

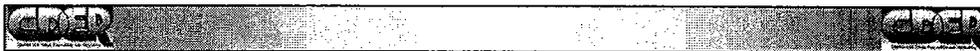
CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

BLA 125118/000

Chemistry Review(s)



Review Cover Sheet

BLA STN 125118/0

Orencia™ (Abatacept)

Bristol Myers Squibb

Division of Therapeutic Proteins

Joy Williams, Ph.D. HFD-122

Susan Kirshner, Ph.D. HFD-122

Elizabeth Shores, Ph.D. HFD-122

Ennan Guan, Ph.D. HFD-122

Edward Max, MD, Ph.D. HFD-122

Division of Monoclonal Antibodies

Barbara Rellehan, PhD HFD-123

Steven Kozlowski, MD HFD-123



CMC Review Data Sheet

1. **BLA#** STN 125118/0
2. **REVIEW #:** 1
3. **REVIEW DATE:** 23-NOV-2005
4. **REVIEWERS:** Joy Williams, Ph.D.
Susan Kirshner, Ph.D.
Elizabeth Shores, Ph.D.
Ennan Guan, Ph.D.
Edward Max, MD, Ph.D.
Barbara Rellehan PhD

5. **COMMUNICATIONS AND PREVIOUS DOCUMENTS¹:**
See Appendix 1 for transcripts of all communications

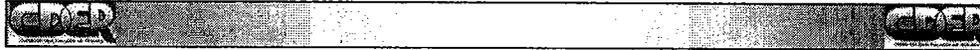
<u>Previous Documents</u>	<u>Document Date²</u>
Pre-BLA Meeting	November 2, 2004
Follow Up	March 18, 2005
Sponsor information request (IR)	July 6, 2005
Agency response to Sponsor IR	July 14, 2005
Agency IR	August 8, 2005
Agency IR	August 10, 2005
Agency IR	August 31, 2005
Agency IR	September 22, 2005
Agency IR	October 14, 2005
Agency IR	November 7, 2005
Agency IR	December 2, 2005
Discussion of PMCs	December 7, 2005
Discussion of PMCs	December 16, 2005

¹Chronology of previous CMC communications between CDER and the firm and/or reviews

²Applicant's letter date or date of review and/or communication with applicant

6. **SUBMISSION(S) BEING REVIEWED:**

<u>Submission(s) Reviewed</u>	<u>Document Date by Desk Copy</u>	<u>Document Date to EDR</u>
STN 124118/0 Original Submission CMA Program CMC Module		March 31, 2005



STN 125118/0/11 Response 74 day letter		August 9, 2005
STN 125118/0/09 IR		June 16, 2005
STN 125118/0/13 IR	August 25, 2005	September 14, 2005
STN 125118/0/13 IR	September 2, 2005	September 14, 2005
STN 125118/0/14 IR	September 12, 2005	September 29, 2005
STN 125118/0/14 IR	September 20, 2005	September 29, 2005
STN 125118/0/18 IR	October 17, 2005	December 6, 2006
STN 125118/0/18 IR	November 7, 2005	December 6, 2005
STN 125118/0/18 IR	November 17, 2005	December 6, 2005
STN 125118/0/18 IR	November 18, 2005	December 6, 2005
STN 125118/0/ IR	December 9, 2005	

7. **NAME & ADDRESS OF APPLICANT:**

Name: Bristol Myers Squibb.
Address: PO Box 4000
Princeton, NJ 08543
Representative: Anthony Calandra, Ph.D..
Telephone: 609-252-7148

8. **DRUG PRODUCT NAME/CODE/TYPE:**

- a) Proprietary Name: Orencia™
- b) Non-Proprietary Name: Abatacept
- c) Code name: BMS
- d) Common name: CTLA4Ig
- e) Drug Review Status: Fast Track, CMA pilot program
- f) Chemical Type: recombinant fusion protein of human CTLA4 and Fc region of human IgG1

9. **PHARMACOL. CATEGORY:** Therapeutic fusion protein of human CTLA4 and FcIgG1.

10. **DOSAGE FORM:** Sterile lyophilized powder.

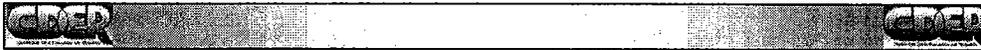
11. **STRENGTH/POTENCY:**

- (i) The product contains mg/vial of Orencia™ (abatacept).
- (ii) Potency is assessed by binding and IL-2 expression assay but mass units (not activity units) are used for dosing.
- (iii) Dating period for vial product is 24 months when stored at 2°C -8°C. Following dilution into saline, the diluted drug product is stable for 24 hours post-dilution when stored at 2-8°C.



12. **ROUTE OF ADMINISTRATION:** After reconstitution in 10 ml of SWFI, the product is for intravenous infusion when added to 100 ml of 0.9% Sodium Chloride for Injection, USP

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13. **ANIMAL- AND HUMAN-DERIVED RAW MATERIALS**

The animal- and human-derived raw materials used in the manufacturing process of abatacept are used in:

Item	C
Vendor	
Source	
Adventitious Agent Control	
Item	
Vendor	
Source	
Adventitious Agent Control	J

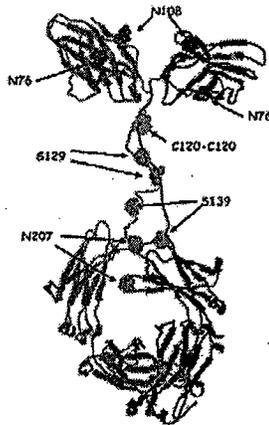
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14. **PRIMARY STRUCTURE, MAIN SPECIES MOLECULAR WEIGHT, HOST SOURCE, MAIN GLYCOSYLATION STRUCTURE/S:**

Abatacept is the USAN name for Bristol-Myers Squibb's fusion protein (CTLA4Ig) comprised of the extracellular domain of the human Cytotoxic T-lymphocyte Antigen-4 (CTLA-4) fused by genetic engineering to human IgG1 immunoglobulin heavy chain Fc sequence including the hinge, CH2 and CH3 domains. IgG1 disulfides were eliminated by the introduction of three Cys→Ser mutations into the IgG1 hinge region sequence. An inter-chain disulfide bond between sequence in the CTLA4 portion of the molecule creates a CTLA4Ig homodimer. This covalent homodimer is referred to as Abatacept "monomer". The C120-C120 disulfide bond is the inter-chain disulfide bond which joins the 2 abatacept polypeptide chains to create the covalently linked homodimer. The predicted MW based on the Abatacept cDNA sequence is 78,800 Daltons. However, the MW obtained by MALDI-TOF is 92,300 Daltons. The 13,500 Dalton difference is due to glycosylation. There are three N-linked glycosylation sites confirmed by peptide mapping to occur at asparagines 76, 108 (both in the CTLA4 region) and 207 (Fc region). Two O-linked glycosylation sites have been identified at Ser 129 and 139. The changes in the Fc region of IgG1 has resulted in the inability of the molecule to fix complement. The sponsor is looking at Fc binding function as a PMC.

Figure 12.S.1.2.FBI: Molecular Model of Abatacept



A model of Abatacept is shown with the N-linked glycosylation sites (N76, N108, and N207), O-linked glycosylation sites (S129 and S139), and the C120-C120 disulfide bond.

Abatacept is a recombinant fusion protein expressed in CHO cells, grown in bioreactors and processed to a high degree of purity. The product is formulated with maltose monohydrate as a lyophile.

15. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE ¹	COMMENTS
				4	acceptable
				4	acceptable
				1	acceptable
				1	acceptable
				4	acceptable
				4	acceptable
				4	acceptable
				4	acceptable
				4	

¹ Action codes for DMF Table:

1 – DMF Reviewed.

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

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

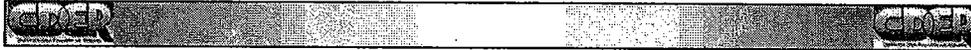
6 – DMF not available

7 – Other (explain under "Comments")

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

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	DESCRIPTION
BB IND		Initial abatacept development



BB IND		
BB IND		

16. **STATUS:** The date of response and recommendation should be noted. The types of consults or related reviews that should be noted are as follows:

OBP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status			Ann deMarco
Labeling Nomenclature Committee			See Lisa Malandro, RPM
OPDRA# 040278	Tradename under review		See Lisa Malandro, RPM
Environmental Assessment			Ann deMarco
TFRB			Ann deMarco

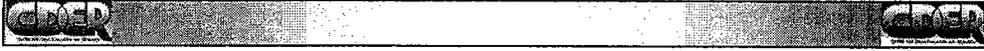
Review trade name for medical error avoidance

17. CMC Inspectional Activities involving product reviewers

1. Bristol Meyers Squibb in Syracuse, NY (June 20, 2005 – July 1, 2005): This facility, owned by Bristol-Myers Squibb, is the site of drug substance manufacture. On site facilities include the manufacturing/production buildings, laboratories (Analytical Biochemistry for in-process testing, Microbiology [] testing, Biologics Quality Control for drug substance and drug product release and annual GMP stability testing, Quality Control Chemistry for raw materials qualification) storage and shipping facilities. The abatacept manufacturing buildings are dedicated to biologics. Bristol-Myers Squibb previously manufactured [

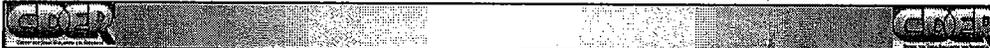
] Prevention of cross-contamination was an important focus of the inspection and was found to be adequate. Product reviewers Joy Williams and Susan Kirshner along with TFRB Inspectors Anne DeMarco participated in this inspection. A 15-item FDA Form 483 was issued to the firm. Five of the items were derived from the product reviewers. Adequate responses to the product reviewer's 483 were received by the agency. The facility was found to be in compliance with cGMPs and capable of manufacturing abatacept drug substance in a consistent manner

2. Additional site inspections were performed under the auspices of CDER/OC but did not involve product reviewers.



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The Chemistry Executive Summary

I. Recommendations

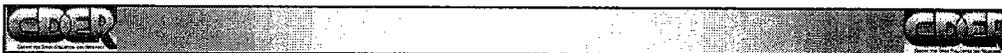
A. Recommendation and Conclusion on Approvability

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of BLA #125118 for Abatacept manufactured by Bristol Myers Squibb. The data submitted in this application support the conclusion that the manufacture of abatacept is well controlled, and leads to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents in a way that meets or exceeds the parameters recommended by FDA. The conditions used in manufacturing have been validated, and a consistent product is produced from different production runs. It is recommended that this product be approved for human use (under conditions specified in the package insert).

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

We propose the following post-marketing commitments:

1. Regarding raw materials and in-process controls:
 - a. To conduct additional validation studies to evaluate the specificity of the () ELISA for assessment of host cell proteins. A summary report and data will be provided by March 31, 2006.
 - b. To establish raw materials specifications and in-process controls for impurities in () A report, proposed controls and data will be provided by October 31, 2006.
 - c. To submit the results and conclusions of the bioburden mapping study together with proposed revisions to your bioburden control program by August 31, 2006.
2. Regarding specifications:
 - a. To re-evaluate all acceptance criteria for currently established release tests of abatacept drug substance and drug product. Results will be provided by March 31, 2006.
 - b. To implement enhanced assay sensitivity controls and establish quantitative and semi-quantitative acceptance criteria for the (



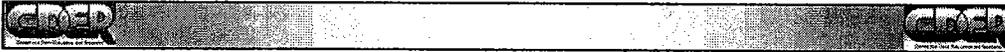
- () methods, respectively. The proposed acceptance criteria and supporting data will be provided by March 31, 2006.
- c. To establish new acceptance criteria for the reference material and for drug substance release for selected peaks observed in the () () profile obtained by () by [December 31, 2006].
 - d. To modify acceptance criteria for the current peptide mapping procedure to include selected peak area and retention times. Report to be submitted by February 28, 2006
 - e. To establish a drug substance release test specification for () () content by February 28, 2006.
 - f. To re-evaluate the appearance specification regarding number of vials tested and to submit revised specifications for this parameter by March 31, 2006.
 - g. To evaluate the revised capillary electrophoresis (CE) method for quantification and or characterization of minor peaks in abatacept drug substance and drug product and submit results of this analysis together with any revised specifications by March 31, 2006.
 - h. To increase precision of the bioassay used for release and stability testing and revise the acceptance criteria accordingly. A summary report together with revised specifications will be provided by July 31, 2006.
3. Regarding assessment of additional product attributes:
- a. To develop the () test for quantification of () for abatacept drug substance and drug product. Results of this analysis together with how this assay will be implemented (i.e. use in specifications or characterization activities) will be submitted by March 31, 2006.
 - b. To further characterize the Fc portion of abatacept for functional activity. Results of this analysis together with how this assay will be implemented (i.e. specifications or characterization activities) will be provided by June 30, 2006.
4. Regarding additional specification/characterization tests:
- a. To develop a () () abatacept species, possibly using () () A report together with proposed specifications will be submitted by December 31, 2006.

- b. To validate the accuracy and specificity of the [] for [] weight species. A summary report and data will be provided by January 31, 2006.
5. Regarding Stability:
- a. To perform a comprehensive analysis of the drug substance and drug product. [] A plan for conducting this work will be provided by February 28, 2006 with a summary report together with any proposed modifications to the stability protocol will be provided by December 31, 2006.
- b. To test [] in drug substance stored at 2° - 8°C for [] days in the final container: [] A report for both studies will be provided by December 31, 2006.
6. Regarding Immunogenicity Assays
- a. To provide updated information for the CTLA4-T reagent used in the immunogenicity assays. Information and data will be provided by July 31, 2006.
- b. To evaluate the inclusion of an additional [] when testing patient samples so as to better [] A report will be submitted by April 28, 2006.
- c. To provide information and data validating the specificity of the [] abatacept [] assay by July 31, 2006.

II. Summary of Chemistry Assessments

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

- General:** Abatacept is the USAN name for Bristol-Myers Squibb's CTLA4Ig product. a fusion protein comprised of the extracellular domain of the human Cytotoxic T-lymphocyte Antigen-4 (CTLA-4) fused by genetic engineering to human IgG1 immunoglobulin heavy chain Fc sequence including the hinge, CH2 and CH3 domains. IgG1 disulfides were eliminated by the introduction of three Cys→Ser mutations into the IgG1 hinge region sequence. An inter-chain disulfide bond between sequence in the CTLA4 portion of the molecule creates a CTLA4Ig homodimer. This covalent homodimer is referred to as Abatacept "monomer". The C120-C120 disulfide bond is the inter-chain disulfide bond which joins the 2 abatacept polypeptide chains to create the covalently linked homodimer. The predicted MW based on the Abatacept cDNA sequence is 78,800 Daltons. However, the MW obtained by MALDI-TOF is 92,300 Daltons. The 13,500 Dalton difference is due to glycosylation.



There are three N-linked glycosylation sites confirmed by peptide mapping to occur at asparagines 76, 108 (both in the CTLA4 region) and 207 (Fc region). Two O-linked glycosylation sites have been identified at Ser 129 and 139.

- **Complexity:** As described above, product is a complex mixture of different isoforms due to post-translational modifications, particularly glycosylation. Glycosylation differences have been shown to impact the pharmacokinetics and clearance of the product. The product is also. [

] Studies in the BLA demonstrate that

[

]

- **Biological activity:** Abatacept functions to selectively block costimulatory signals required for optimal activation of T lymphocytes. Full activation of mature T cells and robust expression of IL-2 requires engagement of the T cell receptor (TCR) by antigen (Signal 1) as well as signaling through a costimulatory receptor (Signal 2) such as CD28. CD28 signaling occurs as the result of engagement of CD80 (B7-1) and CD86 (B7-2) on antigen presenting cells (APCs) and can be blocked by CTLA4-Ig which binds specifically to B7-1 and -2. Presumably, when used to treat patients with rheumatoid arthritis, CTLA4Ig inhibits activation of the T lymphocytes found in the synovium of affected joints.
- **Potency Assays to Measure Activity.** The product is designed to inhibit B7-CD28 mediated costimulation. Two assays are used. The first assay is a binding assay in which [is used to detect binding of Abatacept to recombinant B7-Ig on sensor chips. Activity is measured as concentration as a percent of reference standard binding. This assay is a good indicator of activity of the CTLA4 region to bind appropriate ligands. The second assay is a bioassay in which a Jurkat T cells line has been engineered to express luciferase under control of the human IL-2 promoter. If cells are activated (by anti-CD3 and B7) they will express luciferase at high levels. The addition of Abatacept blocks B7 signals. The assay is a good indicator of the ability of the molecule to inhibit a critical T cell function response i.e. generation of IL-2. While the molecule has been shown incapable of effectively fixing complement, it is possible that the ability of the molecule to bind FcR could contribute to its activity. The sponsor has not investigated this possibility and will be requested as a PMC.
- **Drug Product Presentation:** Orenzia™ is supplied as a sterile, non-pyrogenic lyophile for IV administration. Each vial contains [mg of abatacept, [mg of sodium phosphate monohydrate, [mg sodium chloride, and [mg of maltose monohydrate. The DP is packaged in []

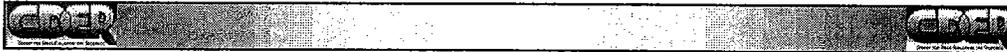


glass vials with [] stoppers and sealed with aluminum, flip off seals single-use vial free of preservatives. Abatacept for Injection, [] g/vial, is a sterile, non-pyrogenic lyophile for intravenous. The product is packaged as kit and contains a sterile, non-siliconized syringe for both reconstitution of the lyophile with 10 ml of SWFI and transfer of the reconstituted solution to the 100 ml 0.9% Sodium Chloride Injection, USP for IV infusion.

- **Excipient:** The product is formulated with maltose monohydrate. Maltose has been shown to interfere with measurements of blood glucose levels with some glucometers. Recently there were cases in which patients receiving maltose in other products were misdiagnosed as having high glucose levels and were treated with insulin. This treatment led to severe hypoglycemia and death in at least one case.
- **DS Manufacture:** Abatacept drug substance is produced as a secreted protein in [] cell culture using a Chinese hamster ovary (CHO) cell line. After expansion, cells are grown in a [] bioreactor in batch mode. [] steps, with

[] The process appears to have been appropriately validated and produces a consistent product that meets its expected quality parameters.

- **DS Purity:** The above process includes steps [] validated [] used to manufacture the product []
- **DS Release Tests:** The tests for release of DS include Capillary electrophoresis (to discriminate Abatacept from a related molecule Belatacept), Isoelectric focusing (to show the distribution of different glycoforms), peptide mapping (to confirm identity and can be used a stability indicating assay), [] HPLC (demonstrating the product has low



levels of [redacted] (to examine purity), monosaccharide analysis (to show consistency of Glycosylation). Some of these assays need to be refined (see PMC section) but they are adequate for approval.

- **Critical Product Attributes**

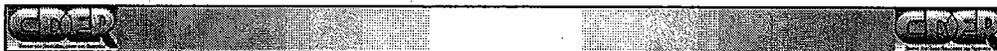
- i. [redacted]
- ii. [redacted]
- iii. [redacted]
- iv. [redacted]

]

- **Development and Comparability:** Bristol-Myers Squibb has designated 6 manufacturing processes (A – E and [redacted]) based on changes to the [redacted] process. Drug product from processes A – E were used in clinical trials, whereas the [redacted] process was not used in clinical trials. The Phase III trials used material manufactured by the current process E. The comparability of drug substance manufactured using the different processes was established by physico-chemical and biological comparability to reference standards.

- **Degradation and Stability.** Abatacept [redacted]

[redacted] of product. However, real time stability data indicate that the product appears to have a robust stability profile. [redacted] Exposure to light has been shown



to cause [redacted] increase activity in the bioassay. A comprehensive characterization of product degradation pathways was not reported and will be the subject of a PMC.

Drug Substance: A drug substance shelf life of [redacted] at -40°C is currently recommended based upon information submitted by the sponsor. Drug substance should be marked "protect from light". Stability studies support interim storage of drug substance at 2°C – 8°C for [redacted] from the last manufacturing step but prior to freezing as well as [redacted] post-thaw but prior to fill, for a total of [redacted].

Drug Product: A drug product shelf life of 24 months stored at 2°-8° C is recommended based upon information submitted by the sponsor. Drug product should be designated as "protect from light."

- Evaluation of the current assay utilized to detect potential human anti-CTLA4Ig antibodies was performed by CMC reviewers (Elizabeth Shores-see [Appendix 3](#)). Antibody binding assays both to the CTLA4 region and to the whole CTLA4Ig molecule were performed. In addition a neutralizing antibody assay was performed. Overall, the results from the assays demonstrated a relatively low rate of immunogenicity in patients (~1.7%). However, trough levels of product can interfere with detection and a subgroup of patients that had not been exposed to product for an appropriate time indicate that the rate may be closer to 6%.

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

- ORENCIA™ is indicated for 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 who have had an inadequate response to one or more DMARDs, such as methotrexate or TNF antagonists. ORENCIA may be used as monotherapy or concomitantly with DMARDs other than TNF antagonists. ORENCIA should be administered as a 30-minute intravenous infusion at the doses specified below. Following the initial administration, ORENCIA should be given at 2 and 4 weeks after the first infusion, then every 4 weeks thereafter. The recommended dose of [redacted] is 300 mg IV infusion every four weeks.

Dose of ORENCIA

Body Weight of Patient	Dose	Number of Vials ^a
< 60 kg	500 mg	2
60 to 100 kg	750 mg	3
> 100 kg	1 gram	4

^a Each vial provides 250 mg of abatacept for administration.



- Orencia™ is supplied as [7] mg/vial, sterile lyophile free of preservatives.
- Orencia™ is prepared for IV infusion by reconstituting each vial with 10 mL of SWFI using the non-siliconized syringe supplied with the product. Using the same syringe, the reconstituted product is added to 100 ml of 0.9% Sodium Chloride for Injection, USP, for intravenous infusion.
- Orencia™ vials should be refrigerated at 2°C-8°C and protected from light. The recommended expiration dating period for Orencia™ Drug Product is 24 months under these storage conditions.

C. Basis for Approvability or Not-Approval Recommendation

- Orencia™ is manufactured by a robust process with precautions for contamination by cell substrate or adventitious agents. Orencia™ is manufactured consistently, resulting in a safe and effective product, and should be approved for the proposed indication.
- Post-marketing commitments described in the recommendations section above will provide additional information to assure the continued safety of the product.

III. Administrative

A. Reviewers' Signature

Product Reviewer: Joy Williams, Ph.D.

Joy Williams 12/21/05

Product Reviewer: Susan Kirshner, Ph.D.

Susan L. Kirshner 12/20/05

Product Reviewer/CMC Team Lead: Elizabeth Shores, Ph.D.

Elizabeth Shores 12/21

Product Reviewer: Susan Kirshner, Ph.D.

Product Reviewer: Ennan Guan, Ph.D.

Ennan Guan 12/21/05



Product Reviewer: Edward Max, MD, Ph.D. *Edward Max 12-22-05*

Product Reviewer: Barbara Rellehan, Ph.D. *Barbara Rellehan 12-22-05*

B. Endorsement Block

Product Team Leader: Elizabeth Shores, Ph.D. *Elizabeth Shores 12/21/05*

Product Deputy Director: Barry Cherney, Ph.D. *Barry Cherney 12-21-05*

Product Division Director: Amy Rosenberg, M.D. *for [Signature] 12-22-05*

C. CC Block

Acting Office Director: Steven Kozlowski, MD.
Division of Therapeutic Proteins File/BLA STN 125104/0

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§ 552(b)(4) Trade Secret / Confidential

§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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 § 552(b)(4) Trade Secret / Confidential

 § 552(b)(5) Deliberative Process

 § 552(b)(4) Draft Labeling

From: Edward E. Max, M.D./Ph.D. *Edward E. Max 12-15-05*
To: BLA: 125118/0, Original Submission
Through: Elizabeth Shores, Ph.D. Acting Deputy Director of OBP
Barry Cherney, Ph.D. Deputy Director, CDER/OPS/OBP/DTP, HFM541
Product: Abatacept *Barry Cherney 12-15-05*
Sponsor: Bristol Myers
Final Date: December 15, 2005

Section 3.2.S.2.3.3.2 Abatacept structural gene: design construction and expression

The abatacept protein contains the extracellular region of human CTLA4 (125 amino acids) fused by genetic engineering to three domains of the human IgG1 immunoglobulin heavy chain (231 amino acids), namely the hinge region, the CH2 domain and the CH3 domain. The protein is expressed in a CHO cell line. Since the signal sequence of the human CTLA4 gene was not characterized, the abatacept gene construct was equipped with the 26 codons encoding the signal sequence from the human oncostatin M gene; this signal sequence is cleaved during protein synthesis so it is absent from the abatacept protein.

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling

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§ 552(b)(5) Deliberative Process

§ 552(b)(4) Draft Labeling