

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*  
**125261**

**MICROBIOLOGY REVIEW(S)**



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
WO Bldg 51  
10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** 11/25/2008  
**To:** Administrative File, STN 125261/0  
**From:** Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT *BC 11/25/08*  
**Endorsement:** Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT *PH 12/1/08*  
Edwin Rivera Martinez, Branch Chief, CDER/OC/DMPQ/MAPCB *E. Rivera 12/01/08*  
**Subject:** New Biologic License Application (BLA)  
**Applicant:** Centocor, Inc.  
**US License:** 1242  
**Facility:** Centocor Biologics, LLC, 4777 LeBourget Drive, St. Louis, MO 63134  
FEI: 3003418999  
**Product:** ustekinumab (CNTO 1275)  
**Dosage:** Liquid in vial, 45 mg/vial and 90 mg/vial, subcutaneous injection  
**Indication:** Treatment of adult patients with moderate to severe plaque psoriasis  
**PDUFA date:** December 28, 2008

**Recommendation:** The drug substance part of this application is recommended for approval from product quality microbiology perspective with the following post-market commitment: Develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest ~~\_\_\_\_\_~~ ) and harvest samples. The acceptance criteria for bioburden in-process controls should be consistent with historical data and reported as CFU/volume tested.

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### Review Summary

Centocor, Inc has submitted this BLA for ustekinumab, a product indicated to treat adult patients with moderate to severe plaque psoriasis. The drug substance is manufactured at Centocor Biologics, LLC, located in St. Louis, Missouri. The drug product (DP) is manufactured at Cilag AG, Hochstrasse 201, 8205 Schaffhausen, Switzerland. The application contains CMC information in an eCTD format.

The pre-license inspection of the drug substance manufacturing site at Centocor Biologics, LLC was conducted by BMT (Bo Chi and Kalavati Suvarna), OBP/DMA (Laurie Graham), and KAN-DO (Warren Lopicka) on 4/14-18/2008. Six observations were issued on Form FDA 483 on April 18, 2008. Responses to the observations were reviewed by a compliance officer in OC/DMPQ and are deemed acceptable.

**Assessment**

**Drug Substance (3.2.S)**

**General Information (3.2.S.1)**

Ustekinumab is a human immunoglobulin G1 (IgG1) monoclonal antibody that binds with high affinity and specificity to, and neutralizes, the p40 protein subunit of human interleukin (IL)-12 and IL-23.

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The expected molecular mass range of these glycoforms is 148079 to 149690 Daltons.

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**Manufacture (3.2.S.2)**

**Manufacturer(s) (3.2.S.2.1)**

Ustekinumab drug substance manufacturing and testing site of the drug substance and process intermediates is:

Centocor Biologics, LLC,  
4777 LeBourget Drive,  
St. Louis, MO 63134  
FEI: 3003418999

Mycoplasma and In-Vitro Assay for Adventitious Agents site is:

\_\_\_\_\_

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Preparation of CNTO 1275 Working Cell Banks may be performed at:  
Centocor Research and Development  
200 Great Valley Parkway  
Malvern, PA 19355  
USA  
FEI: 3001610451

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**Description of Manufacturing Process and Process Controls (3.2.S.2.2)**

Ustekinumab formulated bulk (FB) is manufactured by

\_\_\_\_\_

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**Controls of Critical Steps and Intermediates (3.2.S.2.4)**

Bioburden and endotoxin levels are monitored throughout the manufacturing process. Product Acceptance criteria for in-process controls are listed in Table 1 of this section of the BLA. Summary in-process control data for phase 3 clinical and validation batches are provided.

The bioburden test of bioreactor samples and harvest samples uses \_\_\_\_\_ It was recommended during the PAI \_\_\_\_\_ bioburden test method be used for those samples. The bioburden test for the rest of the in-process samples uses \_\_\_\_\_ method. But only \_\_\_\_\_ sample volume is used in the \_\_\_\_\_ method and the test is duplicated for each sample.

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*Reviewer comment: During the inspection, a 483 observation (# 6) was issued for insufficient sensitivity in the bioburden test used for in-process product samples. Centocor in response to the observation, increased bioburden sample volume to*

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\_\_\_\_\_ samples.

Satisfactory

The bioburden test of the pre-harvest and harvest samples uses \_\_\_\_\_ n the \_\_\_\_\_ The following item will be reviewed as a post-market commitment:

*Develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest \_\_\_\_\_ and harvest samples. The acceptance criteria for bioburden in-process controls should be consistent with historical data and reported as CFU/volume tested.*

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**Process Validation and/or Evaluation (3.2.S.2.5)**

The in-process control results for the three validation lots are provided and are acceptable.

\_\_\_\_\_ were evaluated during the inspection.

*Reviewer comment: It was found during the inspection that the \_\_\_\_\_ process had high rate of failure due to contaminations. The investigations of the contaminations were evaluated during the inspection. Root causes were found and corrective actions were taken. A chart was provided by the firm showing five consecutive successful \_\_\_\_\_ runs after the series of contamination events, including the 6th and 7th commercial run for CNTO 1275, two clinical runs for one Phase III clinical product, and one clinical run for the other product. The \_\_\_\_\_ process for the two Phase III clinical products and CNTO 1275 are the same. Bioburden data for pre-harvest sample for commercial runs #10 and #11 was later requested and submitted to the BLA. The bioburden results were \_\_\_\_\_*

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The product intermediates were not held at manufacturing scale and there is no microbiology data to support the maximum hold time for product intermediates. A 483 observation was made (#5) for process intermediate hold times not validated at manufacturing scale. Centocor in response committed that the \_\_\_\_\_ product intermediates will not be held longer than 24 hours.

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It was also found during the PAI that the sterile hold time for the bioreactor was not properly validated. This was a 483 observation (#4). The firm committed to perform a media hold validation study to validate the \_\_\_\_\_ hold period.

*Satisfactory*

**Control of drug substance (3.2.S.4)**

**Specification (3.2.S.4.1) and Batch analysis (3.2.S.4.4)**

Release specifications for the drug substance are provided in Table 1 of section 3.2.S.4.1. The formulated bulk drug substance is stored \_\_\_\_\_

b(4)

\_\_\_\_\_ Release data for CNTO 1275 FB Phase 3 clinical, validation, and post validation batches were all \_\_\_\_\_ for the bioburden test and between \_\_\_\_\_ for the endotoxin test.

*Satisfactory*

**Validation of Analytical Procedures (3.2.S.4.3)**

**Bacterial endotoxin test**

The endotoxin test uses limulus amebocyte lysate kinetic chromogenic procedure and follows USP <85> (Bacterial Endotoxin Test), the "FDA Guideline on Validation of the Limulus Amebocyte Lysate (LAL) Test as an End-Product Endotoxin Test for Human and Animal Parenteral Drugs, Biological Products, and Medical Devices" (1987), and EP 2.6.14 (Bacterial Endotoxin).

In addition to \_\_\_\_\_ and FB test articles, the following test articles were verified for endotoxin testing: \_\_\_\_\_

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\_\_\_\_\_

The maximum valid dilution and non-inhibitory concentration (NIC) suitable for routine testing of each of the above samples were determined. Three batches of each type of sample were used in the qualification studies. Qualification study results for \_\_\_\_\_ and FB samples were provided. All the test articles had pH values within the recommended range of pH 6.0 to 8.0. The standard curve and endotoxin recovery from positive product controls all met the acceptance criteria.

*Satisfactory*

**Bioburden test**

The bioburden procedure is either a \_\_\_\_\_ assay for total aerobic microbial count performed according to USP <61> (Microbiological Examination of Nonsterile Products: Microbial Enumeration Tests) and EP 2.6.12 (Microbial Examination of Non-sterile Products: Total Aerobic Microbial Count). The \_\_\_\_\_ assay is used for cell-containing test articles while the \_\_\_\_\_ assay is used for other test articles. b(4)

The following samples and microorganisms were used in the qualification studies.

Table 2 Materials employed in the verification of the bioburden procedure

Test Articles	Three CNTO 1275 _____ batches (694860, 694061, 694063) Three CNTO 1275 FB batches (700201, 697057, 699898) Three batches each of cell culture
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Microorganisms	<i>Bacillus subtilis</i> , ATCC <sup>a</sup> 6633 <i>Candida albicans</i> , ATCC 10231 <i>Staphylococcus aureus</i> , ATCC 6538 <i>Escherichia coli</i> , ATCC 8739 <i>Salmonella choleraesuis</i> , ATCC 10708 <i>Aspergillus niger</i> , ATCC 16404 <i>Pseudomonas aeruginosa</i> , ATCC 9027
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Medium and Rinsing Solution	Media and solutions according to SOP
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<sup>a</sup> ATCC = American type culture collection

The acceptance criteria are:

- Positive control plates must be 10 to 100 colony forming units (cfu)/0.1 mL.
- The population of each challenge organism in the test article must be no more than 100 cfu/0.1 mL.
- The recovery of the challenge organisms is not less than 70% of the positive control.

Qualification study results for \_\_\_\_\_ and FB samples were provided and met the acceptance criteria. b(4)

*Satisfactory*

### Container Closure System (3.2.S.6)

The container closure system used for storage and shipping of CNTO 1275 Formulated Bulk (FB) \_\_\_\_\_

\_\_\_\_\_ The container closure integrity validation results were evaluated during the PAI and were acceptable.

*Satisfactory*

**Stability (3.2.S.7)**

The manufacturing process for CNTO 1275 formulated bulk (FB) includes \_\_\_\_\_ points, the pH-adjusted and \_\_\_\_\_ and FB produced in \_\_\_\_\_. Both \_\_\_\_\_ manufacturing the CNTO 1275 Final Vialled Product (FVP). No microbiological attributes are monitored. b(4)

*Reviewer comment: The stability program and data should be reviewed by the OBP/DMA reviewer.*

*Satisfactory*

**Environmental Assessment:**

A claim for a categorical exclusion from preparing an Environmental Assessment under 21 CFR 25.31(a) was provided by the firm, and that to the knowledge of Centocor, Inc., no extraordinary circumstances exist that would otherwise require an environmental assessment.

**cGMP Status:**

Firm	Inspection Date	Classification	Profiles
Centocor Biologics, LLC, 4777 LeBourget Drive, St. Louis, MO 63134 FEI: 3003418999	4/14-4/18/2008	VAI	_____ TRP

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\_\_\_\_\_ NAI \_\_\_\_\_ CTL

Centocor, 200 Great Valley Parkway, Malvern, PA, was last inspected by Team Biologics in November 2006. The inspection was initially classified OAI by the investigator due to inadequate quality oversight of deviations and investigations, among other findings. The inspection received further review by an OE Compliance Officer and was subsequently reclassified to VAI after review of the firm's response. This site is also scheduled for surveillance coverage this fiscal year.

The Manufacturing Assessment and Preapproval Compliance Branch has completed the review of the 483 observations of the recent CBER requested BIMO inspection of \_\_\_\_\_. The deficiencies found during this inspection do not implicate any cell banks manufactured by \_\_\_\_\_ for the Centocor BLA STN 125261/0. b(4)

Therefore, there are no pending or ongoing compliance actions or investigations to prevent approval of STN 125261/0 at this time.

**Conclusion**

- I. The drug substance section of the BLA is recommended for approval from a product quality microbiology perspective with the following post-market commitment:

Develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest \_\_\_\_\_, \_\_\_\_\_, and harvest samples. The acceptance criteria for bioburden in-process controls should be consistent with historical data and reported as CFU/volume tested.

b(4)

- II. Information and data in this submission not related to microbial control of the drug substance should be reviewed by an OBP reviewer.
- III. The pre-approval inspection of the drug substance manufacturing site Centocor Biologics, LLC was conducted on 4/14-18/2008. Six Form FDA 483 observations were issued at the conclusion of the inspection on 4/18/08 (see below). Responses to the observations were reviewed by a compliance officer in OC/DMPQ and are deemed acceptable. The inspection was classified as VAI. The implementation of the corrective actions will be evaluated during the next surveillance inspection.

The following Form FDA 483 observations were issued during the inspection of the drug substance manufacturing site:

Centocor Biologics, LLC,  
4777 LeBourget Drive,  
St. Louis, MO 63134  
FEI: 3003418999

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

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\_\_\_\_\_  
*Staphylococcus aureus*, *Staphylococcus epidermidis*, *Kocuria carniphila*, and *Paracoccus* species (record ID 34247).

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

- 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. Specifically, during the sterile hold validation \_\_\_\_\_

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study

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

6) There is insufficient sensitivity in the bioburden test used for in-process product samples. Specifically, only a sample volume is used with the method

Cc: WO51: Chi  
WO51: Rivera Martinez  
WO51: Hughes  
WO22: Kang  
HFD-123, Rellahan  
HFD-123, Graham  
HFD-123, Sihag  
HFD-328, TFRB Blue Files (STN 125261)

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Post-market commitment for CMC drug substance section:

Develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest ~~\_\_\_\_\_~~  
~~\_\_\_\_\_~~ ) and harvest samples. The acceptance criteria for bioburden in-process controls should be consistent with historical data and reported as CFU/volume tested.

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
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10903 New Hampshire Ave.  
Silver Spring, MD 20993

**Date:** December 1, 2008  
**To:** Administrative File, STN 125261/0  
**From:** Patricia F. Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/BMT *PFH 12/1/08*  
**Through:** Edwin Rivera, Branch Chief, CDER/OC/DMPQ/MAPCB *E. Rivera 12/01/08*  
**Subject:** Secondary review of New Biologic License Application (BLA)  
**US License:** # 1242  
**Applicant:** Centocor, Inc.  
**Mfg Facilities:** Drug substance – Centocor Biologics, LLC St. Louis, MO 63134,  
FEI=3003418999  
Drug product - Cilag AG, 8205 Schaffhausen, Switzerland, FEI= 3002806695  
**Product:** ustekinumab (CNTO 1275)  
**Dosage:** Liquid in vial, 45 mg/vial and 90 mg/vial, subcutaneous injection  
**Indication:** Treatment of adult patients with moderate to severe plaque psoriasis  
**Due Date:** December 28, 2008

**Recommendation for approvability:** BLA 125261 is recommended for approval from a microbial control, sterility assurance and microbiology product quality perspective. CMC Sections 3.2.S and 3.2.P were assessed by Bo Chi, Ph.D. in two review memos to the file dated November 25, 2008 and September 24, 2008. The following post marketing commitment (PMC) should be communicated to the sponsor:

*Develop and implement a bioburden test method that uses an increased sample volume for the determination of bioburden in the pre-harvest \_\_\_\_\_ and harvest samples. The acceptance criteria for bioburden in-process controls should be consistent with historical data and reported as CFU/volume tested.*

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**Executive Summary:**

The drug substance Section of the BLA (Section 3.2.S) was assessed from a microbial control perspective and is recommended for approval. However, one post approval commitment relating to the bioburden test method at the pre-harvest and harvest steps should be communicated to the BLA sponsor. The BLA describes a \_\_\_\_\_ method that used only \_\_\_\_\_ of sample volume to monitor bioburden at the pre-harvest and harvest steps. The firm should commit to develop and implement a bioburden test method that uses an increased sample volume for the bioburden test. Ideally a \_\_\_\_\_ method should be developed and should replace the currently used \_\_\_\_\_ method.

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STN: 125261/0 Centocor, Inc.

The drug substance is manufactured at Centocor, LLC, located in St. Louis, Missouri (FEI=3003418999) and a pre-license inspection of this facility was conducted by a Team of FDA inspectors consisting of BMT reviewers Bo Chi, Ph.D. and Kalavati Suvarna, Ph.D., by OBP/DMA reviewer Laurie Graham, M.S. and investigator Warren Lopicka from the Kansas FDA District Office on April 14-18, 2008. Six 483 observations were presented to the firm at the closeout of the inspection. The inspection found that the firm had inadequately validated the \_\_\_\_\_ e operations which resulted in a high \_\_\_\_\_ failure rates due to contaminations. Cleaning of shared equipment was not verified between product campaigns and written procedures were not always followed. \_\_\_\_\_ hold times were not adequately validated and in-process intermediate hold times were not validated at scale. Finally, the bioburden test used for in-process product samples lacked adequate sensitivity.

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Centocor has satisfactorily responded to the 483 observations by implementing or committing to implement corrective actions. For example, Centocor has committed to validate the \_\_\_\_\_ hold time with a media simulation and to implement in-process intermediate hold times \_\_\_\_\_. In response to the bioburden observation (#6), the firm has committed to increase the sample volume to \_\_\_\_\_ for bioburden monitoring \_\_\_\_\_. However, since the responses did not address the sensitivity of the bioburden test method at the pre-harvest and harvest steps, a post marketing commitment for the test at these steps should be communicated to the firm (see paragraph above).

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The drug product section of the BLA (Section 3.2.P) was reviewed from a sterility assurance and microbiology product quality perspective and as amended, is recommended for approval. The review assessed the microbiological attributes of the drug product, the sterilization validation of the equipment and components in direct contact with sterile product in

\_\_\_\_\_

The sponsor commits to monitor samples of the drug product lots on stability initially, annually and at expiry for sterility and endotoxin post approval. A container closure integrity test in lieu of a sterility test, such as ? \_\_\_\_\_ will be implemented in the future.

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The drug product is manufactured at Cilag AG, Hochstrasse 201, 8205 Schaffhauser, Switzerland (FEI=3002806695). This facility was inspected in June 21-28, 2008 by DFI/ORA and found to have an acceptable compliance status. The pre-approval inspection in support of this application was waived by OC/DMPQ/BMT.

STN: 125261/0 Centocor, Inc.

Cc:

WO Bldg 51: Rivera Martinez

WO Bldg 51: Chi

WO Bldg22: Smoot

WO Bldg 51: BMT Blue Files (125261)

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Food and Drug Administration
Center for Drug Evaluation and Research
WO Bldg 51
10903 New Hampshire Ave.
Silver Spring, MD 20993

Date: 9/24/2008
To: Administrative File, STN 125261/0
From: Bo Chi, Ph.D., CDER/OC/DMPQ/MAPCB/BMT BC 9/24/08
Endorsement: Patricia Hughes, Ph.D., Team Leader, CDER/OC/DMPQ/MAPCB/BMT PP 9/25/08
Edwin Rivera Martinez, Branch Chief, CDER/OC/DMPQ/MAPCB E Rivera 9/25/08
Subject: New Biologic License Application (BLA)
Applicant: Centocor, Inc.
US License: 1242
Facility: Cilag AG, Hochstrasse 201, 8205 Schaffhausen, Switzerland
FEI: 3002806695
Product: ustekinumab (CNTO 1275)
Dosage: Liquid in vial, 45 mg/vial and 90 mg/vial, subcutaneous injection
Indication: Treatment of adult patients with moderate to severe plaque psoriasis
PDUFA date: December 28, 2008

Recommendation: The drug product part of this application, as amended, is recommended for approval from sterility assurance and product quality microbiology perspective.

Review Summary

Centocor, Inc has submitted this BLA for ustekinumab, a product indicated to treat adult patients with moderate to severe plaque psoriasis. The drug substance is manufactured at Centocor Biologics, LLC, located in St. Louis, Missouri. The drug product (DP) is manufactured at Cilag AG, H6chstrasse 201, 8205 Schaffhausen, Switzerland. The application contains CMC information in an eCTD format.

Assessment

Drug Product

Description of the Composition of the Drug Product (3.2.P.1):

The CNTO 1275 final vialled product (FVP) is supplied as a sterile solution in a single use 2 mL Type I glass vial stopper and a aluminum seal and plastic light green flip-off button. The FVP formulation is composed of 90 mg/mL CNTO 1275 with excipient concentrations of sucrose, and polysorbate 80, pH 6.0. CNTO 1275 FVP is manufactured in two doses, a 45 mg vial (0.5 mL) and 90 mg vial (1.0 mL). No excipients of human or animal origin and no novel excipients are used in the manufacture of CNTO 1275

b(4)

32 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

BLA STN125261/0, Centocor, ustekinumab

HFD-123, Graham

HFD-123, Sihag

HFD-328, TFRB Blue Files (STN 125261)

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