CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

BLA 125118/000

Administrative/Correspondence Reviews

PEDIATRIC PAGE

BLA # : 125118 Supplement Type (e.g. SE5): _____ Supplement Number: N/A

mp Date: April 1, 2005 Action Date: December 23, 2005

HFD - 170 Trade and generic names/dosage form: ORENCIA (abatacept)

Applicant: Bristol-Myers Squibb Therapeutic Class: N/A

Indication(s) previously approved: NA

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: _____

Is there a full waiver for this indication (check one)?

- ☐ Yes: Please proceed to Section A.
- X No: Please check all that apply: X Partial Waiver X Deferred ____ Completed
  NOTE: More than one may apply
  Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ☐ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Other: _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min____	kg____	mo.____	yr. 0	Tanner Stage____
Max____	kg____	mo.____	yr. 2	Tanner Stage____

Reason(s) for partial waiver:

- ☐ Products in this class for this indication have been studied/labeled for pediatric population
- ☐ Disease/condition does not exist in children
- ■ Too few children with disease to study
- ☐ There are safety concerns
- ☐ Adult studies ready for approval
- ☐ Formulation needed
- ☐ Other: _____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.** 2	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.** 16	**Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other: Studies are in progress

Date studies are due (mm/dd/yy): November 30, 2005

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

/s/ Malandro 12/20/05
Lisa Malandro
Regulatory Project Manager

cc: **BLA 125118**
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03)

6/1/05

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 125118 **Supplement Type (e.g. SE5):** _____ **Supplement Number:** N/A

FDA Received Date: April 1, 2005 **Action Date:** October 1, 2005

HFM _____ **Product and Proprietary names/dosage form:** abatacept

Applicant: Bristol-Myers Squibb **Therapeutic Class:** N/A

Indication(s) previously approved:

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Reducing the signs and symptoms of rheumatoid arthritis, and improving the physical function in adults with moderateley to severse active RA

Is there a full waiver for this indication (check one)?

☐ **Yes: Please proceed to Section A.**

☑ **No: Please check all that apply:** ☐ **Partial Waiver** ☑ **Deferred** ☐ **Completed**
NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____	kg_____	mo._____	yr._____	Tanner Stage_____
Max_____	kg_____	mo._____	yr._____	Tanner Stage_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**

☐ Too few children with disease to study
☐ There are safety concerns
☐ Adult studies ready for approval
☐ Formulation needed
☐ Other:_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____	**kg**_____	**mo.**_____	**yr.**0	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**17	**Tanner Stage**_____

Reason(s) for deferral:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☑ **There are safety concerns**
☑ **Adult studies ready for approval**
☐ **Formulation needed**
Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Comments:

Enter into CBER Communication as: Memo/Other (OT) Summary: Pediatric Page; and update special characteristics code in RMS/BLA.

This page was completed by:

Erik Laughner

Regulatory Project Manager

cc: NDA/BLA #
HFD-960/ Grace Carmouze

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT THE DIVISION OF PEDIATRIC DRUG DEVELOPMENT, HFD-960, 301-594-7337.

(revised 12-22-03;revised 8-10-04 for RMS/BLA use)

STN BL 125118_0
Abatacept (BMS-188667, CTLA4Ig)

356h ITEM 20 - OTHER INFORMATION - REQUEST FOR DEFERRAL OF SUBMISSION OF PEDIATRIC INFORMATION

Sponsor: Bristol-Myers Squibb Company

Product Name: Abatacept

Indication: Reducing the signs and symptoms of RA, inducing a major clinical response, inhibiting the progression of structural damage, and improving physical function in adults with moderately to severely active RA.

Age Groups Included in the Deferral Request:

Males or females (not nursing and not pregnant) 6-17 years of age inclusive with a diagnosis of Juvenile Rheumatoid Arthritis (JRA) or Juvenile Idiopathic Arthritis (JIA).

Reason for not Including the Entire Pediatric Population:

Children from birth thru 5 years of were excluded from ongoing study IM101033 (described below). The younger pediatric population was excluded until we could first determine the safety and efficacy of abatacept in an older pediatric population.

Reason for Deferring Studies:

BMS is currently conducting a clinical trial in the pediatric population that is outlined below. Based on a March 25, 2003 End of Phase 2 Meeting with the Agency, it was agreed that a pediatric program would be initiated with the phase 3 program, but that the study data would not need to be included in the initial marketing application. A pediatric study (IM101033) was submitted and reviewed by the Agency, subsequently revised based on FDA recommendations and then initiated in December 2003 (details are included below). In a Pre-BLA Meeting with the Agency on October 12, 2004, the Agency agreed a request for deferral was appropriate for this program based on this information.

Description of Ongoing Studies:

Protocol Title: Study IM101033 - A Phase III, Multi-Center, Multi-National, Randomized, Withdrawal Study to Evaluate the Safety and Efficacy of BMS-188667 in Children and Adolescents with Active Polyarticular Juvenile Rheumatoid Arthritis (JRA)

Statement of Purpose: To investigate whether BMS-188667 (CTLA4Ig) will have greater clinical efficacy when compared with placebo alone in pediatric subjects with active Juvenile Rheumatoid Arthritis (JRA) or Juvenile Idiopathic Arthritis (JIA).

Primary Objective: The study will compare the clinical efficacy of BMS-188667 versus placebo in children and adolescents with JRA/JIA in whom a response had been initially induced by 4 months of open-label therapy. Following 6 months of double-blind treatment, clinical efficacy will be measured by the time to occurrence of JRA/JIA disease flare during the double-blind treatment period.

Description of Subject Population: Males or females (not nursing and not pregnant) 6 – 17 years of age, inclusive at screening. Males and females of childbearing potential are eligible only if they practice effective contraceptive measures.

- Diagnosis of JRA or JIA utilizing the standard criteria for one of the following categories:
  - JRA (ACR criteria): pauciarticular, polyarticular or systemic disease onset and polyarticular course
  - JIA (ILAR criteria): extended oligoarticular, polyarticular (RF+),
  - polyarticular (RF-), or systemic with a polyarticular course
- Subjects must have a history of at least 5 joints with active disease and must have currently active articular disease.

Study Status: Number of Patients Planned: 200 (Enrolled), 128 (Randomized)

Current Status:

Patients Screened (Enrolled)	130
Patients Treated in 4-Month Open-Label Period	112
Patients Randomized into 6-Month Double-Blind Period	55

Projections:

Full study enrollment is expected by 4th Quarter 2005. Completion of randomization is expected by April 2006, LPLV expected by October 2006, Top line results available by December 2006.

Bristol-Myers Squibb Company

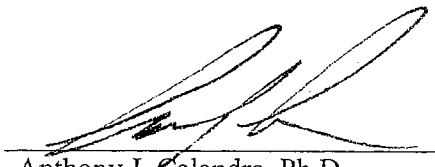
BL 125118

ABATACEPT (BMS-188667, CTLA4Ig)

INITIAL APPLICATION - RHEUMATOID ARTHRITIS

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred under section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.



12/17/04

Anthony J. Calandra, Ph.D.
Director, Global Regulatory Strategy
Bristol-Myers Squibb Company
P.O. Box 4000, D32-08
Princeton, NJ 08543-4000
Phone: (609) 252-7148

Certification Date

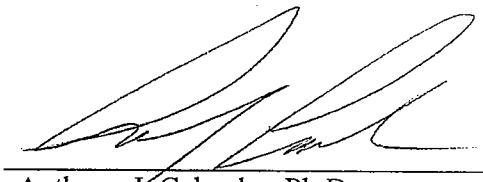
BL 125118

ABATACEPT (BMS-188667, CTLA4Ig)

INITIAL APPLICATION - RHEUMATOID ARTHRITIS

CERTIFICATION: DEBARRED PERSONS

As required by Section 306(k)(1) of the Federal Food, Drug and Cosmetics Act, Bristol-Myers Squibb Company certifies that it has not used and will not use in any capacity the services of any person listed as debarred as of the Date of Debarment List Debarment List under Section 306 (a) or (b) of the Federal Food, Drug and Cosmetics Act in connection with this Application.



12/7/04

Anthony J. Calandra, Ph.D.
Director, Global Regulatory Strategy
Bristol-Myers Squibb Company
P.O. Box 4000, D32-08
Princeton, NJ 08543-4000
Phone: (609) 252-7148

Certification Date

6 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

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

OFFICE DIRECTOR'S DECISIONAL MEMORANDUM

Date: Thursday, December 22, 2005
BLA: #125118
Sponsor: Bristol-Myers Squibb
Proprietary Name: Orencia (abatacept)
Author: Robert J. Meyer, MD, Director, ODE II

Summary: This is the first review cycle for this application considered submitted as of January 30, 2004 (it had been a continuous marketing application), with an action goal date of December 31, 2005.

Abatacept is the USAN name for a synthetic, soluble fusion product consisting of two human-derived proteins/protein fragments: the extracellular portion of the Cytotoxic T-lymphocyte-associated Antigen-4 (CTLA-4) and the hinge fragment of the Fc portion of human IgG immunoglobulin. One reason for targeting CTLA-4 is that genetic polymorphisms of this molecule have been implicated as being a risk factor for rheumatoid arthritis (RA). By incorporating the extracellular portion of the CTLA-4 protein, abatacept is intended to bind to the CD80/86 receptor on the antigen presenting cells, thereby preventing t-cell activation. Cellular immunity, including t-cells, is thought to play a major role in the activity of rheumatoid arthritis, the target indication for abatacept. In addition to decreasing t-cell activation and proliferation, abatacept is proposed to decrease inflammatory cytokines, and secondarily decrease antibody production including rheumatoid factor. This is the first RA therapy to specifically target the CTLA-4 pathway, so this is currently a unique option for RA patients, since the other biologic DMARDs either work through blocking TNF or though IL-1 receptor antagonism.

The drug, a reconsitituted lyophilized powder, is given biweekly initially, and then monthly after the first month. The sponsor conducted a reasonably thorough clinical program to assess the effects of abatacept on the signs, symptoms, functional consequences and radiographic progression of RA given in addition to non-biologic disease modifying therapies (or DMARDs).

CMC: Abatacept is produced as a secreted protein in [redacted] cell culture using a chinese hamster ovary (CHO) cell line. The drug product is a sterile, non-pyrogenic lyophile for intravenous administration. Each vial contains [redacted] mg of abatacept, [redacted] mg of sodium phosphate monohydrate, [redacted] mg sodium chloride, and [redacted] mg of maltose monohydrate. The product as produced 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 subject to [redacted] and other post-translational changes. Studies in the BLA demonstrate that [redacted]

can increase the potency of the product. Further, although this product has been shown to be immunogenic at a low level, [ ] can increase the immunogenicity of other therapeutic proteins and therefore this was a consideration in the product review.

The product reviews were Joy Williams, Ph.D., Susan Kirshner, Ph.D., Elizabeth Shores, Ph.D., Ennan Guan, Ph.D., Edward Max, MD, Ph.D., Barbara Rellehan PhD. After a thorough review, the following are their recommendations:

> *"The Division of Therapeutic Proteins, Office of Biotechnology Products,OPS, CDER, recommends approval of BLA #125118 for Abatacpet[sic] 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)."*

There are a number of relatively minor post-marketing CMC commitments and agreements to finalize various specifications and to provide further information and validation. These will be included in the action letter.

[

]

Pharm-Tox: The Pharm/Tox reviews were done by Hana Ghantous, PhD and Anita O'Connor, PhD. The sponsor conducted general toxicity, carcinogenicity, reprotoxicology studies and immunotoxicology studies. While this human fusion protein was clearly immunogenic in animals under certain circumstances, it was active (and non-immunogenic) at relevant doses in both rodents and non-human primate models. In fact, the most clinically relevant findings of the PT studies relate to the carcinogenicity findings, a consequence of the drug's activity. The product was not mutagenic or clastogenic. Carcinogenicity testing was done per ICH in a single rodent species, CD-1 mice. This study showed that at the end of approximately 86 weeks (study was terminated due to 25% survivability), the mice developed lymphoma at rates above expected baselines, with lymphoma being the cause of death in about 50% of treated mice. The lymphoma was statistically deemed treatment-related, but not dose-related. Additionally, mammary carcinomas were also found and statistically shown to be treatment related for the two highest doses of abatacept studies (65 and 200 mg/kg). Both of these tumors have been related to mouse retroviruses and hence these likely represent a manifestation of chronic immune suppression rather than any direct carcinogenic mechanism of abatacept. It should also be noted that in reprotoxicology studies, there were no effects of the drug in terms of teratogenicity despite demonstrated fetal exposure, though f1 generation females showed a dramatic increase in t-cell-dependant antibody response (with thyroiditis in one rat). Abatacept has also been shown to be present in rat milk. All of these relevant findings will be reflected in labeling, with the

pregnancy category recommended to be a — The Pharm/Tox reviewers also recommend approval.

Clinical Pharmacology: The clinical pharmacology review was done by Anil Rajpal, MD. This review found that abatacept showed dose proportional PK when given either subcutaneously or intravenously. The terminal half-life of the drug given IV is between 10 – 19 days and appears dose independent (clearance was also dose independent in animals). The values of half-life did not differ substantially in various patient groups and/or normals. The drug has a small volume of distribution (about 0.1 L/kg) indicating it mainly stays intravascular. When dosed according to label recommendations (biweekly through the first 3 doses, then monthly), steady state is reached by the end of the second month, with minimal subsequent accumulation. There were no PK drug-drug interactions demonstrated with either methotrexate or etanercept. Population PK showed that the only significant variable in dosing was weight (increased clearance with increasing weight), thereby leading to a dosing strategy that varies by weight.

Finally, it is worth noting that the changes in product production did not lead to apparent differences in relevant PK parameters in healthy subjects, supporting that the product to be marketed should perform as investigated in clinical trials.

The clinical pharmacology reviewer recommends approval as well.

Clinical/Statistical: The clinical review team was Keith Hull, MD (primary) and Jeff Siegel, MD (secondary). Their recommendations each are for approval. Below I will highlight the efficacy and safety data supporting approval.

Efficacy:
This application was given Fast Track status and therefore received the requisite input on issues related to development, including study design and endpoints. The sponsor conducted one phase 2 a study (dose finding), two phase 2 b studies and three phase 3 studies in support of their application. The first phase 2 dose finding study (**IM103-002**) studied RA patients who were considered inadequate responders to DMARD therapy. They received no significant background treatment during the study. The patients were randomized to doses of 0.5, 2 and 10 mg/kg for 3 months with the primary endpoint being the change in the ACR 20 (percent of patients achieving a 20 percent improvement in their ACR score). Note that this study also assessed treatment with BMS224818, a closely related compound at the same nominal doses. This study showed that at the day 85 assessment, the ACR 20 in placebo was 31% as opposed to 23, 44 and 53% for abatacept 0.5, 2 and 10 mg/kg respectively.

The sponsor then took doses of 2 and 10 mg/kg into their dose-ranging phase 2 study, **IM101-100**. This was performed for a treatment period of 6 months on the background of methotrexate (MTX) therapy in 339 patients not adequately responding to MTX. In this study, the 2 mg dose showed a numerically superior response to placebo after day 60 on the ACR 20, but it was not statistically significant. However, the 10 mg/kg dose was numerically superior by day 15 and statistically superior at day 60 and beyond out to day 360. The differential between drug and placebo did not appreciably change after day 180. The sponsor chose to then utilize 10 mg/kg as their dosage for phase 3 trials.

The first phase 3 trial, **IM 101-102** was a 1 year placebo-controlled randomized study of abatacept 10 mg/kg in 652 patients, with a 2:1 randomization of drug:placebo. Patients were deemed inadequate responders to MTX, but were maintained on the MTX during the treatment period. The controlled portion of the trial was 1 year in duration. Patients were well-matched demographically and reasonably representative of typical RA patients. This study showed results very similar to the shorter phase 2 study, in that there was clear, statistically significant response to abatacept by day 15 on the ACR 20 and this continued to increase out to at least 6-months, at which point the differential of ACR 20 responders was about 28% (68% active vs. 40% placebo). It is notable that while the ACR 20 seemingly reached a plateau at this point, the ACR70 continued to increase overall and in relation to placebo out to day 365 (20% vs. 7% at day 180; 29% vs. 6% at day 365). The ACR 20 results were consistent over various demographic groupings (age, gender, weight, duration of disease and presence of RF). The co-primary endpoint in this study was the HAQ (a standardized disability questionnaire thought to reasonably assess function). Responders for the HAQ are required to improve by 0.3 units, a more conservative cut off than what has been "validated" in the literature (0.22 units at one year). On this co-primary, there was again a statistically significant and convincingly important difference at one year, with 64% responders in the abatacept group, vs. 39% in placebo. Sensitivity analyses to impute missing data in various ways did not substantially change the findings on either primary endpoint. Additionally in this study, radiographic changes were assessed in 586 patients by 3rd party, blinded assessors where erosions were assessed in 20 joints (from radiographs of the hands and feet) and narrowing in 19 joints. While both groups showed progression of the radiographic deterioration on average, the progression with active drug was lower than with placebo (+ MTX in both groups) alone, with a change of 1.21 units in active versus a change of 2.32 units with placebo total (erosions and joint space narrowing). This was also significant. This study clearly showed the efficacy of abatacept at the 10 mg/kg dose given over 1 year in patients who are on MTX but have had unsatisfactory improvement on various clinically important parameters.

Study **IM101-029** was a 6 month randomized, placebo-controlled study in patients who were deemed inadequate responders to prior anti-TNF therapy, of which they were washed out for 4 – 8 weeks prior to randomization, while MTX could be maintained. The total n=391 with a 2:1 randomization. The primary endpoints were again the ACR20 and the HAQ and the dose was 10 mg/kg. Failure of anti-TNF therapy (infliximab and etanercept) was defined as at least 10 swollen and 12 tender joints with an elevated CRP after at least 3 months of TNF therapy and could have been proximate(about 40%) or distant failures (60%). Note, however, that since patients were not re-randomized to anti-TNF therapy, it cannot be strictly said that these patients are uniquely responsive to abatacept, should they "respond" as RA is not monotonous in its activity and it may be that this same group of patients, if re-randomized to TNF-blockers, would have also improved compared to placebo. In any case, the sponsor showed significant improvements in both the ACR 20 and HAQ at 6 months. The ACR again separated out by day 15 and was seemingly plateauing by day 169, at which points the ACR 20 responders were about 50% vs. 20% in placebo. Again, this response was consistent over various demographics, including how recently they were on anti-TNF therapy and which they had received (and some had received both). In the HAQ, 47% of active vs. 23% of placebo patients showed a response at 6 months.

It is worth noting that an additional phase 2 efficacy study was done – study IM101-102, which looked at the addition of abatacept (*2 mg/kg*) or placebo to an anti-TNF therapy (etanercept) in 121 patients over a 12 month period, again with a 2:1 randomization. The primary endpoint was the ACR20 at day 180. While there were numerical trends towards additional efficacy, none reached statistical significance (and there were clearly safety signals of enhanced immunosuppression with resultant infections). At this point, there is reason to specifically not recommend concomitant treatment of abatacept and TNF-blockers, but no affirmative data to suggest it is clearly useful (albeit this study utilized a lower dose than will be approved for therapy as a single DMARD or with concomitant non-biologic DMARDs).

Safety:
Over 1900 patients received abatacept in controlled clinical trials, with over 2300 receiving abatacept in open-label trials (including extensions) for a total safety database of close to 2700 patients, the majority of whom received the drug for 12 months or more. Cumulative patient exposure in controlled trials was 1688 person-years. This is a relatively robust pre-marketing database.

There were 23 deaths in clinical trials, 15 during double blind treatment. Out of these 15, the percentage of patients dying who were on drug is just below, but essentially the same as, placebo. Most of the deaths were cardiovascular (not surprising given the known increased risk in RA patients). However, there was one cancer death and one infection death in the drug treatment group and one cancer death and two infection-related deaths with placebo (placebo patients were often on other DMARD therapy). In open-label trials, there are also a mixture of events with apparent CV deaths predominating, but with some cancer events. Of note, there was a patient who developed a B-cell lymphoma that was diagnosed on day 1086 of treatment, dying 29 days later. However, without continued controls, it is hard to make any conclusions about drug attribution with any of these cases and in many it seems unlikely (though, not perhaps the lymphoma case – where attribution is simply uncertain). There is no gross signal in the occurrence of deaths suggesting a clear drug-related concern.

For outcomes less dire than death, there was a bit more signal of some excess events that could therefore be attributable to drug, with Serious AEs occurring at a rate of 13.6 with drug, vs. 12.3% with placebo and 5.5% of patients discontinuing due to an AE on drug vs. 3.9% on placebo. There was also an overall excess of all reported AEs, with 88.8% of abatacept treated patients reporting an AE vs. 84.9% on placebo. However, the most common AEs where there was an excess number of patients reporting events with drug were reasonably benign – headache, nasopharyingitis, dizziness, and hypertension. For serious AEs, there were some notable excesses with abatacept treatment, including infections (3.0 vs. 1.9%) and neoplasms (1.4 vs. 1.1%). When patients receiving background biologic treatment in RCTs were considered, these differences were even more striking: serious infections (4.4 vs. 1.5%) and malignancies (1.5% vs. 0).

The total number of patients with infections was 54% on abatacept vs. 48% for placebo. The excess of serious infections did not seem to reduce to any particular category, but included pneumonias, URI (nasopharyngitis), cellulites, UTIs, GI, GU and skin. Herpes infections were

singled out by the sponsor due to cell-mediated immunity concerns and there did not seem to be a significant signal of concern in terms of excess events or quality of events. For TB, there were 2 cases of TB (presumed) on drug and one in a placebo-patient, which given the relative exposures means there is no imbalance against abatacept. Other biologic DMARDs certainly are known to increase the TB risk, particularly for reactivation of latent disease, and it is assumed this would be true of abatacept as well.

A particular issue for this drug, given its mechanism of action and the preclinical findings, is the effect it may have in permitting cancer to become manifest. Overall, there is a slight excess of malignancies found during the RCTs, as stated above. When looked at in broad classes, this seems to have arisen in the hematologic (0.1 vs. 0) and non-melanoma skin (0.8 vs. 0.6) classifications. Obviously, all tumors were unusual in numbers and the timing of their emergence often makes drug causality (for even permissive effects) uncertain, if not unlikely.

An evaluation of cancer rates for various tumors of interest (lung and lymphoma amongst them) do not show a rate in the abatacept patients that is clearly different from those seen in the SEER cancer statistics review of 1998-2002, though the standardized incidence ratio for lung and lymphoma are elevated with lower bounds of the C.I.s that border on excluding unity. However, when compared to RA observational cohorts, the incidence of cancer overall and of subtypes is more in line with what has otherwise been documented in this population, perhaps reflective of either some element of RA itself and/or DMARD therapy. The evidence to date suggests that if there is a causative or permissive effect of abatacept on cancer, the resultant risk does not fall out of bounds of what might otherwise be experienced by an RA patient.

With any new protein product, immunogenicity is an issue and this was assessed by BMS in phase 2 and 3 trials. Surprisingly (given that this product is a fusion of human proteins) there was some baseline reactivity to abatacept even in previously unexposed normals that was shown to be related to the Fc portion of the molecule. However, very few patients seroconverted and developed antibodies to the CTLA-4 portion of the molecule (<1%) following 6-months of treatment. Very little sign of important systemic allergy was seen in trials, though one patient on drug discontinued due to leukocytoclastic angiitis and there were 2 cases of anaphylactoid or anaphylaxis reactions (out of 2688 patients treated). Overall, immune response to the agent does not appear to pose unreasonable safety or efficacy issues.

In the safety study, there were 37 patients with COPD treated with abatacept and 17 on placebo. The COPD patients on drug had higher rates of exacerbations, including serious adverse events. While this experience would not lead one to withhold treatment from COPD patients, it does warrant precautions in the labeling to alert physicians to use it in COPD patients with care and to be cognizant of this potential for worsening.

Clinical note: To date, pediatric use has not been addressed by the sponsor. Given the occurrence of a relevant population (JRA), they will need to do so in the future.

Data Integrity/Financial Disclosure:
DSI conducted two clinical site reviews for this application and the sponsor provided financial disclosure information per requirements. These issues were carefully considered and attended to

by Dr. Hull in his review and there are no issues with regard to data integrity or financial conflicts that undermine the ability to rely on the clinical data for this BLA.

Labeling/Nomenclature: The name Orencia has been found acceptable in the DMETs recommendation. The sponsor has responded to input on labeling from the division, the ODE, DDMAC, and DMETS. It has been found to be acceptable, with the exception of the needing more explicit instructions with regard to syringe use.

Planned Action:
I believe BMS has provided sufficient data to show this product is safe and effective for its proposed indications, considering the severity of RA as a chronic disease and considering that despite recent advances in disease-modifying therapy, many patients cannot either tolerate or respond to the existing therapies. Therefore, having a new option with a different mechanism of action is important. While this product (and other potent DMARDs) likely poses infectious and perhaps oncologic risks, these small risks seem well balanced by the effects not just on signs and symptoms, but on patient function and on joint destruction. With proper labeling of the risks, patients and physicians should be able to choose whether such an option is right for them.

I plan to approve this BLA for "reducing signs and symptoms, including major clinical response, impeding the progression of structural damage, and improving physical function in adult patients with moderately to severely active" RA. In keeping with other biologics, the agent will be given a "second-line" status for those who have inadequately responded to other DMARDs, including anti-TNF therapy until such time that use experience or other data show it clearly has a role as a first-line DMARD. Note that Orencia should not be used concomitantly with TNF given the results of the phase 2 concomitant study and there will be a less directive recommendation against use with anakinra, since no data on concomitant use were submitted..

There are several clinical phase 4 commitments in place that will lead to useful data, particularly with regard to infection and malignancy risk.

- To conduct pediatric studies in patients 2 – 16.
- To complete the proposed pharmacovigalence plan as proposed by BMS:

    a. Protocol IM101045A, a pharmacoepidemiology study to assess the short term (2 years) and potential long-term (4years) risk of hospitalization due to infection (all hospitalized infections, hospitalized pneumonia, and all opportunistic infections) among patients with RA treated with abatacept in comparison to other DMARDs within a large cohort of individuals with commercial health insurance. This study will also characterize patients receiving abatacept and monitor any off-label use.

    b. Protocol IM101045B, proposed as an observational prospective pharmacoepidemiology cohort study to assess the short and long-term risk of malignancies and infection in patients with RA treated with abatacept in comparison to other DMARDs within an existing registry containing patients with rheumatoid arthritis. Follow-up will be for at least 5 years after the last patient is enrolled.

- To continue the open label extensions of 5 studies (IM101-100, IM101-101, IM101-102, IM101-029, IM101-031) to obtain data and perform appropriate safety analyses for 5-years' exposure to abatacept for 1000-1500 patients.

1 Page(s) Withheld

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

___ § 552(b)(5) Deliberative Process

___ § 552(b)(4) Draft Labeling

Malandro, Lisa

From: deMarco, Ann L
Sent: Wednesday, December 21, 2005 6:28 PM
To: Malandro, Lisa
Subject: FW: Facilities Issues for STN 125118: Abatacept: [redacted]
Importance: High

12/22/05

FYI. Ann
-----Original Message-----
From: Lopez, Teddi
Sent: Wednesday, December 21, 2005 6:16 PM
To: Uratani, Brenda W
Cc: deMarco, Ann L; Cruz, Concepcion; Smedley, Michael; Silverman, Steven; Famulare, Joseph; McGinnis, Joseph (CDER)
Subject: FW: Facilities Issues for STN 125118: Abatacept: [redacted]
Importance: High

Brenda

I'm sending this message to you on Coki's behalf.

Thanks
Teddi

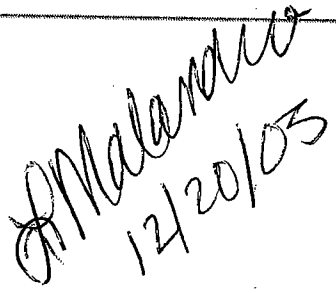
The Investigations and Preapproval Compliance Branch has completed the review and evaluation of the compliance check request for the subject site and application. There are no pending or ongoing compliance actions that would prevent approval of STN 125118/0 at this time. The inspection and compliance history of [redacted] has been reviewed and found to be acceptable.

Please note that the inspection conducted by Team Biologics on July 19 – August 10, 2005 was initially classified as OAI by ORA/OE with a WL recommendation, but will be reclassified as VAI after review by CDER/OC Case Management. The firm's corrective actions will be verified upon the next Team Biologics inspection.

Coki Cruz

Malandro, Lisa

From: Malandro, Lisa
Sent: Tuesday, December 20, 2005 2:37 PM
To: 'Anthony J Calandra'
Cc: Malandro, Lisa
Subject: STN 125118/0 Abatacept Labeling
Importance: High



Tony,
Attached are the FDA-revised PI and PPI, as well as Division's responses to the revisions that you made to the PI on December 15, 2005. Please review these documents and send me your response as soon as possible (preferably **by** Thursday, December 22, 2005). The clinical postmarketing commitments and agreements that you prepared look acceptable and should be formally submitted to the application. For each PMC, please include the required dates for each milestone (protocol submission, conduct and reporting). When completed, the CMC PMCs should also be submitted formally to the application.
If you have any questions, please do not hesitate to contact me.
Thanks,
Lisa

Lisa Malandro
Regulatory Health Project Manager
Division of Anesthesia, Analgesia and Rheumatology Products; HFD-170
301-796-1251
fax-301-796-9722

13 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

MEMORANDUM

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

DATE: December 15, 2005

TO: STN 125118 Study File

FROM: Lisa Malandro

L Malandro 12/15/05

SUBJECT: **PSC meeting**
STN 125118, Orencia (abatacept)

It was agreed between the Division of Anesthesia, Analgesia and Rheumatology Products and the Division of Drug Risk Evaluation that a preapproval safety conference was not necessary for this application since the Divisions have worked closely together on the safety issues during review of the Risk Management Plan.

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

12-14-05

MEMORANDUM

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

DATE: December 8, 2005

TO: STN 125118 Study File

FROM: Lisa Malandro /Malandro 12/9/05

SUBJECT: **Clinical PMC Discussion: 12/8/05**
STN 125,118, Orencia (abatacept)

The following PMCs and agreements were presented to and discussed with the Sponsor during a teleconference held on 12/8/05. The Sponsor will submit their proposal.

1. Complete the proposed pharmacovigalence plan as proposed:

    a. Protocol IM101045A , proposed as a nested case-control study to assess the risk of hospitalization due to infection (all hospitalized infections, hospitalized pneumonia, and all opportunistic infections) among patients with RA treated with abatacept in comparison to other DMARDs within a large cohort of individuals with commercial health insurance.

    b. Protocol IM101045B, proposed as a cohort study to assess the risk of malignancies and infection in patients with RA treated with abatacept in comparison to other DMARDs within 2 existing registries containing patients with rheumatoid arthritis.

2. Commitment to continue the open label extension study(ies) to obtain data and perform appropriate safety analyses for 5-years' exposure to Orencia for 1000-1500 patients.

Abatacept (ORNECIA) proposed **AGREEMENTs** (Clinical Review)

1. Collecting and analyzing data (including spontaneous post-marketing reports) on the incidence rate of lung cancer in smokers and non-smokers of RA patients treated with abatacept.

2. Conducting a pregnancy registry, with concurrent controls, for women who become pregnant while exposed to abatacept to identify the pregnancy outcome and postnatal health status of the children.

3. Collecting and analyzing data (including spontaneous post-marketing reports) on the incidence of AEs and SAEs in patients receiving both leflunomide and abatacept.

4. Collecting and analyzing data (including spontaneous post-marketing reports) on the incidence of AEs and SAEs in patients with COPD who receive abatacept.

DISCUSSION:

In general, the Sponsor agreed with the Division's proposed post-marketing commitments and agreements. They will submit a proposal to the application for review.

MEMORANDUM

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

DATE: December 7, 2005

TO: STN 125118 Study File

FROM: Lisa Malandro 12/7/05

SUBJECT: **Information request: 12/2/05**
STN 125,118, Orencia (abatacept)

The following questions were posed to the Sponsor during a teleconference held on 12/2/05.

1. As noted in the PAI, the maximum cycle number allowed for your [ ] based on small-scale studies did not translate to maximum cycle number for the manufacturing scale [ ] Please provide an explanation for the disparity between the small-scale and manufacturing scale results.
2. Please explain how you monitor [ ] and [ ] integrity during routine use for all your [ ] Please explain how [ ] is/was qualified/validated on the commercial scale [ ] and provide data supporting the qualification/validation.
3. The Sponsor should maintain the – month test point for in the post-approval stability protocol for drug substance.
4. The Stability protocol for the reference standard is insufficient.
   a. The sponsor should include the proposed tighter standards for the reference standard.
   b. How do you control for the amount of degradation products in the reference standards?
   c. Please include all the tests used for qualification of the reference standard in the protocol. [

Performing the [ ] analyses is not relevant for the stability studies.

To: BLA 125118

Product: Abatacept (CTLA4-Ig)

From: Joy Williams

Bristol-Myers Squibb participants: Charlene Craig, Anthony Calandra, Michel Grace, Tobias Massa, David Smolin, Thomas Vanden Boom, Elizabeth Yamashita,

FDA Participants: Joy Williams, Elizabeth Shores, Barry Cherney, Lisa Malandro, Ann deMarco

L Malandro 12/22/05

Teleconference Date: December 16, 2005 2:00 pm

Subject: The purpose of this call was to discuss the PMCs and other issues relating to BLA 125118. A summary of the discussion and a list of the PMCs discussed are provided below.

DRAFT CHEMISTRY, MANUFACTURING AND CONTROLS 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 specifications for impurities in [ ] A report, proposed specifications 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 [redacted].

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 summit revised specifications for this parameter by March 31, 2006.

g. To evaluate a revised the capillary electrophoresis (CE) method for quantification and or characterization of minor peaks in abatacept drug substance and drug product and summit 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 [ ] 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 [ ], in the final container [ ]
] A report for both studies will be provided by December 31, 2006.

Discussion of PMCs #1b and #2c were initiated by the Sponsor. Specifically, the Sponsor asked for clarification regarding the term "specification" as applied in PMC #1b. The Agency indicated that the wording could be adjusted to allow for the use of in-process testing as a means of [ ] Regarding PMC #2c, the Sponsor asked whether and/or how, the establishment of new acceptance criteria for the [ ] profile would impact on comparability assessments made for drug substance manufactured at Syracuse and at the Lonza facility. The Agency stated that new acceptance criteria would not have to be in place prior to submission of data to support comparability of drug substance manufactured at Syracuse and at Lonza. However, the Agency stressed that data from [ ] profiling would be critical in the establishment of comparability.

Additional discussion regarding questions posed to the Sponsor by Ann deMarco. The Sponsor verified that [ ] the extent possible using [ ] assay. Regarding concerns about enodtoxin specifications for raw materials, the Sponsor indicated that all raw materials which come into direct product contact do indeed have endotoxin specifications. When asked about endotoxin specifications for [ ] the Sponsor stated that [ ] are acceptable for use. The source currently in use has a lower endotoxin [ ] originally used (and still permitted for use as a backup source). Monitoring of the commercial scale [ ] has revealed no evidence of endotoxin buildup and release after [ ]

Final discussion centered around the submission of the supplement for Lonza. The Sponsor committed to sending the Agency background information for the comparability testing for Lonza drug substance by December 19, 2005.

MEMORANDUM

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

DATE: December 7, 2005

TO: STN 125118 Study File

FROM: Lisa Malandro

SUBJECT: **CMC PMC Discussion: 12/7/05**
STN 125,118, Orencia (abatacept)

The following PMCs were presented to and discussed with the Sponsor during a teleconference held on 12/7/05. The Sponsor will submit their proposal.

1. To implementing better assay sensitivity controls and establish quantitative and semi-quantitative acceptance criteria for the [ ] methods performed for release testing of abatacept drug substance and Orencia drug product and qualification of reference standards. The proposed acceptance criteria and supporting data will be provided by March 31, 2006.
2. To establishing new acceptance criteria for the reference standards and for drug substance release for [ ]; profiling by [ ] based the manufacturing history of abatacept. New acceptance criteria will be provided by March 31, 2006. A new reference standard will be qualified by [fill in date]
3. To re-evaluating all the release specifications and acceptance criteria after production of **[fill in number of batches]** batches of abatacept drug substance (from the Syracuse facility) and drug product. The results will be provided by [Fill in date].
4. To developing [ ] abatacept species. Acceptance criteria for [ ]; for drug substance and drug product release and stability will be established. The release specifications will be added to the drug substance and drug product certificate of analysis. The results of the validation studies and the new acceptance criteria will be provided by [Fill in with date].
5. To characterizing the Fc portion of abatacept for functional activity associated with this region of the IgG1 molecule. Tests should include Fc receptor (FcR) binding ability. The results will be provided by [fill in with date].

6. To validating the accuracy and specificity of the [ ] assay for the detection of [ ] weight species using [ ] method(s). The results of the studies will be provided by [fill in with date].

7. To performing a comprehensive analysis of the drug substance and drug product [ ] to permit better characterization of the drug substance and drug product over time and to establish appropriate acceptance criteria for stability tests. The results will be provided by [fill in date].

8. To testing [ ] in drug substance stored at [ ] in the relevant container closure system(s). The results will be provided to the FDA by [insert date].

9. To extending the validation studies conducted for the [ ] ELISA to include assessment of the spectrum of [ ] recognized by the [ ] antibodies.

10. To setting specifications for minor peaks present in the electropherogram for the CE procedure or characterizing these peaks to determine whether specification is necessary and to validating CE inter- and intra-assay precision.

11. To better defining acceptance criteria for the peptide mapping procedure to include objective criteria such as retention times and peak areas.

DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

MEMORANDUM **Center for Drug Evaluation and Research - Food & Drug Administration**
Laboratory of Immunobiology, Division of Monoclonal Antibodies - HFD-123
NIH Campus, Bldg. 29B, Rm. 3NN06, 8800 Rockville Pike, Bethesda, MD 20892
Telephone (301) 827-0715 - Facsimile (301) 827-0852

Date: 01-Dec-05

From: Barbara Rellahan DMA, OBP, CDER BJR 12/16/05

To: BLA 125118

Through: Acting Deputy Director, DMA, OBP, CDER 12/21/05

Subject: Consult Review for DTP, OBP, CDER on Fc-region functionality of Abatacept

Indication: Rheumatoid Arthritis
Sponsor: Bristol-Myers Squibb Company (BMS)

Executive summary: BMS does not have data that adequately addresses whether the Fc-region of the fusion protein plays a role in its clinical activity. Protein characteristics that influence Fc-region activity such as amino acid sequence and glycosylation are monitored during drug substance lot release. Therefore, the lack of complete understanding on whether the Fc-region plays a role in the clinical activity of abatacept and no direct control for Fc-region activity in lot release does not pose a product quality issue that would preclude licensure of the protein.

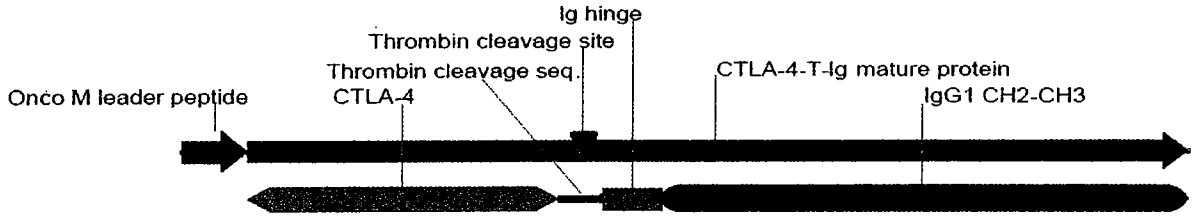
Fc-region functionality could be an issue after licensure in terms of comparability analyses and understanding adverse events or toxicities that are seen when abatacept is used in a larger number of people. It is therefore recommended that the FDA ask BMS to commit to investigating the functionality of the Fc-region more thoroughly and determine whether it interacts with Fc-receptors and mediates ADCC activity.

The following should be communicated to the sponsor:

1) The data you have submitted as a characterization of the functionality of the Fc-region of your fusion protein are inadequate. For example, the studies that investigated the ability of abatacept to interact with Fc-receptors did not include controls, such as Fc-receptor blocking antibodies, to demonstrate binding to cells was mediated specifically by an Fc-receptor. In addition, no dose-titration was performed so an estimate of the relative affinity (compared to a positive control antibody/protein) could not be determined. We therefore request that you commit to performing a more in-depth investigation of Fc-region functionality that includes but may not be limited to,
   a. A determination of the relative affinity of abatacept for the CD16, CD32 and CD64 receptors.
   b. A determination of the relative ability of abatacept to mediate antibody dependent cellular cytotoxicity. This study should include samples from at least 8-12 human donors.
   c. A more in-depth determination of the relative ability of abatacept to mediate complement mediated cellular cytotoxicity. This study should include multiple types of complement such as human plasma derived and baby rabbit complement.

Material reviewed:
Reference is made to the above BLA 125118 for Abatacept. Response to question received 31 May 2005, Fc region (Study reports 930006519, 930011015, and 930010937) and STN# 125118/0/18.

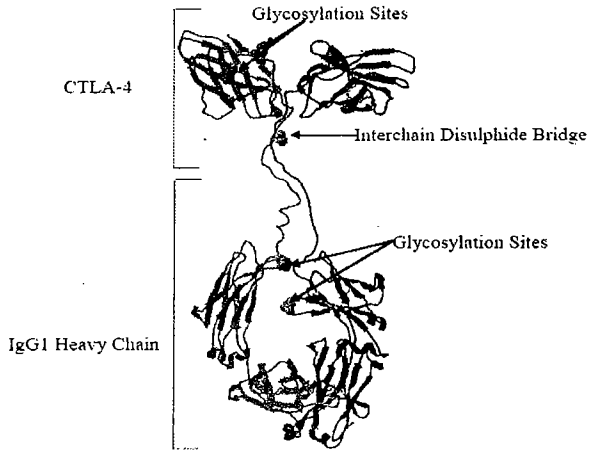
Background:
Abatacept is a fusion protein between the extracellular portion of CTLA4 and human IgG1. CTLA4 is attached to an IgG1 hinge region which is followed by the constant heavy chain regions 2 and 3. See below for schematic.



Translation of CTLA-4-T-Ig
401 aa

Abatacept has 4 mutations in its Fc region. Three hinge region cysteine residues (Cys130, 136, and 139) normally involved in interchain disulfide bonding in the Fc region have each been mutated to serine. These mutations were made to improve protein production. The molecule is held together by a single disulfide bond within the CTLA4 region. The submission states that these mutations also resulted in reduced complement fixation but data to this effect is not included. The fourth mutation of proline to serine at amino acid 148 inadvertently happened during the genetic engineering by PCR. The direct impact of a change at this position has not been evaluated. The predicted structure of abatacept as determined by the sponsor is shown in Figure 1..

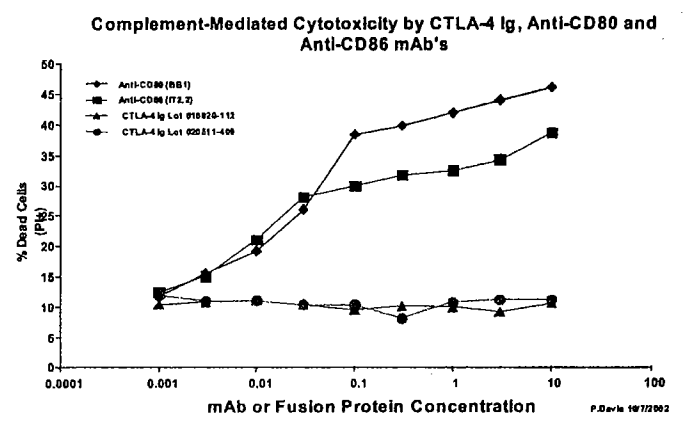
Figure 1: Predicted Structure of Abatacept (based on modeling)



Review of the data:

1. Complement-dependent cellular cytotoxicity. Used an EBV-transformed B7+ human B cell line (PM-LCL) as the target cells. Tested two lots of abatacept (#010920-112 and 020511-409) and two other murine anti-B7 antibodies (anti-CD86, IT2.2 mIgG2b and anti-CD80, BB1, mIgM) from [ ] [ ] as positive controls. Purchased Low-tox-H rabbit complement from [ ] for the complement source. Results indicated no complement killing of the target cells in the presence of abatacept while the positive controls each gave a significant level of killing. It is not clear that they included a control that only had the antibodies added and no complement.

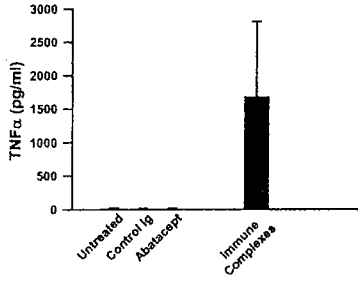
Figure 1: Complement Dependent Cellular Cytotoxicity is Mediated by Anti-CD80 and Anti-CD86 mAbs but not CTLA4-Ig



2. Binding of abatacept to Fc receptors. Cell lines used were the Raji B cell line and a macrophage-derived cell line U937. The U937 cell line expresses CD32 (FcγRII) and CD64 (high affinity FcγR1) but no B7 antigens. Data indicated that both human IgG1 and abatacept bound the U937 cells. Because the U937 cells do not express B7, the sponsors state that these data suggest that the binding was mediated through CD32 or CD64. Raji cell which only have B7 antigens but not CD64 or CD16, bound abatacept but not human IgG1. These data are said to suggest that abatacept does not bind CD32. However, there was no positive control to demonstrate binding by CD32 so a definitive conclusion can not be made. This is a very rudimentary analysis of Fc receptor binding. Because blocking anti-Fc receptor antibodies were not used with the U937 cells, one can not even conclude that the fusion proteins bound the U937 cells via those receptors.

3. Ability of abatacept to induce TNFα production by monocytes. Human monocytes were isolated by elutriation, and incubated with either control Ig fusion protein or abatacept at 30 μg/ml. Supernatant was harvested 6 hours later and assayed for TNFα. Positive control was pre-formed insoluble Ig complexes of goat anti-human IgG mixed with human IgG. Data shown are the average of three replicate samples from four different donors. Data indicates that abatacept does not induce TNFα production from human monocytes. Fc-receptor expression was not determined for the monocytes used. Anti-Fc-receptor blocking antibodies were not used as controls. Therefore these data provide little information regarding the ability of abatacept to bind to Fc-receptors or its ability to activate cells through their Fc-receptors.

Figure 3.1: Treatment of human monocytes with abatacept alone does not induce TNFα production.



On 8/18/05 the following questions were faxed to BMS along with other CMC related issues. BMS was told that this information would not be required for approval of the BLA. A partial response to these issues was submitted on 30-Sept-05 in STN # 125118/0/18.

1) Please provide data regarding the role of the Fc-region of Abatacept in its presumed mechanism of action. Specifically, please provide data regarding the Fc-receptor classes that the product binds in humans (with information on human Fc-receptor allotypes where appropriate) and animal models, the tissue distribution of these receptor classes, and the presumed role of this binding in the pharmacokinetics and pharmacodynamics of Abatacept.
2) Please provide data regarding the ability of Abatacept to mediate antibody-mediated cellular cytotoxicity and *in vivo* depletion of $B7^+$ cells.

In regard to issue #1 the sponsor submitted a table summarizing the cellular expression pattern and function of Fc-receptors. They also summarized the studies they performed as described above. [reviewer's note: This report states that one study looked at the ability of abatacept to bind to cells that expressed CD64 and CD16. In the actual study report the cells were stated to express CD64 and CD32.] In regard to data on the ability of abatacept to mediate ADCC and *in vivo* depletion of B7+ cells, the sponsors state that in a psoriasis clinical trial (Abrams et al., 1999. J Clin Invest 103:1243), there was no detectable cellular depletion of CD80/86 (B7) expressing cells suggesting that abatacept does not induce ADCC. This publication does not actually contain data on the subset analysis performed; it merely states that no depletion of B7+ cells was seen.

The response also states that in non-human primate studies no evidence of depletion of peripheral blood lymphocytes was observed following up to 1 year of treatment at up to 9-fold the human exposure based on AUCs. Because abatacept would have a lower affinity for CTLA4 and for Fc-receptors in non-human primate models it is unclear how this data relates to its activity in humans.

Reviewer's comments and recommendations

It seems clear that a major component of the mechanism of action of abatacept is the direct blockage of B7 family members and reduction in the amount of co-stimulation T cells can receive during activation. Whether a secondary component of its action involves the IgG Fc-region and activity such as ADCC or CDC has not been adequately addressed. The data submitted to date may be suggestive that this is not a major aspect of abatacept's activity but because of the deficiencies present within all the studies no real conclusions can be made. The potency assays used to assay its activity for lot release are not designed to measure Fc-region activity (see attachment for lot release assays). However, amino acid sequence of the protein is monitored through peptide mapping and the glycosylation of the protein is also monitored as part of lot release (see attachments for methods). These are the two antibody characteristics that primarily regulate the function of the Fc-region and because they are monitored during lot release, changes to the protein that might affect Fc-region activity are monitored. Therefore, because alterations to the proteins amino acid sequence and glycosylation that might affect the activity of the Fc-region are monitored as part of drug substance lot release, the fact that there is a lack of understanding on whether the Fc-region plays a role in the clinical activity of abatacept is not an issue for licensure of the protein.

Office of Drug Safety

MEMO

To: Bob Rappaport, M.D.
Director, Division of Anesthesia, Analgesia, and Rheumatology Products
HFD-170

From: Felicia Duffy, RN
Safety Evaluator, Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Through: Alina R. Mahmud, RPh, M.S., Team Leader
Denise P. Toyer, PharmD, Deputy Director
Carol A. Holquist, RPh, Director
Division of Medication Errors and Technical Support, Office of Drug Safety
HFD-420

Date: November 2, 2005

Re: ODS Consult 05-0302
Orencia (Abatacept) Lyophilized Powder for Injection; 250 mg/vial
BLA 125118/0

This memorandum is in response to an October 26, 2005 request from your Division for a re-review of the proprietary name, Orencia (BLA 125118/0). The proposed proprietary name, Orencia, was found acceptable by DMETS in reviews dated October 30, 2003 and April 25, 2005 (ODS consults 03-0236 and 03-0236-1). Container labels and package insert labeling were not provided for review and comment.

Since the April 25, 2005 review, DMETS has identified one additional proprietary name, Alinia, as having look-alike similarities to Orencia. Alinia may look similar to Orencia when scripted. Alinia is indicated for the treatment of diarrhea caused by *Giardia lamblia* and *Cryptosporidium parvum*. The beginning of each name can look similar when scripted ("Ali" vs. "Ore") if the "A" is open when scripted and the "l" and "e" are not prominent (see below). Both names share the letter "n" in the fourth position in addition to the same ending (-"ia"). The comparable appearance in name length also contributes to their orthographic similarities (6 letters vs. 7 letters).

Alinia
Orencia

Alinia and Orencia share an overlapping dosage of 500 mg. However, both drug products differ in indication for use (diarrhea vs. rheumatoid arthritis), strength (500 mg and 100 mg/5 mL vs. 250 mg/vial), route of administration (oral vs. intravenous), frequency of administration (every 12 hours x 3 days vs. 30 minute infusion followed by another infusion in two and four weeks; then monthly thereafter), and dosage form (tablets and powder for oral suspension vs. lyophilized powder for injection). Since Orencia is an infusion, it will most likely be prepared in a hospital setting or an

infusion center setting. In either case, the specific instructions for use for Orencia will be indicated (e.g., Orencia 500 mg IV over 30 minutes x1). Despite some orthographic similarities between Alinia and Orencia, the directions for use and product differences (indication for use, strength, route of administration, frequency of administration, and dosage form) minimize the potential for name confusion.

In summary, DMETS has no objections to the proprietary name Orencia. Additionally, DDMAC has no objections to the name from a promotional perspective. We acknowledge that the sponsor revised the labels and labeling in accordance with the DMETS' recommendations in our April 25, 2005 consult (ODS consult #03-0236-1). DMETS has no additional comments in reference to the revised labeling. We consider this a final review. However, if the approval of the BLA is delayed beyond 90 days from the date of this review, the name must be re-evaluated. A re-review of the name before the BLA approval will rule out any objections based upon approvals of other proprietary and/or established names from the signature date of this document.

If you have any questions or need clarification, please contact DMETS Project Manager, Diane Smith, at 301-796-0538.

5 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

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✓ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

9-30-05

7 Page(s) Withheld

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

____ § 552(b)(5) Deliberative Process

____ § 552(b)(4) Draft Labeling

Laughner, Erik

From: Laughner, Erik
Sent: Monday, August 22, 2005 3:47 PM
To: 'anthony.calandra@bms.com'
Subject: 125118 PI label

Importance: High

Dear Dr. Calandra,

Enclosed you will find a PDF file containing the Agency's revisions to the Abatacept PI label for BLA 125118. Please review and if necessary, a TCON can be accommodated for subsequent discussion.

Sincerely,

Erik Laughner, MS
RPM
ODEVI/DRMP
301-594-6218

Abatacept
el_082205_sent ve

Agency's first official revision to label.

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✓ § 552(b)(5) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

AUG 19 2005

Our STN: BL 125118/0

Bristol-Myers Squibb Company
Attention: Anthony J. Calandra, Ph.D.
Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Dr. Calandra:

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

We received your August 9, 2005, amendment to this application on August 11, 2005, and consider it to be a major amendment. Because the receipt date is within three months of the user fee goal date, we are extending the goal date by three months to December 31, 2005, to provide time for a full review of the amendment.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions.

Effective August 29, 2005, the new address for all submissions to this application is:

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

If you have any questions, please contact the Regulatory Project Manager, Erik Laughner at (301) 594-6218.

Sincerely,

Kay Schneider for

Wendy Aaronson, M.S.
Acting Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Telecon

Teleconference Memorandum

Date:	08-18-05
Sponsor Participants:	Tony Calandra, BMS Charlene Craig, BMS
FDA Participants:	Erik Laughner, RPM
Re:	Abatacept
STN:	125118

Discussion:

Informed Dr. Calandra that the 8-9-05 amendment was determined to be a major amendment. This decision will extend goal date by 3 months

Telecon

Teleconference Memorandum

Date: 08-03-05

Sponsor Participants: Tony Calandra, BMS

FDA Participants: Erik Laughner, RPM

Re: Abatacept

STN: 125118

Discussion:

Informed Dr. Calandra that the Sponsor tradename, ORENCIA, had been pproved by DDMAC, DMETS, and DTBIMP. Dr. Calandra also informed me that they were reviewing the Agency's comments to the vial, carton, and packaing for ORENCIA and would be in touch soon with.

Teleconference Memorandum

Date: 08-03-05

Sponsor Participants:
Charlene Craig, CMC Regulatory
Elizabeth Yamashita, CMC Regulatory
Tobias Massa, CMC Regulatory
Anthony Waclawski, Global Regulatory Science
Anthony Calandra, Global Regulatory Science
Lee Tay, Clinical Discovery, PK scientist
Michael Corbo, Development Leader

FDA Participants:

Regulatory
Erik Laughner, M. S.

CMC
Joy Williams, Ph.D.
Susan Kirshner, Ph.D
Barry Cherney, Ph.D.

Facilities
Ann deMarco

Clinical
Ellis Unger, M.D.

Pharm/Tox
Hong Zhao, Ph.D.
Martin (Dave) Green, Ph.D.

Re: Abatacept

STN: 125118

Discussion:

Bristol-Myers Squibb (BMS) had requested an informal tcon with the Agency for discussion on three critical points to assure uninterrupted commercial supply of the abatacept product once introduced into the market. Two issues relate to the sBLA filing for the additional drug substance (DS) manufacturer, Lonza Biologics, and the third involves the proposed expiration dating of abatacept DS.

Human PK data

In the April 2005 pre-sBLA meeting with FDA, BMS had proposed that a 28 day interim report be provided in the initial sBLA with the final PK results (71 day) submitted during review. BMS was instructed to submit data from the full PK profile (5 half-lives) in the initial sBLA with the caveat that other options would be considered for potential supply issues. As per protocol, pharmacokinetic sampling was intended to run for 71 days (~ 5 half-lives) followed by statistical comparisons of Cmax and AUC(0-T) and AUC(INF). However, the sBLA submission would be delayed until approximately mid-Nov 2005 to include the full PK profile in the application.

To meet our proposed sBLA submission date of mid-October and provide for a maximum window for a PAI in 2005, does the Agency agree that the initial sBLA provide the PK profile obtained after 57 days (~ 4 half-lives) for assessing the comparability between Lonza- and BMS-derived abatacept with the complete profile being submitted by the end of November?

Agency: We agree with this proposal, provided that we do have the full data by the time indicated.

Lonza Manufacture Scheduling

Lonza 2005 Fall Manufacturing Schedule Overview

Manufacturing Operation	Start Date	Completion Date
[redacted]		
[redacted]		

As can been seen by the table above, the contracted manufacturing slots were selected to coincide with potential inspection in late summer in line with the original timing of the BLA. The next scheduled abatacept manufacturing campaign at Lonza begins in April 2006. Thus, if the PAI cannot be scheduled in the 2005 timeframe, FDA would not be able to inspect the facility while in active manufacture for abatacept until May 2006. This would result in the product not being fully launched and made widely available to patients until 3Q 2006.

BMS therefore requests FDA's agreement to plan for the potential inspection dates in 2005 due to the manufacturing window post sBLA filing. Could the Agency come for inspection anytime during the month of November?

Agency: That should not be a problem. In addition to the TFRB reviewer, we will most likely send a member of the CMC review team as well.

Expiration Dating of Abatacept Drug Substance

FDA commented in the 74 day letter, "Stability data for drug substance provided thus far support a drug substance shelf life of [ ] Real time data from three lots of drug substance in the appropriate container closure system should be provided to extend drug substance shelf life beyond [ ] As a result, BMS has submitted updated DS stability data from the primary lots in the 74 day letter response to support the use of existing commercial inventory. The update includes – week data from the first primary stability lot and - week data from two additional primary stability lots. This updated stability data further support the proposed [ ] shelf life for abatacept DS stored frozen at -40°C. In addition, as presented in the pre-BLA meeting background package, the shelf life for DS and drug product (DP) will be extended post approval via the BLA annual report based on the existing primary long term stability protocols.

The sBLA to be submitted in mid-October will contain the following comparability information, as discussed at the April 2005 teleconference:

- Results from analytical testing of 3 lots of DS manufactured at Syracuse and Lonza including a combination of filed regulatory release tests, extended analyses, additional characterization and co-mixture analysis.
- Certificates of analysis for 3 lots of DP manufactured from 3 lots of DS made at Lonza.
- DS process validation data.
- [ ] month stability data, at recommended storage temperature(s) and accelerated conditions on 3 lots of DS manufactured at Lonza.
- Summary of results from the monkey and human PK studies.

In addition, as discussed at the April 2005 teleconference, BMS will submit an update during sBLA review (end of November) with the 6 month DS and 3 month DP stability data.

To maximize the initial expiration dating for DS, does FDA agree to review updated [ ] stability data on two DS lots that are currently filed with 6 month stability data prior to the PDUFA without extending the review clock? The existing long term DS and DP stability protocols are equivalent to the market life stability protocols hence, BMS will extend expiration dating via the

BLA annual report based on stability data from the primary long term stability lots. Does the FDA concur with this approach?

Agency: This is fine. A [ ] stability update can be submitted to the current BLA at the end of August without impacting the action date. For easier review, please group the data by study and include graphical displays of multiple lots.

Expiration dating can be extended using the annual reporting mechanism . Your plan to supplement the Lonza stability during review of sBLA is acceptable. Following completion of the comparability evaluation, the shelf-life of Lonza material will be the same as the shelf-life determined for the Syracuse material.

Laughner, Erik

From: Laughner, Erik
Sent: Monday, August 01, 2005 2:43 PM
To: 'Anthony J Calandra'
Subject: Review of Carton and Packaging for Abatacept

packaging revision suggestions...

Dear Dr. Calandra,

Enclosed, please find a word file containing our review and suggested revisions to the abatacept container and carton labels. The Agency would appreciate your response within two weeks if possible.

Please feel free to contact me with any questions or concerns.

Sincerely,

Erik Laughner, M.S.
RPM
ODEVI/DRMP
301-594-6218

Agency first official revisions to container and packaging.

3 Page(s) Withheld

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_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

Telecon

Teleconference Memorandum

Date: 07-19-05

Sponsor Participants: Tony Calandra, BMS

FDA Participants: Erik Laughner, RPM

Re: Abatacept

STN: 125118

Discussion:

Dr. Calandra called to inquire about the possibility of an informal TCON with the Agency regarding the Lonza manufacturing site initiation for drug substance. I told the Sponsor that he could send me a secure email outlining his reasoning for such a tcon at which point I would relay it to the review team for their response.

Pasted into this memo is the justification:

---

19 July 2005

Erik Laughner
Regulatory Project Manager
Office of Drug Evaluation VI

Dear Erik,

Bristol Myers Squibb would like to set up an informal teleconference with the abatacept clinical review team in ODE VI to make them aware of our current thinking around launch scenarios for the product. Specific objectives for the call are:

- **Role of a contract manufacturing facility, Lonza Biologics, relative to our ability to ensure adequate supply of product to patients**
- **Provide the clinical review team an understanding of the current launch timelines and the issues that impact that timing.**
- **Agree on next steps for arrangement of a detailed discussion of the filing: including human PK, validation reports and timing for the pre-approval inspection**
- **Decide how to best communicate this further from BMS to FDA**

For planning purposes, BMS is assuming approval of the abatacept BLA by the action date of 1 October 2005. BMS' manufacturing facility in Syracuse, New York was submitted in the BLA as the site of manufacture for the active pharmaceutical ingredient (API). A pre-approval inspection of this facility was recently completed.

BMS discussed its plans for long term supply of the product with the Agency at a preBLA CMC meeting in November 2004 and, subsequently, in an April 2005 meeting where BMS presented its plans for submission of a supplemental BLA (sBLA) to qualify Lonza Biologics (Lonza) as a site of manufacture of API. During these interactions BMS identified Lonza as necessary to assure continued uninterrupted supply of the product.

Current supply from the Syracuse facility is limited. To ensure adequate supply to patients BMS plans to launch with Syracuse material when it is reasonably assured that the Lonza facility is far enough along in the FDA review and approval process. Factors impacting the sBLA include: availability of data elements discussed in the April meeting and the timing of the Lonza pre-approval inspection based on the narrow window of time during which abatacept will be manufactured at Lonza in 2005.

I trust this brief background information is sufficient. Feel free to call me at 609 252 7148 if you require further clarification.

Sincerely,

Anthony J. Calandra, Ph.D
Director, Global Regulatory Science

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___ § 552(b)(4) Draft Labeling

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125118

JUN 23 2005

Bristol-Myers Squibb Company
Attention: Anthony J. Calandra, Ph.D.
Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Dr. Calandra:

Please refer to your biologics license application (BLA) for Abatacept, submitted under the Continuous Marketing Application (CMA)-Pilot 1 program and to your December 20, 2004 reviewable unit (RU) for the Clinical section of your BLA.

We have completed our review of this RU and have identified the following potential deficiency:

Study IM101031 includes patients receiving a wide variety of concomitant DMARDS. Please evaluate whether there is a treatment effect interaction between abatacept and any of the specific DMARDS that patients received during this study. Please provide patient subset analyses of each of the subject- and physician-reported disease outcomes (subject pain assessment, subject global assessment, and physician global assessment) at Day 365, subsetting patients by each of the individual biologic and non-biologic DMARDs.

We are providing these comments to you before we complete our review of your entire application to give you preliminary notice of issues that we have identified. These comments are being provided to you in conformance with the guidance "Continuous Marketing Applications: Pilot 1 – Reviewable Units for Fast Track Products under PDUFA" and do not reflect a final decision on the information reviewed. Issues may be added, deleted, expanded upon, or modified as we review the complete application.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective October 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact the Regulatory Project Manager, Erik S. Laughner, M.S., at (301) 594-6218.

Sincerely,

Jeffrey N. Siegel

Jeffrey Siegel, M.D.
Team Leader
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: April 7, 2005 **DATE OF DOCUMENT:** April 1, 2005	**DESIRED COMPLETION:** June 15, 2005 **PDUFA:** September 30, 2005	**ODS CONSULT #:** 03-0236-1

TO: Marc Walton
Medical Division Director, Division of Therapeutic Biological Internal Medicine Products
HFM-576

THROUGH: Beverly Conner, PharmD
Project Manager
HFD-109

PRODUCT NAME: **Orencia** (abatacept) Lyophilized Powder for Injection 250 mg/vial **BLA#: 125118/0**	**BLA SPONSOR:** Bristol-Myers Squibb Company

SAFETY EVALUATOR: Kim Culley, RPh

RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Orencia from a safety perspective. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.
3. DDMAC finds the name Orencia acceptable from a promotional perspective.

Denise P. Toyer 7/19/05

Denise Toyer, PharmD
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety

Carol Holquist 7/19/05

Carol Holquist, R.Ph.
Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: April 25, 2005

BLA #: 125118/0

NAME OF DRUG: **Orencia** (abatacept) Lyophilized Powder for Injection
250 mg per vial

BLA HOLDER: Bristol-Myers Squibb Company

*****NOTE: This review contains proprietary and confidential information that should not be released to the public.*****

I. INTRODUCTION:

This consult was written in response to a request from the Division of Therapeutic Biological Internal Medicine Products, for a re-review of the proprietary name "Orencia" with regard to potential name confusion with other proprietary or established drug names. The proposed name Orencia was found acceptable by DMETS on October 30, 2003 (see consult #03-0236). In addition, drafts of the proposed indications, dosage and administration, warnings, precautions, and dosage form were submitted for review. At this time, the proposed container labels, carton and insert labeling were submitted for review and comment.

PRODUCT INFORMATION

Orencia represents a new class of agents that block the costimulatory signal required for T-cell activation in an immune response. Orencia is indicated for the reduction of signs and symptoms, inhibition of the progression of structural damage, and improvement of physical function in adult patients with moderate to severe active rheumatoid arthritis. These patients should have suffered an inadequate response to one or more disease modifying anti-rheumatic drugs, including tumor necrosis factor blocking agents. This drug product may be used in combination with methotrexate or other non-biologic disease modifying anti-rheumatic drug therapies. Orencia is available as a single-use vial containing 250 mg of lyophilized abatacept that should be maintained in the refrigerator and protected from light. The product should be reconstituted with 10 mL of Sterile Water for Injection, USP, which should be dissolved by swirling (not shaking). This 10 mL of prepared solution must be further diluted to 100 mL of 0.9% Sodium Chloride. This will yield the following concentration depending on the dose to be administered: 500 (2 vials) is 5 mg/mL, 750 mg (3 vials) is 7.5 mg/mL and 1000 mg (4 vials) is 10 mg/mL. Once diluted, the solution may be stored at room temperature or refrigerated, but the infusion must be completed within 24 hours of preparation. The recommended dose is weight related and described as follows: less than 60 kilograms is 500 mg, 60 to 100 kilograms is 750 mg and greater than 100 kilograms is 1 gram (1000 mg). Orencia should be administered over 30 minutes; the first dose should be followed by another administration in 2 and 4 weeks with subsequent doses monthly. The drug product is proposed to be packaged as one vial and one silicone free syringe.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Orencia to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis Pharma-In-Use database[5] was searched for drug names with potential for confusion. An expert panel discussion was conducted to review all findings from the searches.

A. EXPERT PANEL DISCUSSION

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Orencia. Potential concerns regarding drug marketing and promotion related to the proposed names were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. The Expert Panel identified two names and independent review found four names that were thought to have the potential for confusion with the name Orencia. These six products are listed in Table 1 (see page 4) along with the dosage forms available and usual FDA-approved dosage.

2. DDMAC did not have concerns with Orencia in regard to promotional claims.

[1] MICROMEDEX Integrated Index, 2005, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-05, and the electronic online version of the FDA Orange Book.
[4] WWW location http://tess2.uspto.gov/bin/gate.exe?f=searchstr&state=m2pu5u.1.1
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Established name, Dosage Form(s), Strength(s)	Usual adult dose*	Other**
Orencia™	Abatacept 250 mg Lyophilized Powder For Injection, 15 mL vial	Dosed on patient's weight: < 60 kilograms: 500 mg 60 to 100 kilograms: 750 mg > 100 kilograms: 1 gram 30 Minute Infusion, followed by another infusion in two and four weeks, then monthly thereafter	
[ ]	[ ]	[ ]	LA/SA
[ ]	[ ]	[ ]	LA
Avandia®	Rosiglitazone Maleate Tablets 2 mg, 4 mg and 8 mg	4 mg once daily or in divided doses.	LA
Iressa®	Gefitinib Tablets, 250 mg	250 mg daily.	LA/SA
Droxia®	Hydroxyurea Capsules 200 mg, 300 mg and 400 mg	15 mg/kg/day as a single dose, with increases of 5 mg/kg/day until highest tolerable dose or 35 mg/kg/day is reached.	LA
Avinza®	Morphine Sulfate, Extended-Release Capsules 30 mg, 60 mg, 90 mg and 120 mg	Once daily, up to 1600 mg per day.	LA/SA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)
*** Proprietary and confidential information that should not be released to the public

B. PHONETIC ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Orencia were discussed by the Expert Panel (EPD). No additional names of concern were identified in POCA that were not discussed in EPD.

C. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Orencia, the primary concerns related to look-alike and sound-alike confusion with [ ], [ ] Avandia, Iressa, Droxia and Avinza.

1. [

]

*** Proprietary and confidential information that should not be released to the public.

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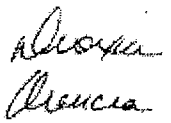
Thus as the products differ in most basic product characteristics, DMETS believes the possibility for confusion between the two names is minimal.

5. Droxia may look like Orencia when scripted. Droxia contains hydroxyurea in 200 mg, 300 mg and 400 mg capsules for the reduction in frequency of painful crises and reduce the need for blood transfusion in adults with sickle cell anemia with recurrent moderate-to-severe painful crises. The recommended dose is 15 mg per kilogram per day to be titrated up to the preferred level of 35 mg per kilogram per day. The orthographic similarities stem from the shared "r" and concluding "ia", which is compounded by the potential for the leading "D" an "O" to share likeness. However, the central "ox" of Droxia should serve to differentiate from the "en" of Orencia.



The potential for confusion exists in three ways: dosing overlap (1000 mg; e.g. 67 kilogram patient receiving 15 mg/kg), possibility for practitioners to confuse the 200 mg strength of Droxia with the 250 mg of Orencia and the possibility for confusion with the 300 mg strength of Droxia and 500 mg dose of Orencia. This confusion would result from the possibility for the "0" of 200 to resemble the "5" of 250 and the likelihood for the leading "3" of 300 to look like a "5" of 500. However, the products differ in dosing frequency (daily compared with monthly after initial titration) and route of administration (oral compared with intravenous) that should deter error in order completion. In addition, the drug products differ in dosage form (capsules compared with vial containing lyophilized powder for injection), storage (room temperature compared to refrigeration), and indication of use (sickle cell anemia compared to rheumatoid arthritis). Due to the differing characteristics, poor orthographic similarities, limited dose overlap (1000 mg) and necessity for multiple of points of confusion (name, route and dose), DMETS believes the possibility for confusion to be minimal.

6. Avinza may look and sound like Orencia when scripted. Avinza contains morphine sulfate as 30 mg, 60 mg, 90 mg and 120 mg extended-release capsules. Avinza is indicated for the relief of moderate to severe pain that requires continuous (around the clock) opioid therapy for an extended period of time. Patients should be dosed daily, up to a maximum of 1600 mg per day. The orthographic similarities stem from the shared central "n" and concluding "ia." In addition, the leading "A" and "O" of Avinza and Orencia, respectively can look alike, which is compounded by the possibility for "v" of Avinza to resemble the "r" of Orencia. Phonetically, the names could be considered to rhyme; thus leading to a cognitive association. In addition, the products share the leading and concluding "ə" sound (as in the word attractive) and the central "n" sound. However, the "v" sound of Avinza compared to the "r" of Orencia should help to differentiate the two names.

The dose may overlap at 750 mg (which is a high dose for Avinza), but Avinza is classified as a schedule II substance that requires a fully completed written order. Thus, the differing characteristics of dosage form (capsule compared with lyophilized powder for injection), dosing frequency (daily compared with monthly after initial titration), route of administration (oral compared with intravenous) and indication of use (pain management compared to rheumatoid arthritis) should serve to curb confusion. This would be true for an inpatient order that may indicate "Avinza 750 mg X1" since the order should also document the route of administration. For outpatient orders, orders will typically indicate strength requested followed by the number of capsules needed to complete the required dose (e.g. Avinza 60 mg # 90 3 qd). Furthermore, pharmacists will question physicians if a misinterpretation of Avinza for Orencia occurred by phone; especially since the drug products differ in strength (30 mg, 60 mg, 90 mg and 120 mg compared with 250 mg). Due to the differing product characteristics and control status of Avinza, DMETS believes the possibility for confusion to be minimal.

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Orencia, DMETS has attempted to focus on safety issues relating to possible medication errors. DMETS has identified several areas of possible improvement, which might minimize potential user error.

A. GENERAL COMMENTS

DMETS questions what happens if the silicone-free disposable syringe is missing and if another syringe is utilized? As there is a push for alternative to [illegible] products, DMETS suggests the sponsor describe in the labeling what were to occur if [illegible] used in the infusion process. This would be beneficial for practitioners who are unaware of the type of tubing, syringes, etc. that are in use. Thus, if the reaction is a visual one (i.e., drug precipitates), the practitioner could discontinue use and correct the error.

B. CONTAINER LABEL

1. Delete the graphic art, as it is too large and distracts from important information on the label.
2. Relocate the strength juxtaposition with the established name to just below or beside (to the right of) the established name, which is the usual location for strength.
3. Revise the strength to read "250 mg/vial", to assure the reader is aware of the strength per vial, not to be confused with a per milliliter strength.
4. To assure the product is properly used, please add the statement "Discard unused portion."
5. Increased the size of the established name to allow for easier reading.
6. If space permits, include the directions for reconstitution and resultant solution. For example, "Once reconstituted with 10 mL of sterile water for Injection, USP the resultant solution will be further diluted to a total volume of 100 mL with 0.9% sodium chloride, which yields concentrations of 5 mg/mL (2 vials), 7.5 mg/mL (three vials) or 10 mg/mL (four vials)."

1 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

b. In reference to the final sentence of the paragraph, provide examples of non-biologic DMARDS to reduce confusion with potential concurrent therapies. This data may be directly taken from the DOSAGE AND ADMINISTRATION section.

2. PREPARATION AND ADMINISTRATION INSTRUCTIONS

See Comments under A and C 3 a-f.

III. RECOMMENDATIONS:

1. DMETS has no objections to the use of the proprietary name Orencia from a safety perspective. This is considered a final decision. However, if the approval of this application is delayed beyond 90 days from the signature date of this document, the name must be re-evaluated. A re-review of the name will rule out any objections based upon approval of other proprietary or established names from the signature date of this document.
2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review to minimize potential errors with the use of this product.
3. DDMAC finds the proprietary name, Orencia, acceptable from a promotional perspective.

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Diane Smith, project manager, at 301-827-1998.

Kimberly Culley, RPh
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud 7/19/05

Alina Mahmud, R.Ph., MS
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

cc: BLA 125118/0
HFD-109: Division Files/Beverly Conner, Project Manager
HFD-109: Marc Walton, Medical Officer
HFD-040: Catherine Gray, Regulatory Review Officer, DDMAC
HFD-420: Diane Smith, Project Manager, DMETS
HFD-420: Kim Culley, Safety Evaluator, DMETS
HFD-420: Alina Mahmud, Team Leader, DMETS

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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125118/0

JUN 14 2005

Bristol-Myers Squibb Company
Attention: Anthony J. Calandra, Ph.D.
Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Dr Calandra:

Please refer to your biologics license application (BLA), submitted under section 351 of the Public Health Service Act, to our Pre-Clinical Discipline Review Letter of May 17, 2005, and to our filing letter dated May 31, 2005. While conducting our filing review we identified the following potential review issues:

PRODUCT INFORMATION

1. Please provide a complete annotated sequence of the entire [ ]CTLA4Ig [ ] vector. You have provided the annotated sequence of only the CTLA4Ig portion of the vector. As per the Q5B ICH guidance, Quality of Biotechnological Products (http://www.ich.org/cache/compo/363-272-1.html#Q5B), the non-CTLA4Ig-coding vector sequence may be taken from the literature.

2. Please provide a detailed description of the methods used [ ] in production of Abatacept. The current submission provides a summary of the process but does not include relevant details including, but not limited to the following:

   a. [ ]

   b. The process used to select a [ ]
   You comment that [ ] but do not give the data used to support selection of [ ]

3. Please provide the protocol to be followed when qualifying a new working cell bank for use in production of Abatacept.

4. Please provide the protocol(s) to be used for monitoring the long term stability of your master and working cell banks.

5. You have provided analytical data for your Research and Process A through E drug substance batches. Included in the batch analyses is [ ] for each batch with the exception of batches produced using Process D. Please provide the missing [ ] values for drug substance batches produced by Process D.

6. You indicate on page 308 of the BLA drug substance module that in-process testing for [ ] has been discontinued, yet at other sites within the BLA (see pgs 1081, 1083), you propose to eliminate these in-process tests. Please clarify this ambiguity. [

]

7. Your present proposal for qualifying new reference standards is inadequate. Specifically, please provide the following:

   a. A description of how you intend to select a batch for designation as a reference standard.

   b. A description of how you intend to control [ ] reference standards over multiple reference standards.

   c. For qualifying new reference standards, release specifications, systems suitability criteria and assay acceptance standards should be more narrowly defined. In addition, drug substance release specification terms [ ] should be well defined for the qualification of new reference standards.

8. Stability data for drug substance provided thus far support a drug substance shelf life of [ ] Real time data from three lots of drug substance in the appropriate container closure system should be provided to extend drug substance shelf life beyond [ ] [ ]

9. Stability data for drug product provided thus far support a drug product shelf life of 12 months. Real time data from three lots of drug product in the appropriate container closure system should be provided to extend drug product shelf life beyond 12 months.

10. Please provide raw data [ ] supporting the stability claims for drug substance and product based on [ ]

11. Where available, please provide raw data [ ] for [ ] supporting claims of reference standard comparability for all the reference standards listed in Table 3.2.S.5.T01.

12. Please provide additional data regarding the [ ] B7-Ig binding assay. All analyses and validation data are presented as a percent of the reference standard. However, it unclear how the numbers were derived. Please provide representative chromatographs and a complete description of data reporting methods.

13. Please provide information that addresses the possible role of the Fc region of the CTLA4Ig molecule. Specifically, please address:

    a. [ ]

    b. [ ]

    c. The role of the Fc region in the mechanism of action of Abatacept.

FACILITIES INFORMATION

14. Since [ ] will perform [ ] testing of [ ] as well as [ ] testing [ ], we request that you include the name, full address, and manufacturing responsibility for the contract facility that performs these tests in section 3.2.S.2.1 Manufacturers. It is *not* necessary to include contract laboratories that test excipients used in media formulation.

15. Table 3.2.S.6.2T01 identifies the material of construction for the [ ] manufactured by [ ] used for Abatacept drug substance. Please provide the following additional information regarding the [ ] Assembly, [ ] part number [ ]

    a. The material of construction is reported as [ ]. The text immediately below the word [ ] states that [ ] does not use [ ] Please clarify.

    b. Describe the material of construction of the cap-liner or provide a DMF number and *Letter of Authorization* (LOA) where we can obtain this information.

16. We request that you include in section 3.2.P.3.1 the name, full address, and manufacturing responsibility for the following firms:

    a. [ ] the manufacturer of the [ ]

    b. [ ], the contract facility that [ ] used for the drug product.

17. The sterile silicone-free syringe that will be co-packaged in the commercial presentation is identified as a Secondary Packaging Component in section 3.2.P.7.2. A package component that is or may be in direct contact with the drug product is considered a primary package by FDA. Please provide the following information relating to the syringe:

    a. Overall general description.

    b. Name, product code, manufacturer, physical description.

    c. Materials of construction.

    d. Specifications.

    e. Analytical Testing Methods.

18. Please provide Letters of Authorization for DMFs [ ] referenced in section 3.2.P.7.2 concerning syringe material.

19. Please submit Letters of Authorization for [ ] DMF [ ] and for [ ] DMF [ ] that are specific to Abatacept. The letters should include the DMF submission date and page numbers where information and/or data relevant to Abatacept can be located.

We are providing the above comments to give you preliminary notice of potential review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our complete review. Issues may be added, deleted, expanded upon, or modified as we review the application. If you respond to these issues during this review cycle, we may not consider your response before we take an action on your application. Following a review of the application, we shall advise you in writing of any action we have taken and request additional information if needed.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact the Regulatory Project Manager, Erik S. Laughner, M.S., at (301) 827-4358.

Sincerely,

Erik S. Laughner, M.S.
Regulatory Project Manager
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

MEMORANDUM

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

DATE: June 14, 2005

TO: Erik Laughner, Regulatory Project Manager
Division of Review Management and Policy (DRMP)
HFD-109

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: DSRCS Review of Patient Labeling for Orencia (abaptacept), BLA 1251118/0

Background and Summary

The following is the revised patient labeling for Orencia (abaptacept), BLA 1251118/0. We have simplified the wording, made it consistent with the PI, and removed unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications). We have put this PPI in the patient-friendly format that we are recommending for all patient information, although, this format is not required for voluntary PPIs. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds.

These revisions are based on draft labeling submitted by the sponsor. Patient information should always be consistent with the prescribing information. All future relevant changes to the PI should also be reflected in the PPI.

Comments and Recommendations:

1. Orencia is a biologic product that is prepared and administered intravenously only by healthcare care professionals in healthcare settings. The main purpose of FDA approved patient labeling is to provide information to patients on the safe and effective use of a drug product that is primarily used on an outpatient basis without direct supervision by a healthcare provider. Medication Guides (for products with serious and significant health

concerns, primarily for outpatient prescriptions used without direct medical supervision) and Patient Package Inserts (PPIs) for estrogen-containing products and oral contraceptives are required patient labeling that must be dispensed by a pharmacist with outpatient prescriptions. All other PPIs are voluntary and generally do not reach the patient unless they are packaged in unit-of-use packages with outpatient prescriptions dispensed directly to the patient. There is no requirement to print voluntary PPIs and no mechanism for the dispensing of any patient information in supervised medical settings. For these reasons it is unlikely that patients receiving Orencia will receive the FDA approved patient labeling.

2. The PI, **PRECAUTIONS** section, *Information for Patients* subsection states, "Patients should be provided the Orencia Patient Information Leaflet and provided an opportunity to read it prior to each treatment session." For the reasons stated in #1 above, it is unlikely that a patient will receive the Orencia Patient Information Leaflet. The sponsor should describe the mechanism they have put in place to ensure a supply and distribution of this voluntary information or they should remove the statement from the PI.

   Refer to 21 CFR 201.67 (f)(2). The PI, **PRECAUTIONS** section, *Information for Patients* subsection should contain information for healthcare providers to give to patients for the safe and effective use of the drug, e.g., counseling tips. This section should be expanded to include the important risk information that healthcare providers should give to patients via counseling.

Please call us if you have any questions.

2 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

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

TELECONFERENCE

From: Erik Laughner, M.S., Regulatory Project Manager, DRMP
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Date: 6/13/05 ~11:00AM

Sponsor: Bristol-Myers Squibb, BLA 125118

Product: Abatacept

Subject: Discuss Pharmacovigilance Plan

Sponsor Representatives: Kannan Natarajan, Group Director Biostatistics and Programming
MaryLou Skovron, Group Director Epidemiology
Teresa Simon, Associate Director Epidemiology
Dan Mac Neil, Executive Director Clinical Safety
Michael Corbo, Global Development Leader
Tony Calandra, Director, Global Regulatory Science

I along with Keith Hull and Jeff Siegel called the Sponsor to discuss with them their Abatacept Pharmacovigilance Plan (dated April 4, 2005), encompassing two draft protocols, IM101045A, and IM101045B. The Agency informed the Sponsor that we had received a ODS review of these protocols for study or high risk neoplasia and infection associated with Abatacept. The comments were read to the Sponsor.

The Agency inquired when the Sponsor would be submitting the detailed protocols and the Sponsor stated that it should be before the action date on the application. The Sponsor also informed the Agency that at the moment they have not begun the studies.

The Agency Then Discussed Other Issues

Agency: On the lymphoma ratios, have you submitted that information to us with the whole database?

Sponsor: That information was submitted with the 120 safety update.

Agency: Did you have a common malignancy table?

Sponsor: Yes, We have summarized the most common types (lung, lymphoma, breast, skin).

Agency: With other products, we have seen the SIR calculated for the top 7 malignancies and would like that. How soon can you get it to us?

Sponsor: We will generate a table of observed vs. expected malignancies for the top 7 and calculate SIR and confidence intervals. You should have it within a week.

Agency: In material submitted last week, it appears that there is an increased risk of infection with concomitant treatment of other DMARDs. Is our understanding correct that you saw rates of infection that rose with increased duration of exposure and then appeared to stabilize?

Sponsor: The higher rate of infection was apparent at the 6 month cut. We are uncertain about how the infection rate varies at earlier time points.

Agency: Do you believe that with early combination treatment with other biologic DMARD's there is no large risk of infection, but with chronic dosing, the risk increases?

Sponsor: We haven't defined it that crisply. Rather, combination therapy appears to have increased risk and we view this as an overall signal of concern.

Agency: Have you ruled out the idea of using abatacept and a TNF blocker based on these data?

Sponsor: It is possible that with a future controlled trial that combining abatacept with a TNF blocker may prove acceptable but we are recommending against that use at the present time.

Agency: Have you sent in revised labeling regarding the issue of combination therapy?

Sponsor: A combination use warning has already been mentioned in the initial labeling. We describe AE's of serious infections and caution patients.

The Sponsor agreed to submit the pharmacovigilance plan protocols and at that time would ask for additional feedback from the Agency.

The Agency also gave the Sponsor a heads up on some possible PMC requirements including a pregnancy registry, smoking registry (rate of lung cancer risk with RA and abatacept), as well as pediatric studies.

MEMORANDUM

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

DATE: June 2, 2005

TO: Jeff Siegel, MD
CDER Division of Therapeutic Biological Products
HFD-109

THROUGH: Mark Avigan, MD, CM, Director
Division of Drug Risk Evaluation (DDRE),
HFD-430

Gerald Dal Pan, MD, MHS, Director
Division of Surveillance, Research and Communication Support,
(DSRCS) HFD-410

FROM: Allen Brinker, M.D., M.S., Epidemiology Team Leader,
DDRE, HFD-430

Judy A. Staffa, Ph.D., R.Ph., Epidemiology Team Leader,
DSRCS, HFD-410

DRUG: Abatacept

BLA #: 9,391

SPONSOR: BMS

SUBJECT: High-level review of two protocols outlining study of risk of neoplasia and infection associated with abatacept following approval and utilization within the population

PID #: D050275

Introduction

Per discussion with members of the Reviewing Division (HFD-109) on May 10, 2005, each of the three therapeutic biologics approved for the treatment of rheumatoid arthritis

(infliximab, etanercept, and adalimumab) has been approved with a commitment to follow a large cohort of patients exposed during clinical trials. In a submission (received April 6, 2005) entitled **Abatacept Pharmacovigilance Plan** (dated April 4, 2005), the abatacept sponsor includes such a study, indicating a commitment to follow "over 2000 patients...for at least 5 years." In addition, the abatacept sponsor includes two additional draft protocols, IM101045A and IM101045B, for studies to be conducted following approval. This brief memorandum follows a request from HFD-109 to provide brief, high level comments on these two draft protocols which outline the study of the risk of neoplasia and hospitalized infection associated with abatacept. Although the abatacept sponsor refers to these two study descriptions as "**protocols**," these are really **protocol synopses**. Thus, without access to the full protocols, it is possible that our review of these studies may cite a concern or deficiency that is actually addressed in the complete protocols.

Protocol IM101045A

The proposed design is a nested case-control study to assess the risk of hospitalization due to infection (all hospitalized infections, hospitalized pneumonia, and all opportunistic infections) among patients with rheumatoid arthritis treated with abatacept in comparison to other disease-modifying, anti-rheumatic agents within a large cohort of individuals with commercial health insurance.

Comments:

1. *The study is to be carried out in the United Health Care (UHC) database, and the size of the*

   population (covered lives) is stated to be 20 million. This estimate includes more covered lives than FDA has been aware of in this data source; perhaps the investigators will include health care plans not accessed by FDA in the past because of the inability to obtain medical records. If medical records are not available, then appropriate prior evidence supporting the validity of the studied outcomes in claims databases should be provided. As hospitalization for infection is reasonably common, the study should be powered for this endpoint

even in the event that the population available to study is smaller than 20 million. However, the incidence of opportunistic infections (i.e., TB) is considerably less common and uptake of abatacept within the practicing community is unpredictable. Slow uptake could force extension of the expected 3 to 4-year study timetable in order to preserve study power for rare outcomes.

2. *In order to quantify the risk of infection associated with use of the drug(s), it will be important to have substantial clinical information on participants, since clinical characteristics that relate to being treated with the drug(s) may relate to the development of infections. For example, patients with more advanced disease may be placed on these medications, and it might be the case that those with more advanced disease would also be predisposed to infection. Claims data will not have all the clinical information necessary to account for such potential confounders, since these databases are designed for administrative purposes.*

3. *When operationalizing the criteria that will be used to assess patient exposure to biologic disease modifying drugs (BDMs), specific attention should be paid to the fact that these drugs are injectable and therefore may be billed either as services provided by physicians (e.g., CPT procedure codes), or prescriptions dispensed from pharmacies (e.g., NDC codes) which are then administered at home or in the physican's office. An appropriate understanding of the billing methods used will insure complete ascertainment of the drug-exposed population.*

4. *For patients over the age of 65 years, Medicare is the primary insurer; the health plans within UHG are typically secondary insurers and only pay for claims denied by Medicare. Therefore, claims paid by Medicare will not appear in UHG data – this will result in incomplete claims for hospitalized infections (the outcome of interest), as well as possibly physician outpatient claims for administering the drugs (exposures of interest). Efforts need to be made to understand the extent of missing information on outcomes and exposures of interest in the elderly population and to determine whether a valid study of this*

type can be conducted of this issue in this database for this group, or whether they should be excluded.

5. *Although the protocol synopsis states that risk models will be developed using "propensity-score" matching, this technique, like other modeling processes (e.g., logistic models), is based on the extent of available data. Thus, "propensity-score matching" cannot make up for important clinical data that is not included in claims data. It will be vital in any analysis to collect important clinical data from at least a sample of the control group in order to address confounding and/or channeling.*

Protocol IM101045B

A cohort study to assess the risk of malignancies and infection in patients with rheumatoid arthritis treated with abatacept in comparison to other disease-modifying, anti-rheumatic agents within 2 existing registries containing patients with rheumatoid arthritis.

Comments:

1. *The protocol sites two specific registries of individuals with rheumatoid arthritis: the National Data Bank for Rheumatic Diseases (NDB) and the Consortium of Rheumatology Researchers of North America (CORRONA) database. Inclusion of patients from registries outside the US will also be considered. A recent (Nov 2004) article[1] using the NDB reported a rheumatoid arthritis cohort of approximately 21,000. A recent (Feb 2005) article[2] citing the CORRONA database reported approximately 3,000 patients, including patients with both rheumatoid arthritis and osteoarthritis. The protocol includes an estimate that a minimum of 5,000 patients initiating treatment with abatacept will accrue 20,000 patient-years experience on drug. This estimate is predicated to some degree by numerous factors, including marketing forces. If uptake is slower than anticipated, then the study will need to be extended in order to preserve study power.*

2. *The protocol states that multiple efforts will be undertaken to locate the status of patients who have left the registry. We would encourage all such efforts to limit patients lost-to-follow-up and censor data from such patients to the last visit in which their status (yes/no) was ascertained.*

We appreciate that the sponsor recognizes that although studying the outcome of hospitalized infections in automated claims data appears appropriate, that studying the risk of malignancies in such data would be inappropriate. Given the relatively long latencies that may be associated with drug-associated malignancies, maximizing patient follow up in the cited registries will be a key feature of the ultimate validity of the study.

3. It is of interest to obtain detailed clinical information on patients who develop certain opportunistic infections, such as TB, while treated with abatacept. To this end, access to medical records, and appropriate follow-up for this small sub-set of patients should be considered. Results of such a study might guide strategies to mitigate risk for opportunistic infections in the future. For example, an evaluation of TB cases might be planned to determine:

- *whether patients were at increased risk for TB due to demographic characteristics*
- *whether patients were screened with PPD skin testing prior to treatment with abatacept,*
- *results of PPD skin testing and/or other TB screening measures*
- *whether patients were treated with a TB regimen such as INH during treatment with abatacept*

Other comments on proposed studies:

For both studies, ODS requests that the sponsor submit full detailed protocols, when available, for our review and comment.

References

1. Wolfe F, Michaud K. Fatigue, rheumatoid arthritis, and anti-tumor necrosis factor therapy: an investigation in 24,831 patients. J Rheumatol 2004;31(11):2115-20.

2. Greenberg JD, Bingham CO 3rd, Abramson SB, et al. Reed G, Sebaldt RJ, Kremer J. Effect of cardiovascular comorbidities and concomitant aspirin use on selection of cyclooxygenase inhibitor among rheumatologists. Arthritis Rheum 2005;53(1):12-7.

Allen Brinker, M.D., M.S.,
Epidemiology Team Leader, DDRE, HFD-430

Judy A. Staffa, Ph.D., R.Ph.,
Epidemiology Team Leader, DSRCS, HFD-410

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

TELECONFERENCE

From: Erik Laughner, M.S., Regulatory Project Manager, DRMP
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Date: 5/31/05 ~1:00PM

Sponsor: Bristol-Myers Squibb, BLA 125118

Product: Abatacept

Subject: Request for information

Sponsor Representative: Dr. Anthony J. Calandra; Bristol-Myers Squibb

I called Dr. Anthony J. Calandra to let him that we would be faxing him the filing letter for 125118 today. In addition, Joy Williams, product reviewer, had asked me to relay a request for information to Dr. Calandra for the CMC reviewable unit:

"Review of your BLA 125118 has indicated that minimal information is supplied regarding the human immunoglobulin G1 constant region portion of the CTLA4Ig fusion protein. You have stated [redacted] but have not included data to indicate how this change has affected functional properties of the Fc region. Specifically, we would like you address and to include results of any experiments performed to assess the capacity of the altered Fc region to fix complement, to bind to human Fc receptors, or to otherwise impact the functions associated with the Fc region of immunoglobulin."

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125118/0

MAY 3 1 2005

Bristol-Myers Squibb Company
Attention: Anthony J. Calandra, Ph.D.
Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Dr Calandra:

This letter is in regard to your biologics license application (BLA) submitted under section 351 of the Public Health Service Act.

We have completed an initial review of your application dated April 1, 2005, for Abatacept to determine its acceptability for filing. Under 21 CFR 601.2(a) we have filed your application today. The user fee goal date is October 1, 2005. This acknowledgment of filing does not mean that we have issued a license nor does it represent any evaluation of the adequacy of the data submitted.

While conducting our filing review, we identified potential review issues and will be communicating them to you on or before June 14, 2005.

Please refer to http://www.fda.gov/cder biologics/default.htm for important information regarding therapeutic biological products, including the address for submissions Effective Oct 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact the Regulatory Project Manager, Erik S. Laughner, M.S., at (301) 827-4358.

Sincerely,

Earl Dye

Earl S. Dye, Ph.D.
Director
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Compliance
Therapeutics Facilities Review Branch

CONVERSATION RECORD

Date:	May 26, 2005
Center Representatives:	Ann L. deMarco, CDER/OC/DMPQ/TFRB, HFD-328 ald 12-14-05 Erik Laughner, HFD-109
Organization Representatives	Anthony Calandra, Director Global Regulatory Strategy
Organization	Bristol-Myers Squibb
Subject:	STN 125118/0
Product:	Abatacept (Orencia®) lyophilized powder, 250 mg/vial
To:	File for STN 125118/0

Summary of Conversation:

I requested the name and address for *all* facilities that perform contract services relating to Abatacept. None are listed in the manufacturer sections of the BLA (3.2.S.2.1 and 3.2.P.3.1) which should include contract testing and manufacturing facilities. I informed them I had identified three contractors that should be listed from reading batch records and the BLA, namely, [ ], and the firm that [ ] I explained that I need to be sure that I have a full list of contractors as soon as possible since the compliance status of each must be determined prior to BLA approval.

Concerning information about the syringe filed in section 3.2.P.7.2 of the BLA, I explained that the 510k was filed by [ ]. device listing is from [ ] Based upon this information, it does not appear that [ ] manufacturer as Dr. Calandra stated. I requested they verify the name and address of the facility where the syringe is manufactured and of the firm that sterilizes the syringe. I also asked them to determine what mode of sterilization is used, [ ]

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

TELECONFERENCE

ESL

From: Erik Laughner, M.S., Regulatory Project Manager, DRMP
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Date: 5/24/05 3:00 PM

Sponsor: Bristol-Myers Squibb, BLA 125118

Product: Abatacept

Subject: Need for Advisory Committee

Sponsor Representative: Dr. Anthony J. Calandra and others; Bristol-Myers Squibb

I, along with Keith Hull and Johanna Clifford called Dr. Anthony J. Calandra and explained to him that an internal decision had been made to take this application to advisory committee on the grounds that it was a NME, and not because of any obvious safety concerns.

Dr. Calandra was informed that Johanna Clifford is the Executive Secretary for this committee and she stated that she would be sending a letter regarding logistics and that the tentative date for the meeting will be September 15-16. She also mentioned that there was an attempt to move up this date to the beginning of September. The meeting will most likely take place in the AC conference room which has a capacity of ~150 people.

Dr. Calandra raised some concern regarding the timing of this advisory committee, the labeling review process, and the action date of the application; assuming it was in fact a priority review. Dr. Hull stated that he would speak with Jeff Seigel regarding this and get back to the sponsor.

Dr. Calandra inquired as the status of the application filing and he was informed that a formal letter will be issue by May 31, 2005. Dr. Calandra also inquired about the pharmacovigiliance plan submitted to the Agency for review. I informed him that once the clinical team can get together with the Office of Drug Safety to finalize our thoughts, we can then arrange a TCON.

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

Memorandum

Date: May 23, 2005

From: *Erik S. Laughner, DRMP, HFD-108*

To: STN 125118

Subject: Meeting Summary

Meeting Date: May 20, 2005 **Time:** 11:00AM

Meeting Requestor/Sponsor: Internal

Product: abatacept

Proposed Use: Treatment of Rheumatoid Arthritis.

Type of meeting: Internal

Meeting Purpose: To determine whether STN may be filed.

DISCUSSION:

Attendance was taken and the major milestones for this application reviewed.

Pre-Clinical

Content and format of the electronic submission were suitable for filing. The review team was informed that the toxicology reviewable unit (RU) was largely complete and that a discipline review (DR) letter was sent to the Sponsor with no major issues identified. Some suggested changes to the labeling section regarding pregnancy and possible CAC involvement on carcinogenicity finding were identified. This raised the issue that this is BMS' first biologic and as such the Sponsor has chosen to treat this biologic as a small molecule and follow those regs.

Clinical

Content and format of the electronic submission were suitable for filing. The clinical team relayed to the review group that a pharmacovigiliance plan had been submitted by the Sponsor and that ODS was specifically involved. Future PMC studies were being evaluated which include a long term study to look at 1000-1500 patients for 5yrs also the development of a smoking registry for lung cancer incidence.

The issue of an advisory committee determination was raised and a decision had still not been made.

CMC/Facilities

Content and format of the electronic submission were suitable for filing. However, there most likely will be some deficiencies identified which will be conveyed to the Sponsor either in the filing letter or the 74 day letter.

The CMC/facilities team informed the review group that [redacted] A June 20th inspection is planned and they hope to have their review substantially complete by the end of July.

FDA Attendees:

Erik Laughner
James Reese
Keith Hull
Jeff Siegel
Anita O'Connor
Kyung Lee
Hsien Ju
Dianne Tesch
Ellis Unger
Hanan Ghantous
Joy Williams
Wendy Shores
Ed Max
Susan Kirshner
Ann deMarco
Anil Rajpal

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20852

Our STN: BL 125118

MAY 17 2005

Bristol-Myers Squibb Company
Attention: Anthony J. Calandra, Ph.D.
Director, Global Regulatory Strategy
P.O. Box 4000
Princeton, New Jersey 08543-4000

Dear Dr Calandra:

We have reviewed the PRE-CLINICAL reviewable unit to your biologics license application (BLA) for Abatacept, dated November 15, 2004. At this time, we have not identified any potential review issues and do not require any additional studies. However, we do have the following comments:

1. Changes in immune function observed at a dose of 200mg/kg in the F1-generation females which consisted of an increase (9-fold) in the T-cell-dependent antibody response and inflammation of the thryoid gland of one rat should be added to the pregnancy category section of the labeling.

2. The mouse carcinogenicity study will be submitted to the executive carcinogenicity assignment committee (CAC) for review. Following the review by the CAC, we shall advise you in writing if there are any changes to the labeling text on carcinogenicity.

We are providing these comments before completing our review of your entire application to give you advance notice of PRE-CLINICAL issues that we have identified. These comments are subject to change as we complete the review of your application. You may, but are not required to, respond to these comments. If you respond, we may or may not consider your response before taking a complete action on your application. If we determine that your response constitutes a major amendment, we will notify you of this decision in writing. We are continuing to review the remaining sections of your application. We will send you final comments, to which you must respond, after completing our review.

Please refer to http://www.fda.gov/cder/biologics/default.htm for important information regarding therapeutic biological products, including the addresses for submissions. Effective Oct. 4, 2004, the new address for all submissions to this application is:

CDER Therapeutic Biological Products Document Room
Center for Drug Evaluation and Research
Food and Drug Administration
12229 Wilkins Avenue
Rockville, Maryland 20852

If you have any questions, please contact the Regulatory Project Manager, Erik Laughner, M.S., at (301) 594-6218.

Sincerely,

Martin Green

Martin Green, Ph.D.
Associate Director Pharmacology and Toxicology
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

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

TELECONFERENCE

From: Beverly Conner, R.Ph., Pharm.D., Regulatory Project Manager, DRMP
Division of Review Management and Policy
Office of Drug Evaluation VI
Center for Drug Evaluation and Research

Date: **4/14/05** **4:00 PM**

Subject: **Abatacept Patient Package Insert**

Sponsor Representive: Dr. Anthony J. Calandra, Bristol-Myers Squibb

I called Dr. Anthony J. Calandra and asked if he could submit a word version of the Patient Package Insert (PPI). I explained to him that DSRCS of the Office of Drug Safety will be reviewing the PPI from the perspective of patient comprehension and readability and they have requested an electronic copy of the PPI in word format for editing purposes. Dr. Calandra stated he would send the word copy by e-mail and submit a formal copy to the BLA at a later date.

I noted to Dr. Calandra that the company did not have the PPI attached to the package insert and asked what the company plans on doing. When he sent the word PPI he stated in the e-mail that the patient package insert will be attached to the physician's package insert by perforation.

Dr. Calandra was also informed that ODE VI has requested a consult for the re-evaluation of the tradename Orencia (previously found to be acceptable by CBER on 11/27/03).

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

Memorandum

DATE: **April 4, 2005**

FROM: Marc Walton, M.D.
Director
Division of Therapeutic Biological Internal Medicine Products
Office of Drug Evaluation and Research VI

SUBJECT: Designation of BLA application review status
Sponsor: Bristol-Myers Squibb Company
Product: Abatacept
Indication: Treatment of Rheumatoid Arthritis

TO: BLS File STN 125118/0

The review status of this file submitted as a BLS application is designated to be:

Standard Priority

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

Memorandum

Date: Monday, April 4, 2005; 3:30 - 6:15 PM

From: Beverly Conner, Pharm.D., RPM, DRMP, ODEVI, CDER

Subject: COMMITTEE MEETING FOR STN 125118/0

To: File - STN 125118/0

PRODUCT: Abatacept, CTLA4Ig humanized recombinant fusion protein; Proposed Tradename is Orencia.

Original BLA Application: For the treatment of Rheumatoid Arthritis

PLACE: Conference room, WOC 2, 6th FL-G

First Action Date: September 30, 2005

Review Updates

Product

- Dr. Wendy Shores gave a slide presentation on the CTLA4Ig molecule. Potential immunogenicity issues and assay validation were also discussed.

Clinical Site Monitoring

- Bioreseach Monitoring status: Dianne Tesch identified two clinical monitoring sites for inspection. They are [ ] (Investigator: E. Jane Herron Box, M.D.) and The Center for Rheumatology; located in Albany, NY (Investigator: Joel M. Kramer, M.D.).

Pharmacology/Toxicology

- Dr. Hanan Ghantous noted that numerous animal studies have been completed by the company including fetal development studies, carcinogenicity and binding studies to determine effect on immune system. A decision will need to be made as to whether the carcinogenicity studies for this biologic should be presented to the CDER Carcinogenicity Committee.

Pharmacokinetics

- Anil Rajpal, the PK reviewer noted that there was a process change from Phase 1 to Phase 3. The company has decided to dose all patients on a body weight basis of 10 mg/kg. Lower weight subjects appear to have less efficacy.

Clinical

- Dr. Keith Hull, the clinical reviewer presented an overview of the clinical reviewable unit. Additional analyses for the clinical section data were suggested and discussed by the committee members. The statistical analysis of clinical information is ongoing per Dr. Kyung Lee.

Other Issues

- Tradename issues: DMETS has been consulted for evaluation of the tradename Orencia. Originally the tradename was submitted to CBER for review and was conditionally approved.

- Catherine Gray be the DDMAC representative for promotional labeling issues.

- The need for an advisory committee meeting for abatacept was briefly discussed, a decision will need to be made between the filing and midcycle meeting.

- A one-hour filing meeting has been set-up for May 20, 2005.

MILESTONES

The Full Application for Abatacept from Bristol Myers received April 1, 2005. The milestones listed below for Abatacept were discussed during the meeting.

MILESTONES

Non-clinical Pharmacology and Toxicology
Review for substantial completeness: (goal date 1/15/05) completed filing memo 1/13/05
Discipline review action for the non-clinical Pharmacology and Toxicology: May 18, 2005

Clinical and Clinical Pharmacology
Review for substantial completeness: Goal Date: February 20, 2005
Discipline review action for Clinical and Clinical Pharmacology: June 23, 2005

Complete Application received - Clock started April 1, 2005

Committee Assignment Goal date: April 15, 2005

First Committee Meeting Goal Date: April 22, 2005

Filing Meeting Goal Date: May 16, 2005

Filing Action Goal Date: May 31, 2005

Deficiencies identified action date: June 14, 2005

First Action Due Date: Friday, September 30, 2005

Attendees:

Marc Walton
Karen Weiss
Leah Ripper
Rigoberto Roca
Bob Rappaport
Eric Laughner
Keith Hull
Kyung Lee
Hanan Ghantous
Anil Rajpal
Wendy Shores
Jeff Siegel
Amy Rosenberg
Aloka Chakravaraty
Joy Williams
Bo Zhen
Diane Tesch
Beverly Conner

✓ Transcript and Quick minutes

____Sponsor's Briefing Material

____ FDA'S Briefing Material

5 PAGES REMOVED. SEE THE ADVISORY COMMITTEE MEETING INFORMATION LOCATED ON THE FDA WEBSITE BELOW:

http://www.fda.gov/ohrms/dockets/ac/

5 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

_____ § 552(b)(5) Draft Labeling

8-15-05

LICENSING ACTION RECOMMENDATION

Applicant: Bristol-Myers Squibb **STN:** 125118/0

Product:

Orencia (abatacept)

Indication / manufacturer's change:

For 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 an inadequate response to one or more DMARDs, such as MTX or a TNF antagonist.

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

RECOMMENDATION BASIS

■ Review of Documents listed on Licensed Action Recommendation Report

■ Inspection of establishment ☐ Inspection report included

■ BiMo inspections completed ■ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

☐ Review of Environmental Assessment ☐ FONSI included ■ Categorical Exclusion

■ Review of labeling Date completed 12/23/05 ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

■ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch N/A

CLEARANCE – REVIEW

Review Committee Chairperson: [signature] Date: 12/22/05

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

[signature] Date: 12-22-05

[signature] Date: 12/23/05

DMPQ Division Director*: See attached Date: _____

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

■ Compliance status checked ■ Acceptable ☐ Hold Date: 12/23/05

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) [signature] Date: 12/23/05

Responsible Division Director [signature] Date: 12/23/05
(where product is submitted, e.g., application division or DMPQ)

Form DCC-201 (05/2003)

LICENSING ACTION RECOMMENDATION

Applicant: Bristol-Myers Squibb **STN:** 125118/0

Product:
Orencia (abatacept)

Indication / manufacturer's change:
For 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 an inadequate response to one or more DMARDs, such as MTX or a TNF antagonist.

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

RECOMMENDATION BASIS

■ Review of Documents listed on Licensed Action Recommendation Report

■ Inspection of establishment ☐ Inspection report included

■ BiMo inspections completed ■ BiMo report included

☐ Review of protocols for lot no.(s) _____

☐ Test Results for lot no.(s) _____

☐ Review of Environmental Assessment ☐ FONSI included ■ Categorical Exclusion

■ Review of labeling Date completed _____ ☐ None needed

CLEARANCE – PRODUCT RELEASE BRANCH

■ CBER Lot release not required

☐ Lot no.(s) in support – not for release _____

☐ Lot no.(s) for release _____

Director, Product Release Branch N/A

CLEARANCE – REVIEW

Review Committee Chairperson: Jeffrey M. Boyd Date: 12/22/05

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

Barry Cheung for A. Rosenberg Date: 12-22-05

_____ Date: _____

DMPQ Division Director*: Joseph McGuire Date: 12-22-05

* If Product Office or DMPQ Review is conducted

CLEARANCE – APPLICATION DIVISION

■ Compliance status checked ■ Acceptable ☐ Hold Date: _____

☐ Cleared from Hold Date: _____

☐ Compliance status check Not Required

Regulatory Project Manager (RPM) _____ Date: _____

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

Form DCC-201 (05/2003)

BLA/NDA/PMA
Review Committee Assignment Memorandum

❑Initial Assignment
✪Change

STN: 125118/0

Applicant: Bristol Myers Squibb Co.

Product: Abatacept (CTLA4Ig)

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
	Reg. Project Manager	Admin/Regulatory		
	Reviewer	Admin/Regulatory		
Susan Kirshner	Reviewer	Product*	Barry Cherney	4/1/05
Ennan Guan	Reviewer	Product*	Barry Cherney	4/1/05
	Reviewer	Product		
	Reviewer	Clinical		
	Reviewer	Clinical		
	Reviewer	Clinical Pharmacology		
	Reviewer	Pharm/Tox		
	Reviewer	Biostatistics		
Dianne Tesch	Reviewer	BiMo	Leslie Ball	3/15/05
Hyon Kwon	Reviewer	Safety Evaluator	Robert Kang	4/7/05
	Reviewer	Facility*		
	Reviewer	Facility		
	Reviewer	Pharm/Tox		
	Reviewer	Clin/Imaging		
Catherine Gray	Reviewer	Labeling: DDMAC	Lesley Frank	4/7/05
Jeanne Best	Reviewer	Labeling: DMETS	Tara Turner	4/13/05

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date
L. Lloyd Johnson	reviewer	BIMO	Leslie Ball	3/15/05

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Name Printed _____ Signature_____ Date_____

Memo entered in RMS by: _____ Date: _____ QC by: _____ Date: _____

BLA/NDA/PMA
Review Committee Assignment Memorandum

STN: 125118/0

✪ Initial Assignment
❑ Change

Applicant: Bristol –Squibb Co.

Product: Abatacept (CTLA4Ig)

Addition of committee members

Name	Reviewer Type*	Job Type	Assigned by	Date
Beverly Conner	Reg. Project Manager	Admin/Regulatory	Kay Schneider	1/3/05
	Reviewer	Admin/Regulatory		
Wendy Shores	Reviewer	Product*	Amy Rosenberg	1/17/05
Joy Williams	Reviewer	Product*	Amy Rosenberg	1/17/04
Ed Max	Reviewer	Product	Amy Rosenberg	2/1/05
Keith Hull	~~Reviewer~~ Chairperson	Clinical	Jeff Siegel	1/14/05
	Reviewer	Clinical		
Anil Rajpal	Reviewer	Clinical Pharmacology	Dave Green	1/28/05
Anita O'Connor	Reviewer	Pharm/Tox	Dave Green	1/16/05
Kyung Lee	Reviewer	Biostatistics	Bo Zheng	1/14/05
J. Lloyd Johnson	Reviewer	BiMo		1/14/05
	Reviewer	Safety Evaluator		
Ann L. deMarco	Reviewer	Facility*	Michael Smedley	1/18/04
Gilbert Salud	Reviewer	Facility	Michael Smedley	1/18/05
Hanan Ghantous	Reviewer	Pharm/Tox	Dave Green	1/13/05
Hsien Ju	Reviewer	Clin/Imaging	Lydia Martynec	1/13/05
	Reviewer			

*add inspector, if applicable

Deletion of Committee Member

Name	Reviewer Type*	Job Type	Changed by	Date

***reviewer types**: chairperson, consultant reviewer, regulatory coordinator, reviewer, and reg. project mgr (RPM)

Submitted by RPM:

Beverly Conner
Name Printed

Beverly Conner
~~Signature~~

2/3/05
Date

Memo entered in RMS by: _____ Date: _____ QC by: LB Date: 4-7-05

Regulatory Filing Review Memo for BLAs and Supplements

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

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

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

STN: 125118 Product: Abatacept Applicant: Bristol-Myers Squibb

Final Review Designation (circle one): Standard (Priority)

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

Submission organization (circle one): Traditional CTD

Filing Meeting: Date 05/20/05 Committee Recommendation (circle one): (File) RTF

RPM: S.K SK 05/20/05
(signature/date)

Attachments:

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

Part A. Regulatory Project Manager (RPM)

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed	Y N	
❑ including list of all establishment sites and their registration numbers	Y N	
❑ If foreign applicant, US Agent signature.	Y N	N/A
Comprehensive Table of Contents	Y N	
Debarment Certification with correct wording (see * below)	Y N	
User Fee Cover Sheet	Y N	
User Fee payment received	Y N	
Financial certification &/or disclosure information	Y N	
Environment assessment or request for categorical exclusion (21 CFR Part 25)	Y N !	CANT FIND IN SUBMISSION. CALLED SPONSOR TO LOCATE OR SEND IN AS AMENDMENT
Pediatric rule: study, waiver, or deferral	Y N	
Labeling:	Y N	
❑ PI –non-annotated	Y N	
❑ PI –annotated	Y N	
❑ PI (electronic)	Y N	
❑ Medication Guide	Y N	
❑ Patient Insert	Y N	
❑ package and container	Y N	
❑ diluent	Y N	
❑ other components	Y N	
❑ established name (e.g. USAN)	Y N	
❑ proprietary name (for review)	Y N	

* The Debarment Certification must have correct wording , e.g. "I, the undersigned, hereby certify that XXX Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food Drug, and Cosmetic Act in connection with the studies listed in Appendix XXX." Applicant may not use wording such as "To the best of my knowledge,.."

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization of paper and electronic components sufficient to permit substantive review?: Examples include:	Y N	
❑ legible	Y N	
❑ English (or translated into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	
❑ summary reports reference the location of individual data and records	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
❑ protocols for clinical trials present	Y N	
❑ all electronic submission components usable (e.g. conforms to published guidance)	Y N	
companion application received if a shared or divided manufacturing arrangement	Y N	
if CMC supplement:		
❑ description and results of studies performed to evaluate the change	Y N	
❑ relevant validation protocols	Y N	
❑ list of relevant SOPs	Y N	
if clinical supplement:		
❑ changes in labeling clearly highlighted	Y N	
❑ data to support all label changes	Y N	
❑ all required electronic components, including electronic datasets (e.g. SAS)	Y N	
if electronic submission:		
❑ required paper documents (e.g. forms and certifications) submitted	Y N	

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

Has orphan drug exclusivity been granted to another drug for the same indication?
If yes, review committee informed? N/A

Does this submission relate to an outstanding PMC? N/A

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

- Name:
- Dates:

Recommendation (circle one): File RTF

RPM Signature: Branch Chief concurrence:

STN 125118/0 Product Abatacept

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

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	Y	(N)	
Quality overall summary [2.3]	Y	N	
● Drug Substance	(Y)	N	
● Drug Product	(Y)	N	
● Facilities and Equipment	(Y)	N	
❑ Adventitious Agents Safety Evaluation	Y	N	
❑ Novel Excipients	Y	N	
● Executed Batch Records	(Y)	N	
❑ Method Validation Package	Y	N	
● Comparability Protocols	(Y)	N	Statement that none are submitted.

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	Y	N	
Drug Substance [3.2.S]			
❑ general info	Y	N	
o nomenclature			
o structure (e.g. sequence, glycosylation sites)			
o properties			
● manufacturers (names, locations, and responsibilities of all sites involved)	(Y)	N	
● description of manufacturing process	(Y)	N	
● batch numbering and pooling scheme			
● cell culture and harvest			
● purification			
● filling, storage and shipping			
❑ control of materials	Y	N	
● raw materials and reagents (Y)			
o biological source and starting materials			
o cell substrate: source, history, and generation			
o cell banking system, characterization, and testing			
❑ control of critical steps and intermediates	Y	N	
● justification of specifications (Y)			
● analytical method validation (Y)			endotoxin only reviewed
o reference standards			
o stability			
● process validation (prospective plan, results, analysis, and	(Y)	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
conclusions)		
❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	Y N	
❑ characterization of drug substance	Y N	
❑ control of drug substance	Y N	
● specification (Y)		
● justification of specs.		
o analytical procedures		
o analytical method validation		
o batch analyses		***Batch analysis consistency:*** Confirmatory lots do not appear to be consecutive from lot number codes.
● consistency (3 consecutive lots) (N) see comment →		
o justification of specs.		
❑ reference standards	Y N	
● container closure system	(Y) N except as noted	***Container/closure system:*** No DMF for cap liner C J description of materials of construction are contradictory about use of C J [3.2.S.6.2.F02 (p.1508)]
❑ stability	Y N	
❑ summary		
❑ post-approval protocol and commitment		
❑ pre-approval		
o protocol		
o results		
o method validation		
Drug Product [3.2.P]		
● description and composition	(Y) N	
● pharmaceutical development	(Y) N	
● manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N except as noted	***Manufacturers:*** Missing manufacturers--- 1) Firm that prepares C J stopers 2) Firm that sterilizes kit syringes
❑ batch formula	Y N	
● description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
● controls of critical steps and intermediates	(Y) N	
● process validation including aseptic processing & sterility assurance:	(Y) N	
● 3 consecutive lots		
● other needed validation data		
❑ control of excipients (justification of specifications; analytical method validation; excipients of	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
human/animal origin) ❑ control of drug product (justification of specifications; analytical method validation) ■ container closure system [3.2.P.7] ● specifications (vial, elastomer, drawings) ● availability of DMF ● closure integrity ● administration device(s) ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	Y N Ⓨ N except as noted Y N	***Availability of DMFs:*** 1) Letter of authorization (LOA) for DMF [ ] ready-to-sterilize [ ] stoppers, is [ ], not Abatacept 2) No LOAs submitted for syringe [ ] DMFs [ ] ***Administration device:*** 1) Syringe listed as secondary pkg [3.2.P.7.2]. Per FDA guidance on container/closures, this is a primary pkg *(pkg that is or may be in direct contact with dosage forms.)* 2) No description or specs for syringe
Diluent (vials or filled syringes) [3.2P'] ❑ description and composition of diluent ❑ pharmaceutical development ❑ manufacturers (names, locations, and responsibilities of all sites involved) ❑ batch formula ❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities) ❑ controls of critical steps and intermediates ❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data ❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients) ❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities) ❑ reference standards	Y N Y N Y N Y N Y N Y N Y N Y N Y N	Not applicable

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity	Y N	Not applicable
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N	
Other components to be marketed (full description and supporting data, as listed above):		Not applicable
❑ other devices	Y N	
❑ other marketed chemicals (e.g. part of kit)	Y N	
Appendices for Biotech Products [3.2.A]		
❑ facilities and equipment ❑ manufacturing flow; adjacent areas ❑ other products in facility ❑ equipment dedication, preparation and storage ❑ sterilization of equipment and materials ❑ procedures and design features to prevent contamination and cross-contamination	(Y) N	
❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production	Y N	
❑ novel excipients	Y N	
USA Regional Information [3.2.R]		
❑ executed batch records	(Y) N	
❑ method validation package	(Y) N	Endotoxin only reviewed
❑ comparability protocols	Y (N)	None submitted

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review? ❑ legible ❑ English (or translated into English) ❑ compatible file formats ❑ navigable hyper-links ❑ interpretable data tabulations (line listings) & graphical displays ❑ summary reports reference the location of individual data and records ❑ all electronic submission components usable	(Y) N (Y) N (Y) N (Y) N (Y) N (Y) N (Y) N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	(Y) N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	(Y) N	
includes data demonstrating consistency of manufacture	(Y) N	
includes complete description of product lots and manufacturing process utilized for clinical studies	(Y) N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	Y N	
certification that all facilities are ready for inspection	Y (N)	Information was provided verbally and in letter dated 4/13/05.
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility ☐ ☐	Y N Y N Y N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	Y N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	(Y) N	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	(Y) N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	(Y) N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	Not applicable

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

The issues noted in this review would not preclude filing. They can be addressed in a 74-day letter.

Recommendation (circle one): (File) RTF

Reviewer: Ann L deMarco 5-24-05 Type (circle one): Product (Chair) (Facility (DMPQ))
(signature/ date)

Concurrence:
Branch/Lab Chief: [signature] Division. Director: _____
(signature/ date) (signature/ date)
5/25/05

STN 125118 Product Abatacept

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

CTD Module 2 Contents	Present?		If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y)	N	
Introduction to the summary documents (1 page) [2.2]	(Y)	N	
Quality overall summary [2.3]	(Y)	N	
❑ Drug Substance	(Y)	N	
❑ Drug Product	(Y)	N	
❑ Facilities and Equipment	(Y)	N	
❑ Adventitious Agents Safety Evaluation	(Y)	N	
❑ Novel Excipients	(Y)	N	
❑ Executed Batch Records	(Y)	N	
❑ Method Validation Package	(Y)	N	
❑ Comparability Protocols	Y	(N)	N/A

CTD Module 3 Contents	Present?		If not, justification, action & status
Module Table of Contents [3.1]	(Y)	N	
Drug Substance [3.2.S]			
❑ general info o nomenclature o structure (e.g. sequence, glycosylation sites) o properties	(Y)	N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y)	N	
❑ description of manufacturing process o batch numbering and pooling scheme o cell culture and harvest o purification o filling, storage and shipping	(Y)	N	
❑ control of materials o raw materials and reagents o biological source and starting materials o cell substrate: source, history, and generation o cell banking system, characterization, and testing	(Y)	N	
❑ control of critical steps and intermediates o justification of specifications o analytical method validation o reference standards o stability	(Y)	N	
❑ process validation (prospective plan, results, analysis, and	(Y)	N	

CTD Module 3 Contents	Present?	If not, justification, action & status
conclusions) ❑ manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)	(Y) N	
❑ characterization of drug substance	(Y) N	
❑ control of drug substance o specification o justification of specs. o analytical procedures o analytical method validation o batch analyses o consistency (3 consecutive lots) o justification of specs.	(Y) N	
❑ reference standards	(Y) N	
❑ container closure system	(Y) N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	(Y) N	
Drug Product [3.2.P]		
❑ description and composition	(Y) N	
❑ pharmaceutical development	(Y) N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	(Y) N	
❑ batch formula	(Y) N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	(Y) N	
❑ controls of critical steps and intermediates	(Y) N	
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	(Y) N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of	(Y) N	

CTD Module 3 Contents	Present?	If not, justification, action & status
human/animal origin)		
❑ control of drug product (justification of specifications; analytical method validation)	(Y) N	
❑ container closure system [3.2.P.7] o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity o administration device(s)	(Y) N	
❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results o method validation	(Y) N	
Diluent (vials or filled syringes) [3.2P']		
❑ description and composition of diluent	Y N	N/A
❑ pharmaceutical development	Y N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
❑ batch formula	Y N	
❑ description of manufacturing process for production through finishing, including formulation, filling, labeling and packaging (including all steps performed at outside [e.g., contract] facilities)	Y N	
❑ controls of critical steps and intermediates	Y N	
❑ process validation including aseptic processing & sterility assurance: o 3 consecutive lots o other needed validation data	Y N	
❑ control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)	Y N	
❑ control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)	Y N	
❑ reference standards	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
❑ container closure system o specifications (vial, elastomer, drawings) o availability of DMF o closure integrity ❑ stability ❑ summary ❑ post-approval protocol and commitment ❑ pre-approval o protocol o results	Y N Y N	N/A
Other components to be marketed (full description and supporting data, as listed above): ❑ other devices ❑ other marketed chemicals (e.g. part of kit)	(Y) N Y (N)	N/A
Appendices for Biotech Products [3.2.A] ❑ facilities and equipment o manufacturing flow; adjacent areas o other products in facility o equipment dedication, preparation and storage o sterilization of equipment and materials o procedures and design features to prevent contamination and cross-contamination ❑ adventitious agents safety evaluation (viral and non-viral) e.g.: o avoidance and control procedures o cell line qualification o other materials of biological origin o viral testing of unprocessed bulk o viral clearance studies o testing at appropriate stages of production ❑ novel excipients	Y N (Y) N (Y) N	See response of Facility Reviewer
USA Regional Information [3.2.R] ❑ executed batch records ❑ method validation package ❑ comparability protocols	(Y) N (Y) N Y (N)	N/A

CTD Module 3 Contents	Present?	If not, justification, action & status
Literature references and copies [3.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	(Y) N	
❑ legible	(Y) N	
❑ English (or translated into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
❑ summary reports reference the location of individual data and records	(Y) N	
❑ all electronic submission components usable	(Y) N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	(Y) N	
includes production data on drug substance and drug product manufactured in the facility intended to be licensed (including pilot facilities) using the final production process(es)?	(Y) N	
includes data demonstrating consistency of manufacture	(Y) N	
includes complete description of product lots and manufacturing process utilized for clinical studies	(Y) N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
certification that all facilities are ready for inspection	Y N	see response of Facility Reviewer
data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	(Y) N	
if not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List:	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
☐ LAL instead of rabbit pyrogen ☐ mycoplasma ☐ sterility ☐ ☐	(Y) N (Y) N (Y) N	
identification by lot number, and submission upon request, of sample(s) representative of the product to be marketed; summaries of test results for those samples	(Y) N	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y N	see response of facility reviewer
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y N	See response of facility reviewer
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y N	See response of facility reviewer
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y (N)	N/A

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

Recommendation (circle one): File RTF

Reviewer: [signature] 5/24/05 Type (circle one): Product (Chair) Facility (DMPQ)
(signature/ date)

Concurrence:
Branch/Lab Chief: [signature] (signature/ date)

Division. Director: [signature] 5-24-05 for A. Rosenberg
(signature/ date)

Part C – Non-Clinical Pharmacology/Toxicology Reviewer(s)

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Non-clinical overview [2.4]	(Y) N	
Non-clinical summary [2.6]	(Y) N	
❑ Pharmacology	(Y) N	
❑ Pharmacokinetics	(Y) N	
❑ Toxicology	(Y) N	

CTD Module 4 Contents	Present?	If not, justification, action & status
Module Table of Contents [4.1]	(Y) N	
Study Reports and related info. [4.2]	(Y) N	
❑ Pharmacology	(Y) N	
❑ Pharmacokinetics	(Y) N	
❑ Toxicology	(Y) N	
Literature references and copies [4.3]	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	(Y) N	
❑ legible	(Y) N	
❑ English (or translated into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocol-specified (as opposed to a different, post-hoc analysis) and other critical statistical analyses included	(Y) N	
❑ all electronic submission components usable	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials (when significant changes in manufacturing processes or facilities have occurred)	(Y) N	
for each non-clinical laboratory study, either a statement that the study was conducted in compliance with the good laboratory practice requirements set forth in 21 CFR Part 58 or, if the study was not conducted in compliance with such regulations, a brief statement justifying the non-compliance	(Y) N	

Examples of Filing Issues	Yes?	If not, justification, action & status
animal reproduction studies included, if the biological product is to be administered to people with reproductive potential, unless an explanation of why such studies are not applicable	Y N	
includes carcinogenicity and/or reproductive and developmental toxicology studies deemed necessary by well established agency interpretation or communication during the IND review process	Y N	

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

Recommendation (circle one): File RTF

Pharm/Tox reviewer: H. Glut 1/13/05
(signature/ date)

Branch Chief concurrence: Andrea Weiss 1-13-05
(signature/ date) for Martin D Green

Division. Director concurrence: 1/13/05
(signature/ date)

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	Y N	
Introduction to the summary documents (1 page) [2.2]	Y N	
Clinical overview [2.5]	Y N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	Y N	
❑ Biopharmaceutics and associated analytical methods	Y N	
❑ Clinical pharmacology [includes immunogenicity]	Y N	
❑ Clinical Efficacy [for each indication]	Y N	
❑ Clinical Safety	Y N	
❑ Synopses of individual studies	Y N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	Y N	
Tabular Listing of all clinical studies [5.2]	Y N	
Study Reports and related information [5.3]	Y N	
❑ Biopharmaceutic	Y N	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	
❑ Pharmacokinetics (PK)	Y N	
❑ Pharmacodynamic (PD)	Y N	
❑ Efficacy and Safety	Y N	
❑ Postmarketing experience	Y N	
❑ Case report forms	Y N	
❑ Individual patient listings (indexed by study)	Y N	
o electronic datasets (e.g. SAS)	Y N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	Y N	
❑ legible	Y N	
❑ English (or certified translation into English)	Y N	
❑ compatible file formats	Y N	
❑ navigable hyper-links	Y N	
❑ interpretable data tabulations (line listings) & graphical displays	Y N	

Examples of Filing Issues	Yes?	If not, action & status
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocols for clinical trials present	(Y) N	
❑ all electronic submission components usable	(Y) N	
statement for each clinical investigation:		
❑ conducted in compliance with IRB requirements	(Y) N	
❑ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	(Y) N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	(Y) N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

Examples of Filing Issues	Yes?		If not, action & status
data supporting the proposed dose and dose interval	(Y)	N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y)	N	
adequate characterization of product specificity or mode of action	(Y)	N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	(Y)	N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	(Y)	N	
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y)	N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?		
101100	(Y)	N	(Y)	N	NR	(Y)	N	Y	N	(NR)
101101	(Y)	N	(Y)	N	NR	(Y)	N	(Y)	N	NR
101102	(Y)	N	(Y)	N	NR	(Y)	N	(Y)	N	NR
101029	(Y)	N	(Y)	N	NR	(Y)	N	(Y)	N	NR
101031	(Y)	N	(Y)	N	NR	(Y)	N	(Y)	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR
	Y	N	Y	N	NR	Y	N	Y	N	NR

Y= yes; N=no; NR=not required

STN 125118 Product ABATACEPT Part D Page 4

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

N/A

Is clinical site(s) inspection (BiMo) needed?

Yes. Consult Submitted.

Is an Advisory Committee needed?

~~Not at this time~~ Upon further consideration it was decided that an advisory committee would be needed.

5 5/31/05

Recommendation (circle one): File RTF

Reviewer: [signature] 5/31/05 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: [signature] 5/20/05
(signature/ date)

Division. Director: [signature] for MKW 5/31/05
(signature/ date)

STN 125118 Product Abatacept

Part D – Clinical (Pharmacology, Efficacy, Safety, and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
◻ Biopharmaceutics and associated analytical methods	(Y) N	
◻ Clinical pharmacology [includes immunogenicity]	(Y) N	
◻ Clinical Efficacy [for each indication]	(Y) N	
◻ Clinical Safety	(Y) N	
◻ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	(Y) N	
◻ Biopharmaceutic	Y N	NA
◻ Studies pertinent to Pharmacokinetics using Human Biomaterials	Y N	NA
◻ Pharmacokinetics (PK)	(Y) N	
◻ Pharmacodynamic (PD)	(Y) N	
◻ Efficacy and Safety	(Y) N	
◻ Postmarketing experience	Y N	NA
◻ Case report forms	(Y) N	
◻ Individual patient listings (indexed by study)	(Y) N	
o electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	Y N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
◻ legible	(Y) N	
◻ English (or certified translation into English)	(Y) N	
◻ compatible file formats	(Y) N	
◻ navigable hyper-links	(Y) N	
◻ interpretable data tabulations (line listings) & graphical displays	(Y) N	

Examples of Filing Issues	Yes?	If not, action dates
☐ summary reports reference the location of individual data and records	(Y) N	
☐ protocols for clinical trials present	(Y) N	
☐ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ☐ conducted in compliance with IRB requirements	(Y) N	
☐ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(X) N	N.A
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	Y N	N.A
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	(Y) N	
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	Y N	N.A
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

STN 125118 Product Abatacept

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

Is clinical site(s) inspection (BiMo) needed?

Is an Advisory Committee needed?

Recommendation (circle one): File RTF

Reviewer: Kyung Yul Lee (signature/ date) Type (circle one): Clinical Clin/Pharm (Statistical)

Concurrence:

Branch Chief: _____ (signature/ date)

Division. Director: Alaka Chakravarty (signature/ date) 5/19/05

STN 125118/0 Product Abatacept

Part D – Clinical (Pharmacology, Efficacy, Safety,and Statistical) Reviewers

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	(Y) N	
Introduction to the summary documents (1 page) [2.2]	(Y) N	
Clinical overview [2.5]	(Y) N	
Clinical summary [2.7] (summary of individual studies; comparison and analyses across studies)	(Y) N	
❑ Biopharmaceutics and associated analytical methods	(Y) N	
❑ Clinical pharmacology [includes immunogenicity]	(Y) N	
❑ Clinical Efficacy [for each indication]	(Y) N	
❑ Clinical Safety	(Y) N	
❑ Synopses of individual studies	(Y) N	

CTD Module 5 Contents	Present?	If not, justification, action & status
Module Table of Contents [5.1]	(Y) N	
Tabular Listing of all clinical studies [5.2]	(Y) N	
Study Reports and related information [5.3]	(Y) N	
❑ Biopharmaceutic	(Y) N	
❑ Studies pertinent to Pharmacokinetics using Human Biomaterials	(Y) N	
❑ Pharmacokinetics (PK)	(Y) N	
❑ Pharmacodynamic (PD)	(Y) N	
❑ Efficacy and Safety	(Y) N	
❑ Postmarketing experience	Y (N)	N/A
❑ Case report forms	(Y) N	
❑ Individual patient listings (indexed by study)	(Y) N	
o electronic datasets (e.g. SAS)	(Y) N	
Literature references and copies [5.4]	(Y) N	

Examples of Filing Issues	Yes?	If not, action & status
Content, presentation, and organization sufficient to permit substantive review?	(Y) N	
❑ legible	(Y) N	
❑ English (or certified translation into English)	(Y) N	
❑ compatible file formats	(Y) N	
❑ navigable hyper-links	(Y) N	
❑ interpretable data tabulations (line listings) & graphical displays	(Y) N	

STN 125118/0 Product Abatacept

Examples of Filing Issues	Yes?	If not, action & status
❑ summary reports reference the location of individual data and records	(Y) N	
❑ protocols for clinical trials present	(Y) N	
❑ all electronic submission components usable	(Y) N	
statement for each clinical investigation: ❑ conducted in compliance with IRB requirements	(Y) N	
❑ conducted in compliance with requirements for informed consent	(Y) N	
adequate and well-controlled clinical study data (e.g. not obviously inappropriate or clinically irrelevant study design or endpoints for efficacy)	(Y) N	
adequate explanation of why results from what appears to be a single controlled trial (or alternate method for demonstrating efficacy) should be accepted as scientifically valid without replication	(Y) N	
study design not clearly inappropriate (as reflected in regulations, well-established agency interpretation or correspondence) for the particular claim	(Y) N	
study(ies) assess the contribution of each component of a combination product [21 CFR 610.17]	Y (N)	N/A
total patient exposure (numbers or duration) at relevant doses is not clearly inadequate to evaluate safety (per standards communicated during IND review, or ICH or other guidance documents)	(Y) N	
adequate data to demonstrate safety and/or effectiveness in the population intended for use of the biological product based on age, gender, race, physiologic status, or concomitant therapy	(Y) N	
drug interaction studies communicated as during IND review as necessary are included	(Y) N	
assessed drug effects whose assessment is required by well established agency interpretation or communicated during IND review	(Y) N	
comprehensive analysis of safety data from all current world-wide knowledge of product	(Y) N	

STN 125118/0 Product Abatacept

Examples of Filing Issues	Yes?	If not, action & status
data supporting the proposed dose and dose interval	(Y) N	
appropriate (e.g. protocol-specified) and complete statistical analyses of efficacy data	(Y) N	
adequate characterization of product specificity or mode of action	(Y) N	
data demonstrating comparability of product to be marketed to that used in clinical trials when significant changes in manufacturing processes or facilities have occurred	(Y) N	
inadequate efficacy and/or safety data on product to be marketed when different from product used in clinical studies which are the basis of safety and efficacy determinations	Y (N)	N/A
all information reasonably known to the applicant and relevant to the safety and efficacy described?	(Y) N	

List of Clinical Studies (protocol number)	Final study report submitted?		Financial disclosure or certification submitted?			SAS & other electonic datasets complete & usable?		BiMo sites identified?		
IM101017	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM101003	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM101004	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM101001	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM101005	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM101100	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM101101	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM103002	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM101029	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM101031	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
Y= yes; N=no; NR=not required										
IM101102	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)
IM101200	(Y)	N	Y	N	(NR)	(Y)	N	Y	N	(NR)

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

N/A

Is clinical site(s) inspection (BiMo) needed?

No

Is an Advisory Committee needed?

No

Recommendation (circle one): File RTF

Reviewer: [signature] 4/11/05 Type (circle one): Clinical Clin/Pharm Statistical
(signature/ date)

Concurrence:

Branch Chief: Martin Green 4/20/05 Division. Director: _____
(signature/ date) (signature/ date)

20 Page(s) Withheld

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

_____ § 552(b)(5) Deliberative Process

✓ § 552(b)(5) Draft Labeling

ACTION PACKAGE CHECKLIST

Application Information			
BLA # 125118 NDA #	BLA STN# 0 NDA Supplement #	If NDA, Efficacy Supplement Type	
Proprietary Name: ORENCIA Established Name: abatacept Dosage Form:		Applicant: Bristol-Myers Squibb	
RPM: Lisa Malandro		HFD-170	Phone # 301-796-1251

NDAs only:	505(b)(2) NDAs only:
Application Type: ☐ 505(b)(1) ☐ 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.)	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)): Provide a brief explanation of how this product is different from the listed drug. ☐ If no listed drug, check here and explain: **Review and confirm the information previously provided in Appendix B to the Regulatory Filing Review. Use this Checklist to update any information (including patent certification information) that is no longer correct.** ☐ Confirmed ☐ Corrected Date:

❖ User Fee Goal Date ❖ Action Goal Date (optional)	December 31, 2005 December 23, 2005
❖ Actions	
• Proposed action	☒ AP ☐ TA ☐ AE ☐ NA ☐ CR
• Previous actions *(specify type and date for each action taken)*	☒ None
❖ Advertising *(approvals only)* Note: If accelerated approval (21 CFR 314.510/601.41), advertising must have been submitted and reviewed *(indicate dates of reviews)*	☒ Requested in AP letter ☐ Received and reviewed

❖ Application Characteristics

Review priority: ☐ Standard ☒ Priority
Chemical classification (new NDAs only):

NDAs, BLAs and Supplements:
☒ Fast Track
☐ Rolling Review
☒ CMA Pilot 1
☐ CMA Pilot 2

☐ Orphan drug designation

NDAs: Subpart H
☐ Accelerated approval (21 CFR 314.510)
☐ Restricted distribution (21 CFR 314.520)
Subpart I
☐ Approval based on animal studies

BLAs: Subpart E
☐ Accelerated approval (21 CFR 601.41)
☐ Restricted distribution (21 CFR 601.42)
Subpart H
☐ Approval based on animal studies

NDAs and NDA Supplements:
☐ OTC drug

Other:

Other comments:

❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	☐ Yes ☒ No
• This application is on the AIP	☐ Yes ☒ No
• Exception for review *(file Center Director's memo in Application Summary section)*	☐ Yes ☒ No
• OC clearance for approval *(file communication in EER or Compliance Status Check section)*	☐ Yes ☒ Not an AP action
❖ Public communications (approvals only)	
• Office of Executive Programs (OEP) liaison has been notified of action	☒ Yes ☐ No
• Press Office notified of action	☒ Yes ☐ No
• Indicate what types (if any) of information dissemination are anticipated	☒ None ☐ FDA Press Release ☐ FDA Talk Paper ☐ CDER Q&As ☐ Other

❖ Exclusivity	
• NDAs: Exclusivity Summary (approvals only) *(file Summary in Administrative Documents section)*	☐ Included
• Is approval of this application blocked by any type of exclusivity?	☐ No ☐ Yes
• NDAs/BLAs: Is there existing orphan drug exclusivity for the "same" drug or biologic for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	☒ No ☐ Yes If, yes, NDA/BLA # and date exclusivity expires:
• NDAS: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? *(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)*	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
• NDAs: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application?	☐ No ☐ Yes If yes, NDA # and date exclusivity expires:
❖ Patent Information (NDAs and NDA supplements only)	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions.	☐ Verified ☐ Not applicable because drug is an old antibiotic.
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ☐ Verified 21 CFR 314.50(i)(1) ☐ (ii) ☐ (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	☐ N/A (no paragraph IV certification) ☐ Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification: (1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant	☐ Yes ☐ No

is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))).	
*If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*	
*If "**No**," continue with question (3).*	
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	☐ Yes ☐ No
(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))).	
*If "**No**," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.*	
(4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?	☐ Yes ☐ No
*If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).*	
*If "**No**," continue with question (5).*	
(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?	☐ Yes ☐ No
(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).	
*If "**No**," there is no stay of approval based on this certification. Analyze the*	

next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity). *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	
Summary Reviews	
❖ Summary Reviews (e.g., Office Director, Division Director) *(indicate date for each review)* ❖ BLA approvals only: Licensing Action Recommendation Memo (LARM) *(indicate date)*	Robert J. Meyer, MD December 22, 2005 December 23, 2005
Labeling	
❖ Package Insert	
• Most recent division-proposed labeling (only if generated after latest applicant submission of labeling)	Attached to action letter
• Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version)	Included
• Original applicant-proposed labeling	Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	Included
❖ Patient Package Insert • Most-recent division-proposed labeling (only if generated after latest applicant submission of labeling) • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) • Original applicant-proposed labeling	Attached to action letter Included Included
• Other relevant labeling (e.g., most recent 3 in class, class labeling), if applicable	
❖ Medication Guide • Most recent division-proposed labeling (only if generated after latest applicant submission of labeling) • Most recent applicant-proposed labeling (only if subsequent division labeling does not show applicant version) • Original applicant-proposed labeling • Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (full color carton and immediate-container labels) • Most-recent division-proposed labels (only if generated after latest applicant submission) • Most recent applicant-proposed labeling • Labeling reviews that address only carton and container labels	N/A
❖ Labeling reviews and minutes of any labeling meetings *(indicate dates of reviews and meetings)*	☒ DMETS July 19 & November 2, 2005 ☒ DSRCS June 2 & 14, 2005 ☒ DDMAC September 30, 2005 ☐ Other reviews ☐ Memos of Mtgs
Administrative Documents	

❖ Administrative Reviews (RPM Filing Review/Memo of Filing Meeting/ADRA) *(indicate date of each review)*	Filiing reviews: PM: May 20, 2005 Facility: May 25, 2005 Product: May 24, 2005 PharmTox: June 3, 2005 Clinical: May 3, 2005 Statistical: May 19, 2005 Biopharmaceutics: April 11, 2005
❖ NDA approvals only: Exclusivity Summary *(signed by Division Director)*	☐ Included
❖ AIP-related documents	
❖ Pediatric Page	Included
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification & certifications from foreign applicants are cosigned by US agent. *(Include certification.)*	☒ Verified
❖ Postmarketing Commitment Studies	☐ None
• Outgoing Agency request for post-marketing commitments *(if located elsewhere in package, state where located)*	Included
• Incoming submission documenting commitment	Included
❖ Outgoing correspondence (letters, emails, faxes, telecons)	Included
❖ Internal memoranda, telecons, email, etc.	Included
❖ Minutes of Meetings	
• Pre-Approval Safety Conference *(indicate date; approvals only)*	
• Pre-NDA/BLA meeting *(indicate date)*	
• EOP2 meeting *(indicate date)*	
• Other (e.g., EOP2a, CMC pilot programs)	
❖ Advisory Committee Meeting	
• Date of Meeting	September 6, 2005
• 48-hour alert or minutes, if available	Summary minutes included
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	N/A
CMC/Product Quality Information	
❖ CMC/Product review(s) *(indicate date for each review)* ❖ BLAs: Product subject to lot release (APs only)?	Overall: December 22, 2005 Ennan Guan December 23, 2005 Elizabeth Shores September 20 and December 20 and 21, 2005 Joy Williams, December 21, 2005 Barbara Rellahan Decmber 16, 2005 Susan Kirshner December 20, 2005 Edward E. Max December 15, 2005 ☐ Yes ☒ No
❖ Environmental Assessment (both original and supplemental applications) (check one)	
• ☐ Categorical Exclusion *(indicate review date)(all NMEs and all efficacy supplements that could increase the patient population)*	Included
• ☐ Review & FONSI *(indicate date of review)*	
• ☐ Review & Environmental Impact Statement *(indicate date of each review)*	
❖ NDAs: Microbiology reviews (validation of sterilization & product sterility) *(indicate*	N/A

date of each review)	☐ Not a parenteral product
❖ NDAs: Facilities inspection (include EER printout)	Date completed: ☐ Acceptable ☐ Withhold recommendation
❖ NDAs: Methods Validation	☐ Completed ☐ Requested ☐ Not yet requested ☐ Not needed
❖ BLAs: Facility-Related Documents • Facility review *(indicate date(s))* • Compliance Status Check (approvals only, both original and supplemental applications) *(indicate date, must be completed within 60 days prior to AP)*	Ann DeMarco, December 23, 2005 ☐ Requested ☒ Accepted ☐ Hold ☐ Cleared from hold
Nonclinical Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	Anita O'Connor, PhD: July 21, 2005 Hanaan Ghantous, PhD, DABT: undated
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ ECAC/CAC report/memo of meeting	N/A
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)* ❖ Financial Disclosure reviews(s) or location/date if addressed in another review ❖ Clinical consult reviews from other review divisions/Centers *(indicate date of each review)*	Jeffrey Siegel, MD: December 12, 2005 Keith Hull, MD: November 22, 2005 N/A
❖ Microbiology (efficacy) review(s) *(indicate date of each review)*	☒ Not needed
❖ Safety Update review(s) *(indicate location/date if incorporated into another review)*	N/A
❖ Risk Management Plan review(s) (including ODS) *(indicate location/date if incorporated into another rev)*	☒ None
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	☒ Not needed
❖ Clinical Inspection Review Summary (DSI)	☐ None requested
• Clinical studies *(include copies of DSI letters to investigators)*	Dianne Tesch: August 15, 2005
• Bioequivalence studies *(include copies of DSI letters to investigators)*	
❖ Statistical review(s) *(indicate date of each review)*	☐ None Kyung Yul Lee, PhD: September 12, 2005
❖ Clinical Pharmacology review(s) *(indicate date for each review)*	☐ None Anil K. Rajpal, MD: June 17, 2005