

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125288Orig1s000

CHEMISTRY REVIEW(S)



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From: Susan Kirshner, Ph.D.
Associate Chief, Laboratory of
Immunology
Division of Therapeutic proteins (DTP)

Through: Barry Cherney, Ph.D.
Deputy Director, DTP

BLA Number: STN 125288
Product: Belatacept (CTLA4-Ig)
Sponsor: Bristol Myers Squibb

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, recommends approval of STN125288 for Nulojix (Belatacept) manufactured by Bristol-Myers Squibb for human use (under conditions specified in the package insert). The data submitted in this application are adequate to support the conclusion that the manufacture of Nulojix is well controlled, and leads to a product that is pure and potent. It is recommended that this product be approved

II. APPROVAL LETTER INFORMATION

- The dating period for Nulojix (belatacept) shall be 30 months from the date of manufacture when stored at 2 – 8°C and protected from light. The date of manufacture shall be defined as the date of (b) (4)
- The dating period for drug substance shall be 30 months (b) (4)
- We are approving the stability protocols in the license application for the purpose of extending the expiration dating periods.
- Nulojix is a specified product. Per 21CFR601.2(c)(1) specified products do not need to be on lot release.

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

It should be noted that at the time this memo was written the wording for the PMR and PMCs had not been finalized with the Sponsor.

PMR

- 1) Conduct a study to quantify at the end of the proposed (b) (4)
Provide a worst case risk assessment for those (b) (4), including potential toxicity to humans, in your final report.

Final Report Submission Date: December 2012

PMC

- 2) Conduct a trend analysis of (b) (4) profiles based on the results from 30 consecutively released future drug substance batches. Re-evaluate the acceptance criteria for these product attributes and, if appropriate, submit the revised specifications together with data justification that includes supporting data and reflective of your experience with lots used in the clinical trials.

Final Study Report Submission Date: December 2013

- 3) Conduct a trend analysis for (b) (4) content using an extended characterization (b) (4) to generate informational data and based on the results from 30 consecutively released future drug substance batches, evaluate the need for introducing a validated release method and setting acceptance criteria for this product attribute, or provide justification for not requiring a (b) (4) content release method.

Final Study Report Submission Date: December 2013

- 4) Provide a protocol describing the conditions and criteria which will be applied for assessing the stability of any drug substance lot held for the maximum hold time allowed at each (b) (4)

Final Submission Date: December 2011

- 5) Provide information and summary data on the product specific dye-ingress container closure, integrity test method and provide an updated post-marketing stability protocol replacing the sterility test with CCIT.

Final Report Submission Date: September 2012

- 6) BMS will perform a study to support multiple freezing-thawing of drug substance (DS) that incorporates conditions reflective of the intended use (multiple freeze-thaws, including shipping). Also, BMS will provide DS stability data confirming a cumulative stability limit of greater than 12 months at 2-8°C before and after multiple freeze-thaw cycles. In addition, BMS will provide stability data for drug product produced from DS that has undergone multiple freeze-thaw cycles.

Interim Report Submission Date: December 2011

Final Report Submission Date: December 2013

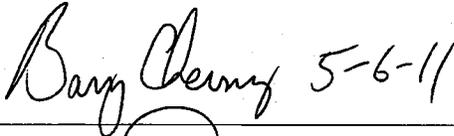
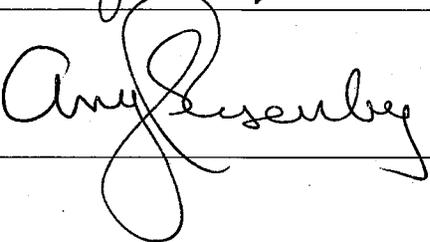
- 10) The company will develop characterization methodology for micron and submicron subvisible particulates using stressed and/or accelerated drug product samples to assess whether a correlation may exist between subvisible particulates in the micron and submicron ranges and propose an appropriate control strategy for drug product stored under the approved conditions.

Final Report Submission Date: December 31, 2012

IV. EXECUTIVE SUMMARY

A. Description of Belatacept

VII. SIGNATURE BLOCK

Name and Title	Signature and Date
Susan Kirshner, Ph.D. Associate Laboratory Chief, Laboratory of Immunology, Division of Therapeutic Proteins	 5/6/11
Barry Cherney, Ph.D., Deputy Director, Division of Therapeutic Proteins	 5-6-11
Amy Rosenberg, M.D. Director, Division of Therapeutic Proteins	 5-6-11



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies
Division of Therapeutic Proteins

Primary Review of Complete Response

**From: Jack Ragheb, M.D.
Senior Supervisory Regulatory Scientist**

**Through: Susan Kirshner, Ph.D.
Associate Chief, Laboratory of Immunology
Division of Therapeutic proteins (DTP)**

**BLA Number: STN 125288
Product: Belatacept (CTLA4-Ig)
Sponsor: Bristol Myers Squibb**

VII. SIGNATURE BLOCK

Name and Title	Signature and Date
Susan Kirshner, Ph.D. Associate Laboratory Chief, Laboratory of Immunology, Division of Therapeutic Proteins	 5/2/11
Jack Ragheb, M.D., Ph.D. Primary Reviewer, Senior Regulatory Research Officer, Division of Therapeutic Proteins	 4/11/11



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From: Susan Kirshner, Ph.D.
Associate Chief, Laboratory of
Immunology
Division of Therapeutic proteins (DTP)

Through: Barry Cherney, Ph.D.
Deputy Director, DTP

BLA Number: STN 125288
Product: Belatacept (CTLA4-Ig)
Sponsor: Bristol-Myers Squibb

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

Suggested language

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, does not recommend approval of STN125288 for Nulojix (Belatacept) manufactured by Bristol-Myers Squibb. The data submitted in this application are inadequate to support the conclusion that the manufacture of Nulojix is well controlled, and leads to a product that is pure and potent. It is not recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

Not applicable

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

Not applicable

(b) (4)



VII. SIGNATURE BLOCK

Name and Title	Signature and Date
<p>Susan Kirshner, Ph.D. Associate Laboratory Chief, Laboratory of Immunology, Division of Therapeutic Proteins</p>	
<p>Barry Cherney, Ph.D., Deputy Director, Division of Therapeutic Proteins</p>	
<p>Jack Ragheb, M.D., Ph.D. Primary Reviewer, Senior Regulatory Research Officer, Division of Therapeutic Proteins</p>	

VII. SIGNATURE BLOCK

Name and Title	Signature and Date
<p>Susan Kirshner, Ph.D. Associate Laboratory Chief Laboratory of Immunology Division of Therapeutic Proteins</p>	<p><i>Susan Kirshner</i> 4-30-10</p>
<p>Barry Cherney, Ph.D. Deputy Director Division of Therapeutic Proteins</p>	<p><i>Barry Cherney</i> 4-30-10</p>
<p>Jack A. Ragheb, M.D., Ph.D. Primary Reviewer Senior Regulatory Research Officer <u>Principal Investigator</u> Division of Therapeutic Proteins</p>	<p><i>Jack A. Ragheb</i> 4-30-10</p>



DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies
Division of Therapeutic Proteins

CMC Review Cover Sheet

Division of Therapeutic Proteins

Jack A. Ragheb, M.D. Ph.D. HFD-122

Joao Pedras-Vasconcelos, Ph.D. HFD-122

Norihisa Sakamoto, Ph.D. HFD-122

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

Susan Kirshner, Ph.D. HFD-122

Division of Monoclonal Antibodies

Barbara Rellehan, PhD HFD-123

Executive Summary

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, does not recommend approval of STN125288 for Nulojix (Belatacept) manufactured by Bristol-Myers Squibb. The data submitted in this application are inadequate to support the conclusion that the manufacture of Nulojix is well controlled, and leads to a product that is pure and potent. It is not recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

Not applicable

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

Not applicable

(b) (4)





DEPARTMENT OF HEALTH & HUMAN SERVICES

Center for Drugs Evaluation and Research – Food and Drug Administration
Office of Biotechnology Products / Office of Pharmaceutical Science
Division of Monoclonal Antibodies
Division of Therapeutic Proteins

The Quality Team Leader's Executive Summary

From: Susan Kirshner, Ph.D.
Associate Chief, Laboratory of
Immunology
Division of Therapeutic proteins (DTP)

Through: Barry Cherney, Ph.D.
Deputy Director, DTP

BLA Number: STN 125288
Product: Belatacept (CTLA4-Ig)
Sponsor: Bristol-Myers Squibb

I. RECOMMENDATIONS AND CONCLUSIONS ON APPROVABILITY

Suggested language

The Division of Therapeutic Proteins, Office of Biotechnology Products, OPS, CDER, does not recommend approval of STN125288 for Nulojix (Belatacept) manufactured by Bristol-Myers Squibb. The data submitted in this application are inadequate to support the conclusion that the manufacture of Nulojix is well controlled, and leads to a product that is pure and potent. It is not recommended that this product be approved for human use (under conditions specified in the package insert).

II. APPROVAL LETTER INFORMATION

Not applicable

III. POST MARKETING COMMITMENTS/POST MARKETING REQUIREMENTS

Not applicable

(b) (4)



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



VII. SIGNATURE BLOCK

Name and Title	Signature and Date
<p>Susan Kirshner, Ph.D. Associate Laboratory Chief, Laboratory of Immunology, Division of Therapeutic Proteins</p>	
<p>Barry Cherney, Ph.D., Deputy Director, Division of Therapeutic Proteins</p>	
<p>Jack Ragheb, M.D., Ph.D. Primary Reviewer, Senior Regulatory Research Officer, Division of Therapeutic Proteins</p>	

APPEARS THIS WAY ON
ORIGINAL

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

07-01-09

BLA/NDA Number: 125288 Applicant: BMS

Stamp Date: 8-12-07

Drug Name: Belatacept BLA/NDA Type: BLA INITIAL

On initial overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?		If not, justification, action & status
Cover Letter	Y	N	
Form 356h completed	Y	N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y	N	
Comprehensive Table of Contents	Y	N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y	N	
Labeling:	Y	N	<i>labeled medication guide can't locate. Will IR</i> <i>n.a.</i>
<input type="checkbox"/> PI -non-annotated	Y	N	
<input type="checkbox"/> PI -annotated	Y	N	
<input type="checkbox"/> PI (electronic)	Y	N	
<input type="checkbox"/> Medication Guide	Y	N	
<input type="checkbox"/> Patient Insert	Y	N	
<input type="checkbox"/> package and container	Y	N	
<input type="checkbox"/> diluent	Y	N	
<input type="checkbox"/> other components	Y	N	
<input type="checkbox"/> established name (e.g. USAN)	Y	N	
<input type="checkbox"/> proprietary name (for review)	Y	N	

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	
<input type="checkbox"/> legible	Y	N	
<input type="checkbox"/> English (or translated into English)	Y	N	
<input type="checkbox"/> compatible file formats	Y	N	
<input type="checkbox"/> navigable hyper-links	Y	N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y	N	
Companion application received if a shared or divided manufacturing	Y	N	<i>n.a.</i>

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Quality overall summary [2.3]	<input checked="" type="radio"/> Y <input type="radio"/> N	n.a.
<input type="checkbox"/> Drug Substance	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Drug Product	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Facilities and Equipment	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Novel Excipients	<input type="radio"/> Y <input checked="" type="radio"/> N	
<input type="checkbox"/> Executed Batch Records	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Method Validation Package	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> Comparability Protocols	<input checked="" type="radio"/> Y <input type="radio"/> N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	<input checked="" type="radio"/> Y <input type="radio"/> N	
Drug Substance [3.2.S]	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> general info	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> description of manufacturing process	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?		If not, justification, action & status
❑ description and composition of diluent	Y	N	
❑ pharmaceutical development	Y	N	
○ preservative effectiveness	Y	N	
○ container-closure integrity	Y	N	
❑ manufacturers (names, locations, and responsibilities of all sites involved)	Y	N	
❑ 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)	Y	N	
❑ controls of critical steps and intermediates	Y	N	
❑ process validation including aseptic processing & sterility assurance:	Y	N	
○ 3 consecutive lots			
○ Filter validation			
○ Component, container, closure depyrogenation and sterilization validation	Y	N	
○ Validation of aseptic processing (media simulations)	Y	N	
○ Environmental Monitoring Program	Y	N	
○ Lyophilizer sterilization validation			
○ Other needed validation data (hold times)	Y	N	
❑ 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			

not applicable

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> method validation package	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> comparability protocols	<input checked="" type="radio"/> Y <input type="radio"/> N	
Literature references and copies [3.3]	<input checked="" type="radio"/> Y <input type="radio"/> N	

Examples of Filing Issues	Yes?	If not, justification, action & status
Content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> legible	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="radio"/> Y <input type="radio"/> N	
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="radio"/> Y <input type="radio"/> N	
Includes appropriate process validation data for the manufacturing process at the commercial production facility	<input type="radio"/> Y <input checked="" type="radio"/> 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)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Includes data demonstrating consistency of manufacture	<input checked="" type="radio"/> Y <input type="radio"/> N	
Includes complete description of product lots and manufacturing process utilized for clinical studies	<input checked="" type="radio"/> Y <input type="radio"/> N	
Describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	<input checked="" type="radio"/> Y <input type="radio"/> 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)	<input checked="" type="radio"/> Y <input type="radio"/> N	
Certification that all facilities are ready for inspection	<input type="radio"/> Y <input checked="" type="radio"/> N	Amendment to be filed
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test	<input checked="" type="radio"/> Y <input type="radio"/> N	

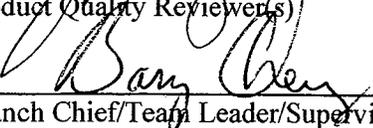
**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
methods used and time intervals for product assessment.		
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: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> sterility	Y N <input checked="" type="checkbox"/> N <input type="checkbox"/> <input checked="" type="checkbox"/> <input checked="" type="checkbox"/> 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	<input checked="" type="checkbox"/> N	
Floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	<input checked="" type="checkbox"/> N	
Description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	<input checked="" type="checkbox"/> N	
Information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	<input checked="" type="checkbox"/> N	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? _____

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

	JACK RAGHEB	8-12-09
Product Quality Reviewer(s)		Date
		8-12-09
Branch Chief/Team Leader/Supervisor		Date

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

BLA/NDA Number: 125288

Applicant: Bristol-Myers Squibb Stamp Date:

Drug Name: Belatacept

BLA/NDA Type: BLA-125288

Initial

07-01-09
~~8-12-09~~

On initial overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed	Y N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y N	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Labeling:	Y N	
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	Y N	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y N	

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	
<input type="checkbox"/> legible	Y N	
<input type="checkbox"/> English (or translated into English)	Y N	
<input type="checkbox"/> compatible file formats	Y N	
<input type="checkbox"/> navigable hyper-links	Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y N	
Companion application received if a shared or divided manufacturing	Y N	

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

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	
<input type="checkbox"/> Drug Substance	Y N	
<input type="checkbox"/> Drug Product	Y N	
<input type="checkbox"/> Facilities and Equipment	Y N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	
<input type="checkbox"/> Novel Excipients	Y N	
<input type="checkbox"/> Executed Batch Records	Y N	
<input type="checkbox"/> Method Validation Package	Y N	
<input type="checkbox"/> Comparability Protocols	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y N	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
<input type="checkbox"/> description of manufacturing process	Y N	
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest		
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y N	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <input type="checkbox"/> cell banking system, characterization, and testing 	Y ✓	
<ul style="list-style-type: none"> <input type="checkbox"/> control of critical steps and intermediates <ul style="list-style-type: none"> <input type="checkbox"/> justification of specifications <input type="checkbox"/> analytical method validation <input type="checkbox"/> reference standards <input type="checkbox"/> stability 	Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions) 	Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) 	Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> characterization of drug substance 	Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> <input type="checkbox"/> specifications <ul style="list-style-type: none"> <input type="checkbox"/> justification of specs. <input type="checkbox"/> analytical procedures <input type="checkbox"/> analytical method validation <input type="checkbox"/> batch analyses <ul style="list-style-type: none"> <input type="checkbox"/> consistency (3 consecutive lots) <input type="checkbox"/> justification of specs. 	Y N Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> reference standards 	Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> container closure system 	Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 	Y N Y N Y N	
Drug Product [3.2.P]		
<ul style="list-style-type: none"> <input type="checkbox"/> description and composition 	Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> pharmaceutical development <ul style="list-style-type: none"> <input type="checkbox"/> preservative effectiveness <input type="checkbox"/> container-closure integrity 	Y N Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) 	Y N	
<ul style="list-style-type: none"> <input type="checkbox"/> batch formula 		

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> 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 Y N	
<input type="checkbox"/> controls of critical steps and intermediates		
<input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> 3 consecutive lots <input type="checkbox"/> Filter validation <input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation <input type="checkbox"/> Validation of aseptic processing (media simulations) <input type="checkbox"/> Environmental Monitoring Program <input type="checkbox"/> Lyophilizer sterilization validation <input type="checkbox"/> Other needed validation data (hold times) 	Y N Y N	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)		
<input type="checkbox"/> control of drug product (justification of specifications; analytical method validation)		
<input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs <input type="checkbox"/> administration device(s) 		
<input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 		
Diluent (vials or filled syringes) [3.2.P']		

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?		If not, justification, action & status
<input type="checkbox"/> description and composition of diluent	Y	N	
<input type="checkbox"/> pharmaceutical development	Y	N	
<input type="checkbox"/> preservative effectiveness	Y	N	
<input type="checkbox"/> container-closure integrity	Y	N	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y	N	
<input type="checkbox"/> batch formula			
<input type="checkbox"/> 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	
<input type="checkbox"/> controls of critical steps and intermediates			
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y	N	
<input type="checkbox"/> 3 <u>consecutive</u> lots			
<input type="checkbox"/> Filter validation			
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	Y	N	
<input type="checkbox"/> Validation of aseptic processing (media simulations)	Y	N	
<input type="checkbox"/> Environmental Monitoring Program	Y	N	
<input type="checkbox"/> Lyophilizer sterilization validation			
<input type="checkbox"/> Other needed validation data (hold times)	Y	N	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)			
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)			
<input type="checkbox"/> reference standards			

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> method validation package	Y N	
<input type="checkbox"/> comparability protocols	Y N	
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	
<input type="checkbox"/> legible	Y N	
<input type="checkbox"/> English (or translated into English)	Y N	
<input type="checkbox"/> compatible file formats	Y N	
<input type="checkbox"/> navigable hyper-links	Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y N	
<input type="checkbox"/> 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	
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test	Y N	

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
methods used and time intervals for product assessment.		
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: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> 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	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? _____

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Yonhisu Sakamoto

 Product Quality Reviewer(s)

Aug 11, 2007

 Date

Bay Chen

 Branch Chief/Team Leader/Supervisor

Aug 11, 2007

 Date

PRODUCT QUALITY (BIOTECHNOLOGY) FILING REVIEW FOR BLA/NDA (OBP & DMPQ)

BLA/NDA Number: 125288 **Applicant:** BMS-Syracuse **Stamp Date:** July 1, 2009

Drug Name: belatacept **BLA/NDA Type:** 10-month *INITIAL*

On initial overview of the BLA/NDA application for filing:

CTD Module 1 Contents	Present?	If not, justification, action & status
Cover Letter	Y N	
Form 356h completed	Y N	
<input type="checkbox"/> including list of all establishment sites and their registration numbers	Y N	
Comprehensive Table of Contents	Y N	
Environmental assessment or request for categorical exclusion (21 CFR Part 25)	Y N	
Labeling:	Y N	
<input type="checkbox"/> PI –non-annotated	Y N	
<input type="checkbox"/> PI –annotated	Y N	
<input type="checkbox"/> PI (electronic)	Y N	
<input type="checkbox"/> Medication Guide	Y N	
<input type="checkbox"/> Patient Insert	Y N	
<input type="checkbox"/> package and container	Y N	
<input type="checkbox"/> diluent	Y N	
<input type="checkbox"/> other components	Y N	
<input type="checkbox"/> established name (e.g. USAN)	Y N	
<input type="checkbox"/> proprietary name (for review)	Y N	

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	
<input type="checkbox"/> legible	Y N	
<input type="checkbox"/> English (or translated into English)	Y N	
<input type="checkbox"/> compatible file formats	Y N	
<input type="checkbox"/> navigable hyper-links	Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y N	
<input type="checkbox"/> all electronic submission components usable (e.g. conforms to published guidance)	Y N	
Companion application received if a shared or divided manufacturing	Y N	

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

Examples of Filing Issues	Yes?	If not, justification, action & status
arrangement		

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	
<input type="checkbox"/> Drug Substance	Y N	
<input type="checkbox"/> Drug Product	Y N	
<input type="checkbox"/> Facilities and Equipment	Y N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y N	
<input type="checkbox"/> Novel Excipients	Y N	
<input type="checkbox"/> Executed Batch Records	Y N	
<input type="checkbox"/> Method Validation Package	Y N	
<input type="checkbox"/> Comparability Protocols	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y N	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y N	
<input type="radio"/> nomenclature		
<input type="radio"/> structure (e.g. sequence, glycosylation sites)		
<input type="radio"/> properties		
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
<input type="checkbox"/> description of manufacturing process	Y N	
<input type="radio"/> batch numbering and pooling scheme		
<input type="radio"/> cell culture and harvest		
<input type="radio"/> purification		
<input type="radio"/> filling, storage and shipping		
<input type="checkbox"/> control of materials	Y N	
<input type="radio"/> raw materials and reagents		
<input type="radio"/> biological source and starting materials		
<input type="radio"/> cell substrate: source, history, and generation		

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?		If not, justification, action & status
<input type="checkbox"/> 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	
<input type="checkbox"/> controls of critical steps and intermediates	Y	N	
<input type="checkbox"/> process validation including aseptic processing & sterility assurance: <ul style="list-style-type: none"> <input type="checkbox"/> 3 <u>consecutive</u> lots <input type="checkbox"/> Filter validation <input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation <input type="checkbox"/> Validation of aseptic processing (media simulations) <input type="checkbox"/> Environmental Monitoring Program <input type="checkbox"/> Lyophilizer sterilization validation <input type="checkbox"/> Other needed validation data (hold times) 	Y	N	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin)	Y	N	
<input type="checkbox"/> control of drug product (justification of specifications; analytical method validation)	Y	N	
<input type="checkbox"/> container closure system [3.2.P.7] <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input type="checkbox"/> availability of DMF & LOAs <input type="checkbox"/> administration device(s) 	█	█	
<input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results <input type="checkbox"/> method validation 	█	█	
Diluent (vials or filled syringes) [3.2.P']			

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> description and composition of diluent	Y N	
<input type="checkbox"/> pharmaceutical development	Y N	
<input type="checkbox"/> preservative effectiveness	Y N	
<input type="checkbox"/> container-closure integrity	Y N	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)	Y N	
<input type="checkbox"/> batch formula		
<input type="checkbox"/> 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 Y N	
<input type="checkbox"/> controls of critical steps and intermediates		
<input type="checkbox"/> process validation including aseptic processing & sterility assurance:	Y N	
<input type="checkbox"/> 3 <u>consecutive</u> lots		
<input type="checkbox"/> Filter validation		
<input type="checkbox"/> Component, container, closure depyrogenation and sterilization validation	■ N	
<input type="checkbox"/> Validation of aseptic processing (media simulations)	Y N	
<input type="checkbox"/> Environmental Monitoring Program	Y N	
<input type="checkbox"/> Lyophilizer sterilization validation		
<input type="checkbox"/> Other needed validation data (hold times)	Y N	
<input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)		
<input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)		
<input type="checkbox"/> reference standards		

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <input type="checkbox"/> container closure system <ul style="list-style-type: none"> <input type="checkbox"/> specifications (vial, elastomer, drawings) <input checked="" type="checkbox"/> <input type="checkbox"/> availability of DMF & LOAs <input checked="" type="checkbox"/> <input type="checkbox"/> stability <ul style="list-style-type: none"> <input type="checkbox"/> summary <input type="checkbox"/> post-approval protocol and commitment <input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <input type="checkbox"/> protocol <input type="checkbox"/> results 		
<p>Other components to be marketed (full description and supporting data, as listed above):</p> <ul style="list-style-type: none"> <input type="checkbox"/> other devices <input type="checkbox"/> other marketed chemicals (e.g. part of kit) 	<p>Y N</p> <p>Y N</p>	
<p>Appendices for Biotech Products [3.2.A]</p> <ul style="list-style-type: none"> <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> <input type="checkbox"/> manufacturing flow; adjacent areas <input type="checkbox"/> other products in facility <input type="checkbox"/> equipment dedication, preparation, sterilization and storage <input type="checkbox"/> procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> <input checked="" type="checkbox"/> avoidance and control procedures <input type="checkbox"/> cell line qualification <input type="checkbox"/> other materials of biological origin <input checked="" type="checkbox"/> viral testing of unprocessed bulk <input type="checkbox"/> viral clearance studies <input checked="" type="checkbox"/> testing at appropriate stages of production <input type="checkbox"/> novel excipients 	<p>Y N</p> <p><input checked="" type="checkbox"/> N</p> <p><input checked="" type="checkbox"/></p> <p><input checked="" type="checkbox"/></p>	

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

CTD Module 3 Contents	Present?	If not, justification, action & status
	Y N	
USA Regional Information [3.2.R]		
<input type="checkbox"/> executed batch records	Y N	
<input type="checkbox"/> method validation package	Y N	
<input type="checkbox"/> comparability protocols	Y N	
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	
<input type="checkbox"/> legible	Y N	
<input type="checkbox"/> English (or translated into English)	Y N	
<input type="checkbox"/> compatible file formats	Y N	
<input type="checkbox"/> navigable hyper-links	Y N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y N	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y N	
<input type="checkbox"/> 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	

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

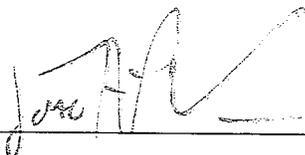
Examples of Filing Issues	Yes?	If not, justification, action & status
Data establishing stability of the product through the proposed dating period and a stability protocol describing the test methods used and time intervals for product assessment.	Y N	
If not using a test or process specified by regulation, data is provided to show the alternate is equivalent (21 CFR 610.9) to that specified by regulation. List: <input type="checkbox"/> LAL instead of rabbit pyrogen <input type="checkbox"/> mycoplasma <input type="checkbox"/> 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	

IS THE PRODUCT QUALITY SECTION OF THE APPLICATION FILEABLE? _____

If the application is not fileable from product quality perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

Joao A Pedras-Vasconcelos
Product Quality Reviewer(s)



8/11/09

Date

**PRODUCT QUALITY (BIOTECHNOLOGY)
FILING REVIEW FOR BLA/NDA (OBP & DMPQ)**

Barry Cheny

8/12-09

Branch Chief/Team Leader/Supervisor

Date