 6/9/11  
**To:** BLA: 125118/107 PAS-Approval of new (b)(4) formulation- complete response to FDA comments  
**Through:** Susan Kirshner, Ph.D. Associate Director of LIM *Danielo Carlucci for Susan Kirshner*  
**Product:** Abetacept *Barry Cherny*  
**Sponsor:** BMS-Syracuse *6-9-11*  
**Indication:** treatment of rheumatoid arthritis resistant to disease modifying anti-rheumatic drugs

**DATES FOR REVIEW PROCESS:**

Received: Feb 11, 2011  
First draft: April 29, 2011  
Revised: June 6, 2011  
Final draft: June 8, 2011  
Decision: June 11, 2011

**Recommendation-**

**BMS provided a complete response to the Agency's questions concerning differences in several critical quality attributes noted between drug substance batches produced using approved (b)(4) formulation, and batches produced using proposed (b)(4) formulation. These differences were found in (b)(4)**

**Sponsor provided evidence that detected differences fell within historical variability of drug substance critical quality attributes. The Sponsor also provided data from approximately (b)(4) new lots that were manufactured since the original submission of this supplement. Only (b)(4) manufacturing and clinical experience but do not exceed it. All other critical quality attributes that were questioned trended well within clinical and manufacturing experience. Therefore the Sponsor has adequately demonstrated comparability between drugs manufactured using either (b)(4)**

**The Agency also questioned whether (b)(4) s that were not adequately captured in the approved host cell protein assay. The Sponsor demonstrated that the present assay is adequate to monitor host cell proteins in drug substance manufactured (b)(4) They also demonstrated that the process adequately clears the host cell proteins. Therefore the Sponsor has adequately addressed this concern.**

**We recommend that PAS be approved.**

**Summary**

Abatacept (Orencia™) is a fusion protein comprised of the extracellular domain of Cytotoxic T-Lymphocyte antigen-4 (CTLA4) and part of a human immunoglobulin G constant region (Cr1),

containing the hinge, CH2 and CH3 domains. Abatacept is thought to selectively block full activation (IL-2 production) of T-lymphocytes by binding specifically to B7-1 and B7-2 on the APC, and inhibiting the co-stimulatory pathway. Abatacept has an apparent molecular mass of 90,619 Da with two homologous glycosylated polypeptide chains of 357 amino acids each linked by an inter-chain disulfide bond. Abatacept is currently approved for use in rheumatoid arthritis patients who have had an inadequate response to one or more disease modifying anti-rheumatic drugs such as TNF inhibitors. On 26 October 2009, BMS submitted the PAS (STN #125118/107) to propose the use of a new formulation of the abatacept chemically defined (CD)

(b) (4) )  
(  
This PAS was not approvable, and generated complete response comments from the Agency. In addition, BMS submitted three amendments, dated 22 January 2010, 25 March 2010 and 21 April 2010 respectively, which also resulted in comments from the Agency. Subsequently, BMS had two meetings with FDA, a Type A meeting on 12 July 2010 and a Type C meeting on 28 October 2010 in order to clarify Agency concerns. In this PAS resubmission, BMS provides the following information:

- 1) Responses to all FDA questions from the CR letter and subsequent meetings with the Agency
- 2) Modified acceptable range limits for (b) (4)
- 3) An end-of-production cell bank prepared from cells grown with CD- (b) (4) (b) (4)

Below are responses to all FDA questions followed by reviewer analysis:

**CR letter comments 4/23/2010**

37 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

INTEROFFICE MEMO

TO: BLA 125118\107 Supplement  
Abatacept (Orencia)

FROM: Molly E. Topper, Ph.D.  
Pharmacology/Toxicology Supervisor  
Division of Pulmonary, Allergy and Rheumatology Products

DATE: May 26, 2011

Bristol-Myers Squibb, Co. submitted a supplement to their Biological License Application (BLA) 125118\107 on February 22, 2011 for Orencia (abatacept) for a change in the manufacture of abatacept that includes the [REDACTED] (b) (4). There are no proposed changes to the approved indication for the supplement. The approved indication is for the reduction of signs and symptoms, inducing major clinical response, inhibiting the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis

In support of the safety of the proposed manufacturing change, the applicant submitted one nonclinical pharmacokinetic (PK) study in Cynomolgus monkeys to compare abatacept prepared from [REDACTED] (b) (4). The primary pharmacology/toxicology reviewer, Lawrence Leshin, DVM, PhD, completed a review of this study and concluded that there were no significant changes in PK parameters in monkeys between the two manufactured products. No changes to the nonclinical sections of the label are recommended. I concur with Dr. Leshin's conclusions. From the nonclinical perspective, an approval of this BLA supplement (107) is recommended.

  
Molly E. Topper, Ph.D.  
Pharmacology/Toxicology Supervisor

5/26/2011



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** November 26, 2010

<b>To:</b> Anand S. Achanta, Ph.D.	<b>From:</b> Colette Jackson
<b>Company:</b> Bristol-Myers Squibb	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b>	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 609-252-6595	<b>Phone number:</b> 301-796-1230

**Subject:** BLA 125118 s107 October 28, 2010, Meeting Minutes

**Total no. of pages including cover:**

**Comments:**

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**Document to be mailed:**                      YES                      xNO

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NOV 26 2010

FOOD AND DRUG ADMINISTRATION  
CENTER FOR DRUG EVALUATION AND RESEARCH

**Meeting Type:** Type C  
**Meeting Category:** Advice  
**Meeting Date and Time:** October 28, 2010, 2:00 PM – 3:00 PM  
**Meeting Location:** via teleconference  
**Application Number:** BLA 125118/s 107  
**Product Name:** Orenicia (abatacept)  
**Received Briefing Package:** September 23, 2010  
**Sponsor Name:** Bristol-Myers Squibb  
**Meeting Requestor:** Anand S. Achanta, Ph.D.  
Director, Global Regulatory Sciences  
**Meeting Chair:** Chandrahas G. Sahajwalla, Ph.D.  
Director, Office of Clinical Pharmacology II  
**Meeting Recorder:** Colette Jackson  
Senior Regulatory Health Project Manager  
**Meeting Attendees:**

**FDA Attendees:**

Office of Drug Evaluation II, Division of Pulmonary and Allergy Products

Sarah Okada, M.D., Clinical Team Leader

Keith Hull, M.D., Clinical Reviewer

Colette Jackson, Senior Regulatory Health Project Manager

Office of Clinical Pharmacology, Division of Clinical Pharmacology 2

Chandrahas G. Sahajwalla., Ph.D., Director

Yun Xu, Ph.D., Acting Clinical Pharmacology Team Leader

Atul Bhattaram, Clinical Pharmacology Reviewer

Office of Biotechnology Products, Division of Therapeutic Proteins

Jack Ragheb, M.D., Ph.D., Product Quality Reviewer

Susan Kirshner, Ph.D., Product Quality Team Leader

**Bristol-Myers Squibb Attendees:**

Anand Achanta, Ph.D., Director, Regulatory, Immunology/Neuroscience

Michael Corbo, RPh, Ph.D., Vice Presiden, Development Leader

Xin Du, Ph.D., Director, Regulatory & Compliance, CMC Biologics

Sanjeev Kaul, Ph.D., Group Director, Clinical Pharmacology

Bindu Murthy, Pharm.D., Associate Director, Clinical Pharmacology,  
Oncology/Immunology

Mark Rosolowsky, Ph.D., Executive Director, Global Regulatory Sciences, CMC

David E. Smolin, Ph.D., Vice-President, Biologics Process and Product  
Development, Technical Operations

Anthony Waclawski, Ph.D., Vice Presiden, Regulatory,  
Immunology/Neuroscience

**1.0 BACKGROUND**

Bristol-Myers Squibb (BMS) sent in a meeting request dated August 5, 2010, to obtain clarification of the Agency's proposal for conducting a comparative, single-dose human PK study to support approval of the CD- (b) (4) prior approval supplement in addition to the in vitro, nonclinical and clinical data that are presented in the assessment of comparability of the CD- (b) (4) change. The briefing package was received on September 23, 2010. Upon review of the briefing package, the FDA responded to BMS's questions via fax on October 27, 2010. The content of that fax is printed below. Any discussion that took place at the meeting is captured directly under the relevant original response in Section 2.0, including any changes in our original position. BMS's question is in *bold italics*; FDA's response is in *italics*; discussion is in normal font.

**2.0 DISCUSSION**

***Question 1: Demonstration of Comparability***

***As discussed and agreed to at the Type A meeting held on 12-Jul-2010, BMS concluded that comparability has been demonstrated through the use of analytical methods and a well-established non-human primate PK model. However, to further support this position human PK data have been obtained from abatacept batches derived from a CD- (b) (4); these batches were released and utilized in ongoing clinical trials. The results of analytical testing of the batches show that they are comparable to abatacept produced from the approved CD- (b) (4) In addition, the unintended CD- (b) (4) similar***

to the levels in the proposed CD- (b) (4) and is thus representative of the proposed (b) (4). These data are intended to provide supportive documentation for the BMS position that comparability with respect to PK has been established through the non-human primate model.

*BMS concludes that these findings support the position that the process change produces comparable product and that no new human PK study is needed to support the approval of the CD- (b) (4) PAS. Does the Agency agree?*

**FDA Response:**

*You provided new human PK study results obtained from abatacept batches derived from a CD- (b) (4) and compared the PK parameters from the "unintended" batch (b) (4) with the already approved product (b) (4). Combined with other studies you have provided, these findings appear adequate to support the complete response of the CD- (b) (4) PAS. However, whether these results support the conclusion that the process change produces a comparable product will be a review issue. We recommend that you submit the full study report in your submission.*

**Discussion:**

BMS stated that they intend to provide the full study report which will contain methodological data sets and conclusions and asked the FDA if this is acceptable. The FDA stated that BMS will need to submit the full study report and data sets for the monkey PK study. BMS stated that they have already submitted the monkey study to the FDA, but they will provide the monkey PK study report and datasets with their resubmission.

The FDA noted that the population PK study will be used to demonstrate human PK comparability. BMS asked which human population PK report the FDA requires. The FDA stated that the briefing package contained human PK data obtained from abatacept batches derived from CD- (b) (4) compared to the PK data of abatacept produced from the approved CD- (b) (4) and the FDA needs to review this data. In addition, the FDA needs BMS to submit the data sets and control streams as well as study outcomes.

The following are the general expectations for submitting pharmacometric data and models:

All datasets used for model development and validation should be submitted as a SAS transport files (\*.xpt). A description of each data item should be provided in a Define.pdf file. Any concentrations and/or subjects that have been **excluded from the analysis** should be flagged and maintained in the datasets.

Model codes or control streams and output listings should be provided for all major model building steps, e.g., base structural model, covariates models, final model, and validation model. These files should be submitted as ASCII text files with \*.txt extension (e.g.: myfile\_ctl.txt, myfile\_out.txt).

A model development decision tree and/or table which gives an overview of modeling steps.

For the population analysis reports we request that you submit, in addition to the standard model diagnostic plots, individual plots for a representative number of subjects. Each individual plot should include observed concentrations, the individual predication line and the population prediction line. In the report, tables should include model parameter names and units. For example, oral clearance should be presented as CL/F (L/h) and not as THETA(1). Also provide in the summary of the report a description of the clinical application of modeling results.

*In addition, provide the following CMC information in your submission.*

1. *In your response to the CR letter provide the following information regarding Table 3.1.4.1 contained in your background document for the Type C meeting dated September 23, 2010.*
  - a. *For the two lots identified in the table, clarify what (b) (4) components were used to determine the (b) (4) concentration.*
  - b. *For DS lot 47819 clarify how the weighted average was determined.*
2. *Identify all the unintended process lots used in NHP and clinical studies being submitted in support of the PAS.*

**Discussion:**

The FDA stated that BMS made over (b) (4) batches with the unintended process lots but only 2 of those were used in the clinical studies and not in non-human primates. BMS explained that 4 lots were used, 2 intentional lots for the non-human primates and 2 unintentional lots.

3. *Provide the end of (b) (4) analysis of the unintended lots used in NHP and clinical studies being submitted in support of the PAS.*

**Discussion:**

BMS stated that they have a list of 9 parameters to be evaluated at the end of fermentation and that they intend to plot the 4 lots (2 lots for the non-human primates and the 2 clinical lots). The FDA stated that we need a better handle on the unintended lots and its data from different studies (monkey, glycoforms, nonclinical and clinical lots) in order to evaluate the product as a whole.

4. Provide the release specifications for (b) (4) in CD- (b) (4) (b) (4)
  
5. To help assess the sensitivity of the monkeys to changes in glycoform distribution, provide a comparative table reporting the DS (b) (4) content of drug product lots used in the monkey PK studies as well as the human PK study.
  
6. As a surrogate of the impact (b) (4) product quality changes, we propose that you trend the (b) (4) (b) (4) vessel alone, as well as that of DS lots produced by the intended manufacturing process. These data should be trended separately. Please indicate the mean titer and 95% CI for the lots. The DS lots used to support PK and clinical studies should be clearly indicated.

**Question 2: Adequacy of Comparability Data**

***Collectively, the data obtained from these in vitro and in vivo (nonclinical) assessments indicate that abatacept derived from CD- (b) (4) (b) (4) is comparable. This is further supported by the additional supportive human PK data presented in Section 3.1.4 of this document. Does the Agency agree?***

**FDA Response:**

*Whether these data support the conclusion that the process change produces a comparable product will be a review issue. See our response to Question 1.*

**Discussion:**

BMS stated that they intend to submit their complete response to our Complete Response letter by the end of January 2011. BMS asked about the duration of the review clock for this resubmission. The FDA stated that the review clock duration will be a standard 4 month clock.

### **3.0 ISSUES REQUIRING FURTHER DISCUSSION**

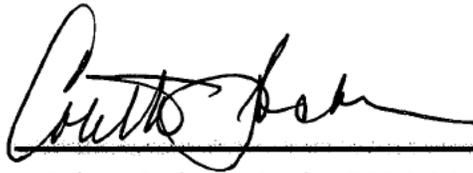
There were no issues requiring further discussion.

### **4.0 ACTION ITEMS**

There were no action items identified during the meeting.

### **5.0 ATTACHMENTS AND HANDOUTS**

There were no attachments or handouts for the meeting.

A handwritten signature in black ink, appearing to read "Colette Jackson", written over a solid horizontal line.

Colette Jackson, Senior RPM, Meeting Recorder

Drafted by: Jackson/ November 16, 2010  
Initialed: Xu/ November 21, 2010  
Sahajwalla/ November 21, 2010  
Bhattaram/ November 21, 2010  
Ragheb/ November 16, 2010  
Kirshner/ November 16, 2010  
  
Finalized: Jackson/ November 26, 2010



Food and Drug Administration  
 Center for Drug Evaluation and Research  
 Office of Drug Evaluation II

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** October 27, 2010

<b>To:</b> Anand S. Achanta, Ph.D.	<b>From:</b> Colette Jackson
<b>Company:</b> Bristol-Myers Squibb	Division of Pulmonary, Allergy, and Rheumatology Products
<b>Fax number:</b>	<b>Fax number:</b> 301-796-9718
<b>Phone number:</b> 609-252-6595	<b>Phone number:</b> 301-796-1230

**Subject:** BLA 125118 Responses to Meeting Questions

**Total no. of pages including cover:**

**Comments:**

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**OCT 27 2010**

Attached are the FDA responses to your questions (in ***bold italics***) regarding Orencia® (abatacept). You have the option of canceling our meeting of October 28, 2010, if these answers are clear to you. If you choose to have the meeting, we will be prepared to clarify any questions you have regarding our responses. However, please note that if there are any major changes to your development plan (based upon our responses herein), we will not be prepared to discuss, nor reach agreement on, such changes at the meeting. Any modifications to the development plan or additional questions, for which you would like FDA feedback, should be submitted as a new meeting request. Please notify the Division as soon as possible if you decide to cancel the meeting.

***Question 1: Demonstration of Comparability***

***As discussed and agreed to at the Type A meeting held on 12-Jul-2010, BMS concluded that comparability has been demonstrated through the use of analytical methods and a well-established non-human primate PK model. However, to further support this position human PK data have been obtained from abatacept batches derived from a CD- (b)(4) these batches were released and utilized in ongoing clinical trials. The results of analytical testing of the batches show that they are comparable to abatacept produced from the approved CD- (b)(4). In addition, the unintended CD- (b)(4) similar to the levels in the proposed CD- (b)(4) and is thus representative of the proposed (b)(4). These data are intended to provide supportive documentation for the BMS position that comparability with respect to PK has been established through the non-human primate model.***

***BMS concludes that these findings support the position that the process change produces comparable product and that no new human PK study is needed to support the approval of the CD- (b)(4) PAS. Does the Agency agree?***

**FDA Response:**

You provided new human PK study results obtained from abatacept batches derived from a CD- (b)(4) and compared the PK parameters from the "unintended" batch (b)(4) with the already approved product (b)(4). Combined with other studies you have provided, these findings appears adequate to support the complete response of the CD- (b)(4) PAS. However, whether these results support the conclusion that the process change produces a comparable product will be a review issue. We recommend that you submit the full study report in your submission.

In addition, provide the following CMC information in your submission.

1. In your response to the CR letter provide the following information regarding Table 3.1.4.1 contained in your background document for the Type C meeting dated September 23, 2010.
  - a. For the two lots identified in the table, clarify what (b)(4) components were used to determine the (b)(4) concentration.
  - b. For DS lot 47819 clarify how the weighted average was determined.
2. Identify all the unintended process lots used in NHP and clinical studies being submitted in support of the PAS.
3. Provide the end of (b)(4) analysis of the unintended lots used in NHP and clinical studies being submitted in support of the PAS.
4. Provide the release specifications for (b)(4)
5. To help assess the sensitivity of the monkeys to changes in glycoform distribution, provide a comparative table reporting the (b)(4) of drug product lots used in the monkey PK studies as well as the human PK study.
6. As a surrogate of the impact of (b)(4) on product quality changes, we propose that you trend the (b)(4)  
(b)(4)  
(b)(4) These data should be trended separately. Please indicate the mean titer and 95% CI for the lots. The DS lots used to support PK and clinical studies should be clearly indicated.

***Question 2: Adequacy of Comparability Data***

***Collectively, the data obtained from these in vitro and in vivo (nonclinical) assessments indicate that abatacept derived from CD-(b)(4) is comparable. This is further supported by the additional supportive human PK data presented in Section 3.1.4 of this document. Does the Agency agree?***

**FDA Response:**

Whether these data support the conclusion that the process change produces a comparable product will be a review issue. See our response to Question 1.

If there are any questions, contact Colette Jackson, Senior Regulatory Health Project Manager, at 301-796-1230.



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Colette Jackson, Senior Regulatory Project Manager

Drafted: CCJ/ October 27, 2010

Initialed by:

Raggio for Barnes/ October 27, 2010

Ragheb/ October 27, 2010

Kirshner/ October 27, 2010

Xu/ October 27, 2010

Finalized: CCJ/ October 27, 2010

Filename: 125118 October 28 2010 Q and A.doc



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125118/107 (CRMTS#7649)

October 5, 2010

Bristol Myers Squibb Company  
Attention: Gary Lazarus, Ph.D.  
Associate Director, World Wide Quality and Compliance  
6000 Thompson Road, Building 22 Mail Stop A-6  
East Syracuse, NY 13057

Dear Dr. Lazarus:

Please refer to your biologics license application (BLA) submitted under the Public Health Service Act for Orencia® (abatacept).

We also refer to the meeting held on July 12, 2010, between representatives of your firm and this Agency. A copy of the official minutes of the meeting is attached for your information.

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 me at (301) 796-0906.

Sincerely,

Melinda Bauerlien, M.S.  
Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Sciences  
Center for Drug Evaluation and Research

Enclosure: Meeting Summary

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:** July 12, 2010  
**From:** Melinda Bauerlien, M.S. Regulatory Project Manager, Office of  
Biotechnology Products  
**To:** STN 125118/107  
**Subject:** Type C, BLA meeting CRMTS# 7649

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**Meeting Date:** July 12, 2010                      **Time:** 9:00 AM – 10:00 AM

**Sponsor:** Bristol Myers Squibb Company

**Products:** Orencia® (abatacept)

**Type of Meeting:** Type A Meeting

**FDA Participants:**

Susan Kirshner, Ph.D., Associate Lab Chief, DTP  
Jack Ragheb, M.D., Product Reviewer, DTP  
Barry Cherney, Ph.D., Deputy Director, DTP  
Melinda Bauerlien, M.S., Regulatory Project Manager, OBP  
Zhihong Li, Ph.D., Reviewer, OTS/OCP  
Yun Xu, Ph.D., Acting Team Leader, OTS/OCP

*Barry Cherney 7-12-10*

**Bristol Myers Squibb Company Participants:**

Xin Du, Ph.D., Director, Regulatory & Compliance, CMC Biologics  
Gary Lazarus, Ph.D., Associate Director, Regulatory & Compliance, CMC  
Mark Rosolowsky, Ph.D., Executive Director, Global Regulatory Sciences –CMC  
David E. Smolin, Ph.D. Vice President, Biologics Process and Product Development  
John Tabor, Ph.D., Vice President, External Manufacturing, Biologics  
Michael Corbo, R Ph, Ph.D., Vice President, Development Lead, Orencia  
Mark Brancieri, Senior Engineer, Biologics, Third Party Manufacturing  
Stephen Hosselet, Ph.D., Director, Biologics Analytical Development and Testing  
Bernhard Schilling, Ph.D., Group Leader, Manufacturing Sciences

**Meeting Purpose:** To discuss the issues listed in the Complete Response letter issued for STN 125118/107.

**Introductory Comment:** Attached are the official minutes from the Agency of the discussion that occurred during the July 12, 2010 meeting.

The sponsor provided a powerpoint presentation which is included in the official meeting minutes.

**Question 1:**

BMS will re-submit the CD- (b) (4) PAS with BMS' response to the Agency's comments in the CR letter, with the addition of new data from a non-human primate PK study. Although BMS believes the DS produced (b) (4) pre-and post (b) (4) change are analytically comparable, BMS acknowledges that there are some minor CMC/quality differences observed between the pre-and post (b) (4) change DS produced (b) (4). Results from the non-human primate PK study further support the comparability of DS manufactured with (b) (4). Does the Agency agree that the information presented below is sufficient for the assessment of the CD (b) (4) PAS?

**Agency's Response:**

No, we do not agree. Considering this is a post-approval manufacturing change, we recommend that you conduct a PK comparability study in human.

**Question 2:**

If the above information presented would not be considered sufficient for the assessment of the CD- (b) (4) PAS, would the Agency have the expectation for an additional non human primate PK study or a human PK study for the approval of the CD (b) (4) PAS?

**Agency's Response:**

See response to Question 1.

**Meeting Discussion:**

**The sponsor presented their monkey and human PK models for Orencea, and explained that the model sensitivity can distinguish between abatacept products that exhibit subtle differences in glycosylation resulting from process changes. They asked for clarification as to why the Agency recommends a PK comparability study in humans, and what additional information the Agency could expect from human PK study.**

**The Agency responded that this is a post-approval manufacturing change, and the change may alter PK profiles. Therefore, a human PK study is needed.**

**Dr. Corbo stated that many batches made (b) (4) were released for commercial and clinical use, and no adverse events were reported.**

The Agency asked for the comparison of the (b) (4) concentration between the “unintended” and the proposed (b) (4)

The sponsor explained that the (b) (4) concentrations between the two (b) (4) are similar, and the (b) (4) concentrations of the proposed (b) (4) were determined by mimicking the (b) (4) concentrations observed in (b) (4) tank (unintended), and detailed comparison could be provided later. During investigation of the (b) (4) situation, (b) (4) were analyzed; (b) (4) of them had concentration (b) (4). Thus, the proposed (b) (4) have (b) (4) concentrations for these (b) (4)

The Agency asked how many lots were made with the (b) (4) tank (b) (4)

The sponsor responded that more than (b) (4) lots were made.

The Agency asked about the productivity of the cells (b) (4) in the proposed (b) (4) and whether the cells experience the same stress as with the currently approved (b) (4)

The sponsor explained that the final production titer of the proposed (b) (4) that of the currently approved (b) (4).

The Agency asked when the sponsor stopped using the (b) (4) produced in the (b) (4) tank (b) (4)

The sponsor stated that the investigation of the (b) (4) was initiated in middle 2006. They stopped the (b) (4) produced in the (b) (4) tank (b) (4) around April/May 2008, when they started the production using the proposed CD- (b) (4). The sponsor stated that they had clinical data for DS manufactured with (b) (4) from (b) (4) tank, which is representative of DS manufactured with the proposed (b) (4)

The Agency responded that it is hard to demonstrate safety and efficacy from the (b) (4) tank (unintended (b) (4) batch. If BMS has relevant data, the Agency would review it. However, the Agency stated that they are skeptical that even if the sponsor could prove that there are no safety concerns, the data would not be sufficient to demonstrate comparable efficacy.

The sponsor asked if there were any differences in CQAs which the Agency reviewers were concerned about that could impact the PK.

The Agency responded that carbohydrate content and glycoform distribution are known to be major contributors to the half life of glycosylated proteins. Therefore the Agency looks closely for changes in glycoform distribution. Data provided in the BLA indicate that glycoform changes do impact abatacept PK.

**Adendum to the meeting minutes:** Based on data provided to the BLA Agency is unaware of any other major contributors to abatacept PK. However if BMS is aware of any they should ensure comparability of that quality attribute and discuss it in their CR response.

The sponsor asked what specific aspects of the clinical study the agency would like to see. Since drug product made from (b) (4) has been both distributed commercially and used in other clinical studies, and the sponsor has established concordance of the monkey and human PK models for Orencia, they asked why the Agency still needs a new clinical human PK study.

The Agency replied that this is the first time that BMS has purposefully and consistently changed the (b) (4) content of the (b) (4) *In vitro* comparability data show this change may affect PK profile of the product due to glycosylation changes. A human PK comparability study will be the only *in vivo* study to bridge the proposed product with CMC change to the already marketed product. The proposed CMC change (b) (4) is a new change for which both the sponsor and the Agency do not have a lot of previous experience. Therefore, the Agency does not think there is enough evidence and previous experience to support using the monkey PK study to replace the human PK study.

The sponsor stated that BMS had demonstrated that their model is sensitive to the CQAs that have the potential to impact clinical performance and that this was more important than how these CQAs are altered by a given process change, such as t (b) (4) (b) (4). The sponsor suggested submitting the available clinical data using DS produced with (unintended) (b) (4) tank to the agency.

The Agency responded that they would review the data, however, if the data is not adequate, the Agency could still require a new human PK study.

The sponsor asked if the Agency could provide feedback within 30 days after receipt of the data from the sponsor.

The Agency stated that this may not be possible based on data complexity, but agreed to provide feedback as soon as possible.

**Question 3:**

In the CR letter, under comments 3a and 3b of “Comparability of DS”, the Agency requested that BMS continue to trend the following CQAs: % HMW, % Monomer, and % deamidation. Based on BMS’ manufacturing schedule, there will not be any abatacept manufacturing using CD- (b) (4) site until 2011. BMS will commit to continue trending these CQAs once the manufacturing data is available. Does the Agency agree?

**Agency Response:**

The Agency acknowledges your intention to continue trending these CQAs but suggest that criteria for identification of out of trend events that would initiate an investigation should be

included in your resubmission. The results of these evaluations should also be incorporated into your periodic evaluation of the quality standards of the drug product under 211.180(d).

**Meeting Discussion:**

**The sponsor accepts the Agency's comments. They suggested that criteria for identification of out of trend events that would initiate an investigation should be included in the sponsor's resubmission. The results of these evaluations should also be incorporated into the sponsor's periodic evaluation of the quality standards of the drug product under 211.180(d).**

**Question 4:**

Comments 2, 3, 4, 5, 6a and 6b of "Process-related impurities" in the CR letter have been addressed in BMS' March 24, 2010 amendment to the CD- (b) (4) PAS. BMS will state that these comments were addressed in BMS' March 24, 2010 amendment and will provide the relevant information in the new submission. BMS will provide no new information in the resubmission of this PAS. Does the Agency agree?

**Agency Response:**

The contents of the March 24, 2010 amendment pertaining to process-related impurities are a review matter, but if BMS believes that amendment fully addresses Comments 2, 3, 4, 5, 6a and 6b of "Process-related impurities" in the CR letter, no additional information on this topic needs to be included in the resubmission in order to initiate an FDA review.

**Meeting Discussion:**

**The sponsor summarized the contents of the March 24, 2010 PAS amendment related to " (b) (4) ."**

**The Agency responded that there could be some differences in (b) (4) impurities at harvest between DS produced with the currently approved (b) (4) and that produced with the proposed CD- (b) (4) provided the final product (b) (4) profiles were the same. The Agency stated that they had performed a high level review of the amendment and that the amendment included the studies that were requested.**

**The sponsor asked the Agency for clarification for the definition of "no difference" in (b) (4) profile as stated in the April 23, 2010 Complete Response letter for the CD- (b) (4) PAS.**

**The Agency responded that "no difference" means that the (b) (4) profile from the proposed (b) (4) is representative of that of the current approved (b) (4) and if there are differences, the differences should not be related to the increases of the (b) (4). The Agency asked whether batches manufactured with (b) (4) tank ("unintended" (b) (4) were used as the pre-change comparators, (in the monkey PK study, for example).**

**The sponsor confirmed that the batches from the “unintended” process were not used as comparators. The monkey PK study was performed using the pre (b) (4) and post (b) (4) change batches.**

**The Agency stated that while it would be expected to see some difference in the (b) (4) profile at harvest in the drug substance, it was important to demonstrate that the process could remove (b) (4) such that drug product made from either (b) (4) formulation would have the same (b) (4) profiles.**

**Question 5:**

In the CR letter, under comment 2 of “Additional comments”, the Agency requested BMS to perform compatibility studies to demonstrate that the (b) (4) have not had an impact on leachables, extractables, or column life span. BMS has performed comprehensive extractables studies on all (b) (4) used in the abatacept process, including toxicology and safety assessments and does not believe the relatively (b) (4) (b) (4) adds sufficient risk to warrant repeating these studies. BMS has also demonstrated the clearance of (b) (4), further reducing any risk of additional extractables. BMS will also provide data from column lifetime studies performed at scale (b) (4) using abatacept process streams which (b) (4) (b) (4) vessel to demonstrate that column lifetime is not impacted by abatacept generated using (b) (4) (b) (4). Does the Agency agree?

**Agency Response:**

The Agency concurs that the relatively (b) (4) concentrations in the (b) (4) does not add sufficient risk to warrant repeating the leachate studies. However, with regard to column life span, (b) (4) may interact with column resins and alter the column life span. We believe information indicating that the (b) (4) do not interact with the relevant (b) (4) and are therefore unlikely to alter column performance maybe used to address this issue. While data generated from the unintended process might be used to support the proposed process, as the (b) (4) content in the unintended process does not exactly match that found in the intended process, we would expect a careful assessment of the variation in (b) (4) content and resulting alteration, if any, in column performance.

**Meeting Discussion:**

**The sponsor accepted the Agency’s comments and there was no further discussion at the meeting.**

**Question 6:**

In the CR letter, under comment 3 of “Additional comments”, the Agency requested that BMS perform a side-by-side comparison of DS produced in (b) (4) under accelerated stability conditions to assure that they have comparable degradation profiles. BMS will leverage existing stability data with DS manufactured with the currently approved media to perform a side-by-side data comparison rather than a new accelerated stability study. Does the Agency agree?

**Agency Response:**

If the comparator for the pre-change product is from the intended process, comparative historical accelerated stability data could be used to assess product comparability but may result in differences due to test performance rather than differences in product characteristics, complicating interpretation of the results. Thus, the Agency strongly encourages the use of side-by-side analysis as the most rigorous assessment of comparability. While meaningful information can be gained by comparing to historical results, particularly with regards to trending, should you choose to use such data, please include all relevant historical data rather than a single batch of the pre-changed DS. Also note that to be a sensitive measure of product comparability, incremental degradation should be observed.

**Meeting Discussion:**

**The sponsor acknowledged the Agency's comments that if the sponsor chose to use historical accelerated stability data, they should include all relevant historical data rather than a single batch of the DS pre-change.**

**The sponsor presented the side-by-side comparison of degradation profile from accelerated stability data of the pre- and post-change DS. The data showed that the (b) (4) results were highly comparable between the pre- and post change DS.**

**The Agency stated they would review the stability data presented by the sponsor and would state their conclusions in an addendum to the meeting minutes regarding this topic.**

**Addendum to the meeting minutes:**

**The Agency concurs that the results presented in the table look comparable. However the data not comprehensive as they are limited to two lots of CD (b) (4) added and one lot of the current (b) (4). Data from additional historical lots are needed to demonstrate that results are within trend. Further, the Agency would want to see representative chromatograms from lot produced with the currently approved (b) (4) and the proposed (b) (4) to support the comparability claim.**

**Question 7:**

To address the issue of unintended (b) (4) into the culture (b) (4), BMS discontinued the use of CD- (b) (4) produced in the (b) (4)

[REDACTED]

Does the Agency agree?

**Agency Response:**

While data generated from the unintended and uncontrolled ( (b) (4) content) process could be used to support the proposed manufacturing change, this information does not provide a rigorous assessment of process consistency and product comparability. BMS has not provided a detailed explanation of how it arrived at the (b) (4) concentrations used in (b) (4)

Since the product approved for marketing authorization was made using the CD- (b) (4) (b) (4) his product should be directly compared to the product produced from the proposed process using CD- (b) (4).

If BMS chooses to include data from DS manufactured using (b) (4) vessel, please segregate this information from data comparing the proposed process to product produced from the approved process by displaying it in separate and clearly marked plots & tables.

**Meeting Discussion:**

**The sponsor confirmed that DS release data from (b) (4)**

**Question 8:**

BMS will provide responses to the Agency's comments in the CR letter. BMS believes the responses outlined in the meeting background package fully address the Agency's comments. Does the Agency agree?

**Agency Response:**

We can not address this question. Our conclusions regarding the adequacy of your responses can only be made once a comprehensive review of the resubmission has been performed. However, we would recommend that in your response to Comment 1.b. (b) (4)

**Meeting Discussion:**

**The sponsor accepts the Agency's comments.**

**Question 9:**

In anticipation of the approval of the CD- (b) (4) PAS, BMS transferred and developed the abatacept manufacturing process at (b) (4) using CD- (b) (4) (b) (4). BMS' current strategy is to proceed with process validation using the (b) (4)

(b) (4) The PAS to qualify the (b) (4) facility will be filed once the process validation has been completed.

Does the Agency agree?

**Meeting Discussion:**

The Agency stated they agree with the sponsor's proposal to use DS manufactured with CD- (b) (4)

The Agency stated that once the CD (b) (4) PAS is approved, the filing of (b) (4) is only a site change. The site change will include the required adaptation of equipment and processes that were presented to agency at the Type C meeting with FDA on 13 April 2010 for BMS' (b) (4) site filing). The Agency stated that if the analytical data were within the approved limits, as deemed by the FDA CMC reviewers, then PK studies would not be necessary. However, if a PK study was necessary, it should be a human PK study.

The sponsor asked if they could use the data from the (b) (4) tank (unintended (b) (4) batch, which were previously released for commercial and clinical use, to support the CD (b) (4) PAS approval. The Agency stated that the sponsor may use the data and possibly waive the PK study if the sponsor could demonstrate: 1) (b) (4) were comparable between the previous "unintended" batch and the new proposed change 2) the sponsor can provide adequate clinical data in the "unintended" batch. However, whether these data are adequate will be a review issue and will need inputs from clinical team. The Agency highly doubted about adequacy of the data because of the limited experience with the data from the (b) (4) tank. The sponsor also mentioned that they may have data with trough concentrations in the previous "unintended" batch and proposed to use a PK/PD modeling approach as a supportive evidence. The Agency stated the sponsor may submit the existing data for review, but the Agency reiterated our doubts on adequacy of the data and reserved the right to request a human PK after review of the existing data.

The Agency asked about the timing of the re-submission of the CD (b) (4) PAS.

The sponsor responded that if the Agency agreed that a new human study was not required they could resubmit the PAS shortly thereafter.



Food and Drug Administration  
Center for Drug Evaluation and Research  
Office of Biotechnology Products

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**FACSIMILE TRANSMITTAL SHEET**

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**DATE:** February 23, 2010

<b>To:</b> Gary Lazarus	<b>From:</b> Melinda Bauerlien Project Manager
<b>Company:</b> Bristol-Myers Squibb	Office of Biotechnology Products
<b>Fax number:</b> 315-432-2619	<b>Fax number:</b> (301) 796-0906
<b>Phone number:</b> 315-431-9375	<b>Phone number:</b> (301) 796-1672
<b>Subject:</b> BL 125118/107	

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**Total no. of pages including cover:** 4

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**Comments:** Following is an information request for the above supplement.

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**Document to be mailed:**                      YES                       NO

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**THIS DOCUMENT IS INTENDED ONLY FOR THE USE OF THE PARTY TO WHOM IT IS ADDRESSED AND MAY CONTAIN INFORMATION THAT IS PRIVILEGED, CONFIDENTIAL, AND PROTECTED FROM DISCLOSURE UNDER APPLICABLE LAW.**

**If you are not the addressee, or a person authorized to deliver this document to the addressee, you are hereby notified that any review, disclosure, dissemination, copying, or other action based on the content of this communication is not authorized. If you have received this document in error, please notify us immediately by telephone at (301) 796-0906. Thank you.**

Please respond fully to the questions and comments below.

1. Given your reasoning for the (b) (4), it is unclear to us under what circumstances you would elect not to use (b) (4) and how you would track DS/DP lots produced by the (b) (4) manufacturing processes. Please provide your rationale for the option of using either (b) (4) in manufacturing and your approach to tracking events associated with the different production processes.
2. BMS has stated in teleconference minutes and supplements that differences in the pattern (b) (4) between the reference material and the test materials are due to method variability, mainly the subjectivity involved in calling the number of bands and possibly variability in the (b) (4) themselves. However, we note that a consistent difference in the pattern of (b) (4) exists between the reference material and the test materials in repeated analyses, with the reference material containing fewer bands as well as differences in the intensities of the bands that are present. We also note that the (b) (4) content of the post change product as shown in Table 3.2.S.2.5.12.3.T01. Because no side-by-side comparisons were performed on the IEF gels, the Agency cannot determine whether the test material differs from drug substance produced using the currently approved (b) (4) or if the reference material is simply not suitable for its intended use. Please provide side by side analysis of the (b) (4) profile from 3 lots of the pre- and post-change product. Please note that differences in the (b) (4) profile between the pre and post change product should be evaluated using your existing knowledge to ensure with a high degree of confidence that these differences will not have an adverse impact upon safety or efficacy. Please include a summary of that evaluation in your response. If your existing knowledge is insufficient, you may need to assess *in vivo* bioavailability of the pre- and post-change product to establish comparability.
3. Regarding your comparability study we have the following additional comments:
  - a. In your assessment of product comparability, you provided side-by-side comparisons of reference material with each of the 3 PV DS lots produced with (b) (4). However, as recommended in FDA's "Guidance concerning demonstration of comparability of Human Biological Products, Including Therapeutic Biotechnology- derived products" (April 1996), "manufacturers should provide to FDA extensive chemical, physical and bioactivity comparisons with side-by-side analyses of the "old" product and qualification lots of the "new" product. Please provide side-by-side analysis for all analytical techniques that benefit from this approach. Since the intended process (the process used to produce the clinical trial material) was performed (b) (4) may confound a comparison, particularly because the amount and type of leachables were not consistent from batch to batch.

- b. Beyond the potential quantitative changes in product attributes explored in PAS (b) (4) your extended characterization of DS should be sufficiently complete to exclude any potential qualitative changes in product attributes due to the use of (b) (4) Extended characterization of DS should included, but is not limited to:
- i. MS spectrum and MS/MS spectrum for both N-linked and O-linked oligosaccharide composition and structure including glycation locations and relative amounts
  - ii. Evaluation of (b) (4)
  - iii. Evaluation of Cell Dependent Cytotoxicity
  - iv. Evaluation of Antibody Dependent Cell Cytotoxicity
  - v. Binding to (b) (4)
- c. Based on the data submitted in your supplement, multiple attributes of the drug substance produced from (b) (4) appears to be out of historical trends including:

■ (b) (4)

■ (b) (4)

■ (b) (4)

If these trends are confirmed by a more rigorous assessment of comparability as recommended above and in FDA guidance, then you will need to provide a justification as to why these differences do not impact the safety or efficacy of the product.

4. (b) (4)

6. We are unable to locate within the eCTD, Section 3.2.S.2.5.3.10, entitled (b) (4)
- a. Please provide the results of the process-related impurities, abatacept (b) (4) profiles in the manufacturing lots from the original process validation studies.
  - b. Please provide the (b) (4) images from the original process validation studies.
  - c. Please provide all carbohydrate ( (b) (4)

- d. If there are retains of the original process validation lots, please perform a side-by-side comparison with (b) (4) materials and DS produced at about the same time as the current PV lots using the currently approved media (e.g. Runs #105-107).
7. We have several additional points that require some clarification:
- a. Please clarify the meaning of Cycle # in the (b) (4) Tables (e.g. 3.2.S.2.5.13.2T01). Does this indicate that the entire DS batch is run through the same (b) (4) times to achieve the (b) (4)? If so, does this represent a change from the original process?
  - b. The acceptable (b) (4) flow rate shown in Table 3.2.S.2.5.12.4.T01 does not reflect the approved CBE-30 125118/71. Please explain.



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service  
Food and Drug Administration  
Rockville, MD 20857

Our STN: BL 125118/107

February 16, 2010

Bristol-Myers Squibb Company  
Attention: Anand Achanta, Ph.D.  
Associate Director  
Global Regulatory Sciences  
P.O. Box 5400  
Princeton, NJ 08543

Dear Dr. Achanta:

Please refer to your supplement to your biologics license application submitted under section 351 of the Public Health Service Act for Orenicia® (abatacept).

We received your January 22, 2010 amendment to this supplement on January 25, 2010, and consider it to be a major amendment. Because the receipt date is within two months of the user fee goal date, we are extending the goal date by two months to April 25, 2010, to provide time for a full review of the amendment.

Please refer to <http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133463.htm> for information regarding therapeutic biological products, including the addresses for submissions.

If you have any questions, please contact the Regulatory Project Manager, Melinda Bauerlien, at (301) 796-0906.

Sincerely,

A handwritten signature in cursive script that reads "Amy Rosenberg".

Amy Rosenberg, M.D.  
Director  
Division of Therapeutic Proteins  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research



**PRIOR APPROVAL SUPPLEMENT  
ACKNOWLEDGEMENT**

Our STN: BL 125118/107

November 3, 2009

Bristol-Myers Squibb Company  
Attention: Anand Achanta, Ph.D.  
Associate Director  
Global Regulatory Sciences  
P.O. Box 5400  
Princeton, NJ 08543

Dear Dr. Achanta:

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

<b>STN:</b>	abatacept
<b>BL [125118/1078]</b>	Orencia®
<b>Reason for the submission:</b>	to allow for the modified CD- <span style="background-color: gray; color: gray;">[REDACTED]</span> <sup>(b)(4)</sup> formulation in addition to the current formulation.
<b>Date of Supplement:</b>	October 26, 2009
<b>Date of Receipt:</b>	October 26, 2009
<b>Action Due Date:</b>	February 25, 2010
<b>US License Number:</b>	1713

Unless we notify you within 60 days of the receipt date that the supplement is not sufficiently complete to permit substantive review, this supplement will be considered filed.

All future correspondence or supportive data relating to this supplemental application should bear the above STN. Please refer to <http://www.fda.gov/AboutFDA/CentersOffices/CBER/ucm133463.htm> for information regarding therapeutic biological products, including the addresses for submissions.

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

If you have any questions, please contact me at (301) 796-0906.

Sincerely,



[Melinda Bauerli, M.S.]  
Regulatory Project Manager  
Office of Biotechnology Products  
Office of Pharmaceutical Science  
Center for Drug Evaluation and Research

## **Bauerlien, Melinda**

---

**From:** Hughes, Patricia  
**Sent:** Wednesday, October 28, 2009 5:09 PM  
**To:** Bauerlien, Melinda; Cherney, Barry  
**Cc:** Ragheb, Jack A; Kirshner, Susan L; Farbman, Mary; Dillon, Laura  
**Subject:** RE: STN 125118/107 RAR PAS

Please assign to Mary Farbman.

Thank you.

Patricia

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

**From:** Bauerlien, Melinda  
**Sent:** Wednesday, October 28, 2009 1:57 PM  
**To:** Hughes, Patricia; Cherney, Barry  
**Cc:** Bauerlien, Melinda; Ragheb, Jack A; Kirshner, Susan L  
**Subject:** STN 125118/107 RAR PAS  
**Importance:** High

OBP has received the following submission from Bristol Myers Squibb:

**Manufacturer:** Bristol Myers Squibb  
**Date of Submission:** October 26, 2009  
**CBER Receipt date:** October 26, 2009  
**DCC Login ID:** 60010270  
**Product:** Orencia (abatacept)  
**STN:** 125118\107\0  
**Action Due Date:** February 25, 2010

**Description:** to allow for the modified CD- (b)(4) formulation in addition to the current formulation

Barry,  
Jack has been assigned as the DTP reviewer. Please let me know if this is not a PAS.

Patricia,  
Please assign a BMT reviewer if needed.

Please use the link below to access the submission.

Thank you,

Melinda Bauerlien

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

**From:** CBER Secure  
**Sent:** Wednesday, October 28, 2009 10:57 AM  
**To:** ddrtpb@cderr.fda.gov; CDER DMPQ BMT PM; CDER-OBP-PM; Sullivan, Matthew  
**Cc:** Almoza, Damus \*; OIT-CBER EDR; Fauntleroy, Michael; CBER DCC EDR  
**Subject:** (Gateway Submitted)DATS Log Number 60010270 loaded by DCC - DO NOT REPLY

This BLA Supplement DATS Log Number 60010270 is now available in the EDR.

This is an eCTD submission. Select the link to access the .enx file:  
<\\cbsap58\M\eCTD\_Submissions\STN125118\125118.enx>

DESCRIPTION:

Applicant: BRISTOL-MYERS SQUIBB/1713

Product: ABATACEPT

Indication: Treatment of rheumatoid arthritis: reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderately to severely active rheumatoid arthritis who have had an inadequate response to one or more Disease Modifying Anti-Rheumatoid Drugs (DMARDs), such as methotrexate or TNF antagonists; Abatacept may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists

Proprietary Name: ORENCIA

APPLICATION INFORMATION:

Application Number: 125118\107\0

eCTD Sequence Number: 0094

CBER Receipt Date: 26-Oct-2009

If you need additional assistance with this submission, please contact ERIC Help Desk at 301-827-ERIC (3742).

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