

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**125261**

**CHEMISTRY REVIEW(S)**



**BLA 125261: Addendum 2**  
**Centocor's Responses to the Agency's**  
**Complete Response Letter**  
**Chemistry, Manufacturing, and Control Assessment**



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## Product Quality Review Data Sheet Addendum

1. **BLA** STN 125261/0
2. **REVIEW#:** 3
3. **REVIEW DATE:** April 23, 2009
4. **REVIEWERS:** Laurie Graham, M.S.  
Barbara Rellahan, M.S., Ph.D. Team Leader
5. **CMC COMMUNICATIONS WITH SPONSOR**  
Information Request Letter, February 23, 2009  
Teleconference on March 11, 2009.
6. **SUBMISSIONS BEING REVIEWED:**  
Submission  
eCTD submission 47 Additional visible particle data for validation and post-validation batches, received November 7, 2008  
  
eCTD submission 48 Response to Deficiency Letter, received November 21, 2008  
  
eCTD submission 53 Response to the Agency's Complete Response Letter, January 9, 2009  
  
eCTD submission 56 Response to the Agency's Information Request of February 23, 2009.  
  
eCTD submission 59 Updated stability data and analysis
7. **SCOPE:** A review of the sponsor's responses to the CMC issues which contributed to the Agency issuing a Complete Response (CR) letter dated December 18, 2008.

### **REVIEW SUMMARY:**

At the end of the original review clock for BLA 125261, the sponsor had two on-going investigations into visible particle results for drug product. There was an out of trend (OOT) investigation and an out of specification (OOS) investigation.

#### OOT Investigation

The focus of the OOT investigation was the increased appearance, in stability samples stored at the recommended storage temperature of 2-8<sup>0</sup>C, of visible particles in drug product validation batches compared to batches used in clinical trials. To date, the sponsor has not been able to determine a root cause for the OOT results. The results to date support that the validation batches 1) demonstrate an increased appearance on stability of visible particles, compared to the batches



used clinically, and 2) these particles represent the normal degradation pathway of the product. However, as result of the OOT results the sponsor has changed to shelf-life of the drug product to 12 months. This, in conjunction with other changes and commitments from the sponsor are considered adequate to address CMC concerns regarding the OOT results.

OOS Investigation

The focus of the OOS investigation was the failure at release of post-validation batches due to high visible particles levels. These OOS results were the basis of the CMC complete response (CR) letter issued for BLA 125261. In the current submission, the sponsor has provided adequate data to indicate that the \_\_\_\_\_ vials are a root cause of the OOS results. Therefore, the increased particles in the OOS results were an artifact of the \_\_\_\_\_ and do not represent particles present in drug product. The sponsor has also provided adequate data to support a change in the pooling procedure to use of glass syringes.

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Recommendation

The sponsor has adequately addressed CMC issues and, from a CMC perspective, BLA 125261 is recommended for approval.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**Addendum to BLA 125261**  
**Chemistry, Manufacturing and Control Assessment**



**Addendum to BLA 125261**  
**Chemistry, Manufacturing and Control Assessment**

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**Product Quality Review Data Sheet Addendum**

1. **BLA#** STN 125261/0
2. **REVIEW #:** 2
3. **REVIEW DATE:** 30-Oct-08
4. **REVIEWERS:** Laurie Graham, M.S. *L. Graham 11/6/08*  
Barbara Rellahan, M.S., Ph.D. Team Leader *B. Rellahan 11/6/08*

**5. COMMUNICATIONS WITH SPONSOR**

<u>Communication</u>	<u>Date</u>
CMC Information Request #6	05-Aug-2008
CMC Information Request #7	05-Sept-2008
CMC Information Request #8	10-Oct-2008
Teleconference with Sponsor	17-Oct-2008
Email to Sponsor	30-Oct-2008

**6. SUBMISSIONS BEING REVIEWED**

The following table list the BLA amendments that are covered in this addendum.

<u>Submission</u>	<u>Content and Date</u>
eCTD 34 of July 30, 2008	Follow-up response to Agency CMC Information Request #4 from July 9, 2008.
eCTD 35 of August 8, 2008	Response to Agency Information Request #6 (August 5, 2008)
eCTD 39 of September 24, 2008	Response to Agency CMC Information Request #7 of September 5, 2008)
eCTD 40 of October 15, 2008	Response to Agency CMC Information Request #8
eCTD 42 of October 20, 2008	Follow-up response to Agency CMC Information Request #8 and teleconference between Agency and Sponsor on October 17, 2008.
eCTD 43 of October 27, 2008	Follow-up response to Agency CMC Information Request #8, teleconference between Agency and Sponsor on October 17, 2008, and eCTD sequence #42.
eCTD 45 of October 29, 2008	Supplemental information to eCTD #43.
eCTD 46 of November 4, 2008	Response to Agency email of October 30, 2008.

7. SCOPE: This addendum contains reviews of information submitted to the BLA after 15-Jul-08 (see submissions outlined above) and updates the original CMC and Executive Summary reviews with some additional information and corrections.

8. BLA Amendment Reviews:

The additional submissions from the sponsor concern the following:

- a) Out-of-trend (OOT) results for stability samples and failures at release for the visible particle assay used for drug product release. It is unclear, at this time, if there is a single or multiple root causes for these results. It is also unclear if the observed increased in visible particle results represents an assay issue, a drug product stability issue, or a combination of both. **As a result of the information on the visible particle assay, from a CMC perspective, the recommendation for approval has been withdrawn. It is now recommended that a Complete Response Letter be issued so that information can be submitted to address the recent OOT and out-of-specification (OOS) results observed with the visible particulate assay.**
- b) The stability indicating properties of the cIEF assay compared to the IEF assay. The sponsor would like to replace the IEF assay, which is currently used for DS and DP release and stability testing, with the cIEF assay. It is unclear, however, if the cIEF is as stability indicating as the IEF assay. This issue has still not been resolved with the sponsor. **It is therefore recommended that the IEF and cIEF assays be run side by side until the sponsor has provided sufficient data to the agency to demonstrate that the cIEF assay is as stability indicating as the IEF assay.**
- c) A re-analysis of the \_\_\_\_\_ concentration data.
- d) CMC Post marketing commitments suggested by the Agency and other CMC issues.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

# Review Cover Sheet

**BLA STN 125261/0**

**Ustekinumab (CNTO1275)**

**Centocor Biologics, LLC**

**Laurie Graham, M.S.**

**Ram Sihag, Ph.D.**

**Division of Monoclonal Antibodies; HFD-123**



# Product Quality Review Data Sheet

1. **BLA#** STN 125261/0
2. **REVIEW #:** 1
3. **REVIEW DATE:** 15-Jul-08
4. **REVIEWERS:** Laurie Graham, M.S.  
Ram Sihag, Ph.D.  
Barbara Rellahan, M.S., Ph.D. Team Leader

5. **COMMUNICATIONS WITH SPONSOR AND SUPPORTING DOCUMENTS:**

<u>Communication/Document</u>	<u>Date</u>
CMC Pre-BLA Meeting	14-May-2007
Filing Review Memo	08-Jan-2008
Teleconference	08-Jan-2008
Information Request Letter #1	13-March-2008
Ustekinumab 483	18-Apr-2008
Teleconference	30-Apr-2008
Cilag Inspection Waiver	25-Mar-2008
Information Request Letter #2	23-May-2008
Teleconference	10-Jun-2008
Information Request Letter #3	09-Jun-2008
Email information request	02-Jul-2008
Information Request Letter #4	09-Jul-2008
Information Request Letter #5	14-Jul-2008
Teleconference	15-Jul-2008

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

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
STN 125261/0	13-Jan-20007
STN 125261/4 (response to IR #1)	31-Mar-2008
STN 125261/6 (response to IR #1)	01-Apr-2008
STN 125261/10 (major amendment)	01-May-2008
STN 125261/11 (response to 4/30/08 teleconference)	13-May-2008
STN 125261/12 (483 response)	16-May-2008
STN 125261/13 (submission of missing stability table)	22-May-2008
STN 125261/14 (response to IR #2)	23-May-2008
STN 125261/15 (response update to 4/30/08 teleconference)	30-May-2008
STN 125261/16 (response to IR #2)	30-May-2008
STN 125261/17 (response to IR# 2)	06-Jun-2008
STN 125261/19 (update to intermediate hold times)	11-Jun-2008
STN 125261/24 (response update to 4/30/08 teleconference, update to 483 responses, response to IR #3)	24-Jun-2008
STN 125261/25 (response to 483-update to bioburden Specifications)	01-Jul-2008
STN 125261/26 (response to email from agency sent 7/2/2008)	10-Jul-2008
STN 125261/27 (response to IR #4)	14-Jul-2008
STN 125261/28 (response to IR #4)	17-Jul-2008

STN 125261/31 (response to IR #4) 18-Jul-2008  
 STN 125261/32 (response to IR #4) 18-Jul-2008  
 STN 125261/33 28-Jul-2008

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

**Name:** Centocor Biologics, LLC  
**Address:** 200 Great Valley Parkway  
 Malvern, PA 19355  
 USA  
 FDA registration number: 3003418999  
**Representative:** Kim Shields  
**Telephone:** 610-889-4486

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

a) Proprietary Name: Not determined  
 b) Non-Proprietary/USAN: Ustekinumab  
 c) Code name: CAS # 815610-63-0  
 d) Common name: CNTO 1275, anti-IL-12/23 p40 human IgG1kappa  
 e) Drug Review Status: Original Application  
 f) Chemical Type: Interleukin receptor inhibitor with ATC subgroup code L04AC  
 g) CAS index/registry no. Immunoglobulin G1, anti- (human interleukin 12 p40 subunit)(human monoclonal CNTO 1275  $\gamma$ 1-chain), disulfide with human monoclonal CNTO 1275  $\bullet$ -chain, dimer/ CAS # 815610-63-0.

**9. PHARMACOL. CATEGORY:** Fully human IgG1 kappa immunoglobulin molecule.

**10. DOSAGE FORM:** Sterile parenteral solution.

**11. STRENGTH/POTENCY:**

- a) The concentration of CNTO 1275 Drug Product is 90 mg/ml.
- b) Potency is defined as percent activity relative to the reference standard, using a cell based assay which measures the inhibition of IL-12 induced IFN $\gamma$  production by an NK cell line, ██████████ Dating period for vialled drug product is ██████████ when stored at 2°C -8°C and protected from light.
- c) Ustekinumab is filled into 2 mL glass vials containing 90 mg or 45 mg of Ustekinumab

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**12. ROUTE OF ADMINISTRATION:** Subcutaneous injection.

**13. ACID (Animal Component Information Database)**

Refer to BLA 125160 review for animal/human derived component information.  
 Also see section 3.2.S.2.3.1 Control of Source and Starting Materials of Biological Origin.

**14. RELATED/SUPPORTING DOCUMENTS:**

DMF #	HOLDER	ITEM REFERENCE D	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENTS
		DS manufacturing facility		N/A		Information for facilities and process is in the BLA. A PAI was

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  ✓   Trade Secret / Confidential (b4)

       Draft Labeling (b4)

       Draft Labeling (b5)

       Deliberative Process (b5)

<sup>1</sup> Action codes for DMF Table:

- 1 – DMF Reviewed.
- Other codes indicate why the DMF was not reviewed, as follows:
- 2 – Type 1 DMF
- 3 – Reviewed previously and no revision since last review
- 4 – Sufficient information in application
- 5 – Authority to reference not granted
- 6 – DMF not available
- 7 – Other (explain under "Comments")

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

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

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	Approve		
Environmental Assessment	Approve	15-Jul-08	Laurie Graham
DMPQ -- memo for Drug Substance facilities review	Approve		Michelle Clark-Stuart
DMPQ -- memo for Drug Product facilities review	Approve		Bo Chi
DDMAC Carton and vial labeling			
OBP Carton and vial labeling	Approve	28-Mar-08	Wang/Rawls
DMETS/DDMAC – tradename review	Pending		
EIR for Ustekinumab	VAI	18-May-08	Chi/ Graham/ Lopicka/ Suvarna
Inspection Waiver for Cilag, AG	Waive PAI	25-Mar-08	Chi/Graham

(1) DMPQ review date states VAI has not been changed since EIR

16. **Inspectional Activities**

A pre-approval inspection (PAI) for CNTO 1275 bulk drug substance and formulated drug substance production at the Centocor, St. Louis facility was conducted on April 14-18, 2008 by TFRB inspectors Bo Chi, and Kalavati Suvarna, ORA inspector Warren J. Lopicka, and product reviewer Laurie Graham. Centocor St. Louis is responsible for manufacturing of CNTO-1275 drug substance, formulated drug substance, QC testing of drug substance, formulated drug substance, and drug product and final QA review and approval. Centocor St. Louis has been inspected by the FDA previously with no regulatory actions, prior warnings or recalls. A six-observation form 483 was issued at the end of this inspection.

- 1) Changes were implemented in manufacturing operations without adequate validation to ensure  
 \_\_\_\_\_  
 For example, after a change in \_\_\_\_\_  
 \_\_\_\_\_  
 \_\_\_\_\_

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- 2) There is a failure to adequately verify the cleaning of shared equipment between different product campaigns.

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- 3) There is a failure to establish and/or follow written protocol procedures in a product intermediate stability study.

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- 4) Procedures designed to ensure that \_\_\_\_\_ remain sterile during storage and prior to use are not adequately validated.

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- 5) There is no assurance that intermediates held for further processing are stored under appropriate conditions to ensure their suitability for use. Specifically, the intermediate hold times were not validated at manufacturing scale \_\_\_\_\_

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- 6) There is insufficient sensitivity in the bioburden test used for in-process product samples. Specifically,

Two additional items were resolved by the firm prior to the end of the inspection. These were: the SOP for the bioburden test was not revised to reflect new sample testing time limits and the SOP for endotoxin did not specify the time limit for in-process sample testing. There were also seven recommendations to the firm during the inspection. These recommendations were:

1. Perform integrity testing of \_\_\_\_\_
2. Tighten the bioburden acceptance criteria for buffer \_\_\_\_\_ hold validation studies to reflect actual data.
3. Use the \_\_\_\_\_ method for bioburden testing of \_\_\_\_\_ sample and harvest sample to allow analysis of appropriate sample volume.

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4. The specification for IEF is "conforms to reference", however the meaning of this specification can be changed depending upon where the test samples are taken from in the manufacturing process. Samples taken upstream in the purification process do not need to conform completely to the reference standard, as the reference standard represents final purified material. A comment was made to the firm that "conforms to reference" should have one meaning and that any changes to this meaning should be clearly documented.
5. A change in the set-up of the IEF gels, with reference standard bracketing test samples, was suggested to help in the interpretation of the results.

6. After reviewing the batch records, it was suggested that changes should made to allow better tracking of \_\_\_\_\_

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7. After reviewing the validation of cell counting by the [redacted] system, it was noted that the [redacted] gives % viability results that are much lower than the previously used manual counting. As % viability is used as a specification at cell thawing, it was suggested that the firm re-evaluate the use of % viability or the current specification. It was also suggested to the firm that the low % viability with the [redacted] may have been a contributing factor in the out of specification results for % viability at thaw of the working cell bank, [redacted]

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The issues and recommendations described above should be followed-up in future inspections.

Inspection at Cilag, AG (FEI: 3002806695) where DP is manufactured under contract to Centocor, was waived. This waiver was based on the criteria as required per SOPP 8410 v.2, "Determining When Pre-licensing/pre-approval Inspections (PLI/PAI) are Necessary." The review committee recommended that the inspection be waived because there are no substantive differences between the drug product manufacturing processes described in the BLA and those used for other licensed parenteral products at Cilag AG. These processes were inspected last year (2007) with no significant regulatory findings.

## 17. Quality Assessment

### a) Review of Module 3.2: Body of Data

The review of module 3.2 is attached as a separate document that also includes review of the immunogenicity assay and the assay to detect neutralizing antibodies.

### b) Module 1: Environmental Assessment

Centocor claims categorical exclusion from the requirements of environmental assessment (BLA section S1.12.14) based on 21CFR25.31. The sponsor provided the calculation for the expected introduction concentration (EIC)-aquatic, which was [redacted]. This was based on a projected production estimate of [redacted] entering the publicly owned treatment works (POTW). There is, therefore, minimal impact expected of Ustekinumab manufacturing on the environment.

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### c) List of Deficiencies

The deficiencies have been addressed in the communications with the sponsor. A number of issues have been resolved as post-marketing commitments (See Chemistry Team Leader Executive Summary).

## 18. Recommendations on Approvability

The data submitted in this application support the conclusion that the manufacture of Ustekinumab 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 the parameters recommended by FDA. The conditions used in manufacturing have been sufficiently validated, and a consistent product is produced from the multiple production runs presented. It is recommended that this product be approved for human use under conditions specified in the package insert.

Administrative

A. Reviewer's Signatures

Product Reviewer: Laurie Graham, M.S. *L. Graham 7/29/08*

Product Reviewer: Ram Sihag, Ph.D. *R. Sihag 7/29/08*

B. Endorsement Block

Product Quality Division Team Leader: Barbara Rellahan, M.S., Ph.D. *Barbara Rellahan 7/29/08*

Product Quality Division Deputy Director: Patrick Swann, Ph.D. *Patrick Swann 7/29/08*

Product Quality Division Director: Kathleen Clouse, Ph.D. *Kathleen Clouse 7/31/08*

C. CC Block

OBP Office Director: Steven Kozlowski, M.D.

DDDP CDTL: Jill Lindstrom, Ph.D.

DDDP Division Director: Susan Walker, M.D.

Division of Monoclonal Antibodies File/BLA STN 125261/0

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

<b>CTD Module 2 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Overall CTD Table of Contents [2.1]	Y N	There is an index.xml file that has table of contents for entire BLA.
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	There are no novel excipients. There is a section that covers all excipients in section 2.3(2.3.P.4)
<input type="checkbox"/> Executed Batch Records	Y N	
<input type="checkbox"/> Method Validation Package	Y N	This could not be found in overall summary (module 2), but it is in module 3.2.P.2.2.1
<input type="checkbox"/> Comparability Protocols	Y N	

<b>CTD Module 3 Contents</b>	<b>Present?</b>	<b>If not, justification, action &amp; status</b>
Module Table of Contents [3.1]	Y N	There is an index.xml file that has table of contents for entire BLA.
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		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y N	

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <li><input type="checkbox"/> justification of specifications</li> <li><input type="checkbox"/> analytical method validation</li> <li><input type="checkbox"/> reference standards</li> <li><input type="checkbox"/> stability</li> <li><input checked="" type="checkbox"/> process validation (prospective plan, results, analysis, and conclusions)      Y    N</li> <li><input checked="" type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes)      Y    N</li> <li><input checked="" type="checkbox"/> characterization of drug substance      Y    N</li> <li><input checked="" type="checkbox"/> control of drug substance      Y    N <ul style="list-style-type: none"> <li><input type="checkbox"/> specification <ul style="list-style-type: none"> <li><input type="checkbox"/> justification of specs.</li> </ul> </li> <li><input type="checkbox"/> analytical procedures</li> <li><input type="checkbox"/> analytical method validation</li> <li><input type="checkbox"/> batch analyses <ul style="list-style-type: none"> <li><input type="checkbox"/> consistency (3 consecutive lots)</li> <li><input type="checkbox"/> justification of specs.</li> </ul> </li> </ul> </li> <li><input checked="" type="checkbox"/> reference standards      Y    N</li> <li><input checked="" type="checkbox"/> container closure system      Y    N</li> <li><input checked="" type="checkbox"/> stability      Y    N <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval <ul style="list-style-type: none"> <li><input type="checkbox"/> protocol</li> <li><input type="checkbox"/> results</li> <li><input type="checkbox"/> method validation</li> </ul> </li> </ul> </li> </ul>		<p>It was unclear whether the batch analysis is from 3 consecutive batches, but the sponsor indicated in a telecon from the filing meeting on 7/8/2008 that the validation runs were consecutive.</p>
<p><b>Drug Product [3.2.P]</b></p> <ul style="list-style-type: none"> <li><input checked="" type="checkbox"/> description and composition      Y    N</li> <li><input checked="" type="checkbox"/> pharmaceutical development      Y    N</li> <li><input checked="" type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)      Y    N</li> <li><input checked="" type="checkbox"/> batch formula      Y    N</li> <li><input checked="" 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</li> <li><input checked="" type="checkbox"/> controls of critical steps and intermediates      Y    N</li> <li><input checked="" type="checkbox"/> process validation including aseptic      Y    N</li> </ul>		

CTD Module 3 Contents	Present?	If not, justification, action & status
processing & sterility assurance: <ul style="list-style-type: none"> <li>○ 3 consecutive lots</li> <li>○ other needed validation data</li> </ul> <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"> <li>○ specifications (vial, elastomer, drawings)</li> <li>○ availability of DMF</li> <li>○ closure integrity</li> <li>○ administration device(s)</li> </ul> <input type="checkbox"/> stability <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval               <ul style="list-style-type: none"> <li>○ protocol</li> <li>○ results</li> <li>○ method validation</li> </ul> </li> </ul>	Y N  Y N  Y N  Y N	It was unclear if 3 consecutive lots were used, but the sponsor indicated in a telecon from the filing meeting on 7/8/2008 that the validation runs were consecutive.
Diluent (vials or filled syringes) [3.2P'] <input type="checkbox"/> description and composition of diluent <input type="checkbox"/> pharmaceutical development <input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved) <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) <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"> <li>○ 3 consecutive lots</li> <li>○ other needed validation data</li> </ul> <input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of	Y N Y N Y N Y N Y N Y N Y N	There is no diluent.

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

CTD Module 3 Contents	Present?	If not, justification, action & status
<ul style="list-style-type: none"> <li>○ testing at appropriate stages of production</li> <li>□ novel excipients</li> </ul>	Y N	This is in section describing DP, 3.2.4.6. There are no novel excipients.
USA Regional Information [3.2.R] <ul style="list-style-type: none"> <li>□ executed batch records</li> <li>□ method validation package</li> <li>□ comparability protocols</li> </ul>	Y N Y N Y N	Not in this section. Found in section 3.2.P.2.21
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	The sponsor indicated in a telecon from the filing meeting on 7/8/2008 that the validation runs were consecutive.
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	Y N	

Examples of Filing Issues	Yes?	If not, justification, action & status
have occurred)		
certification that all facilities are ready for inspection	Y N	There is an indication that a pre-approval inspection was done in August of 2007. This inspection was for REMICADE not the current product. The sponsor indicated in a telecon from the filing meeting on 7/8/2008 that the CNTO1275 Drug Substance facility is ready for inspection.
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 <input type="checkbox"/> <input type="checkbox"/>	Y N Y N Y N	This will be a review, not filing, issue.  LAL conforms to USP and Eu. Ph. Compliant with Eu. Ph. Conforms to Eu. Ph.
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).

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Recommendation (circle one): File RTF

Reviewer: Jamie Mathom <sup>1/25/08</sup> Type (circle one): Product (Chair) Facility (DMPQ)  
(signature/ date)

Concurrence: Barbara Kellorian  
Branch/Lab Chief: Team leader <sup>1/25/08</sup>  
(signature/ date)

Division Director: Raylene Clouse <sup>01/25/08</sup>  
(signature/ date)

**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	
Introduction to the summary documents (1 page) [2.2]	Y	
Quality overall summary [2.3]	Y	
<input type="checkbox"/> Drug Substance	Y	
<input type="checkbox"/> Drug Product	Y	
<input type="checkbox"/> Facilities and Equipment	Y	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	Y	
<input type="checkbox"/> Novel Excipients	Y	3.2.P.4.6
<input type="checkbox"/> Executed Batch Records	Y	3.2.R
<input type="checkbox"/> Method Validation Package	Y	3.2.R
<input type="checkbox"/> Comparability Protocols	Y N	BMT is not responsible for reviewing this.

CTD Module 3 Contents	Present?	If not, justification, action & status
Module Table of Contents [3.1]	Y	
Drug Substance [3.2.S]		
<input type="checkbox"/> general info	Y	
<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	The firm does not state that the sites are ready for inspection. The firm later confirmed in a T-con that the sites are inspection ready.
<input type="checkbox"/> description of manufacturing process	Y	
<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	
<input type="checkbox"/> raw materials and reagents		
<input type="checkbox"/> biological source and starting materials		
<input type="checkbox"/> cell substrate: source, history, and generation		
<input type="checkbox"/> cell banking system, characterization, and testing		
<input type="checkbox"/> control of critical steps and intermediates	Y	
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> analytical method validation		
<input type="checkbox"/> reference standards		
<input type="checkbox"/> stability		
<input type="checkbox"/> process validation (prospective	Y	



CTD Module 3 Contents	Present?	If not, justification, action & status
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"> <li><input type="checkbox"/> specifications (vial, elastomer, drawings)</li> <li><input type="checkbox"/> availability of DMF</li> <li><input type="checkbox"/> closure integrity</li> <li><input type="checkbox"/> administration device(s)</li> </ul> <input type="checkbox"/> stability <ul style="list-style-type: none"> <li><input type="checkbox"/> summary</li> <li><input type="checkbox"/> post-approval protocol and commitment</li> <li><input type="checkbox"/> pre-approval               <ul style="list-style-type: none"> <li><input type="checkbox"/> protocol</li> <li><input type="checkbox"/> results</li> <li><input type="checkbox"/> method validation</li> </ul> </li> </ul>	Y  Y     Y	
Diluent (vials or filled syringes) [3.2P'] <ul style="list-style-type: none"> <li><input type="checkbox"/> description and composition of diluent</li> <li><input type="checkbox"/> pharmaceutical development</li> <li><input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)</li> <li><input type="checkbox"/> batch formula</li> <li><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)</li> <li><input type="checkbox"/> controls of critical steps and intermediates</li> <li><input type="checkbox"/> process validation including aseptic processing &amp; sterility assurance:               <ul style="list-style-type: none"> <li><input type="checkbox"/> 3 consecutive lots</li> <li><input type="checkbox"/> other needed validation data</li> </ul> </li> <li><input type="checkbox"/> control of excipients (justification of specifications; analytical method validation; excipients of human/animal origin, other novel excipients)</li> <li><input type="checkbox"/> control of diluent (justification of specifications; analytical method validation, batch analysis, characterization of impurities)</li> </ul>	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
<input type="checkbox"/> comparability protocols	Y N	BMT is not responsible for reviewing this.
Literature references and copies [3.3]	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	Y	
<input type="checkbox"/> legible	Y	
<input type="checkbox"/> English (or translated into English)	Y	
<input type="checkbox"/> compatible file formats	Y	
<input type="checkbox"/> navigable hyper-links	Y	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	Y	
<input type="checkbox"/> summary reports reference the location of individual data and records	Y	
<input type="checkbox"/> all electronic submission components usable	Y	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	Y	
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	
includes data demonstrating consistency of manufacture	Y	
includes complete description of product lots and manufacturing process utilized for clinical studies	Y N	Not reviewed by BMT.
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	Y N	Not reviewed by BMT.
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	Not reviewed by BMT.
certification that all facilities are ready for inspection	N	The firm later confirmed in a T-con that the sites are inspection ready.
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	
if not using a test or process specified by regulation, data is provided to show the	Y	

Examples of Filing Issues	Yes?	If not, justification, action & status
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 <input type="checkbox"/> <input type="checkbox"/>	Y Y Y	
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	
floor diagrams that address the flow of the manufacturing process for the drug substance and drug product	Y	
description of precautions taken to prevent product contamination and cross-contamination, including identification of other products utilizing the same manufacturing areas and equipment	Y	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	Y	
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).

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Recommendation (circle one): File RTF

Reviewer: Bo Chi 1/9/08 Michelle Clark-Stewart 1/9/08 Type (circle one): Product (Chair) Facility (DMPQ)  
 (signature/ date)

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

Division Director: [Signature]  
 (signature/ date)