

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125289

CHEMISTRY REVIEW(S)

2/26/09

Golimumab BLA STN 125289 CMC Executive Summary



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, NIH Bldg 29B, HFD-123
29B Lincoln Drive, Bethesda, MD 20892

The Quality Team Leader's Executive Summary

From: David M. Frucht, M.D.,
Acting Chief, Laboratory of Cell Biology
Division of Monoclonal Antibodies (DMA)

Through: Kathleen A. Clouse, Ph.D., Director, DMA

BLA Number: 125289
Product: Golimumab (CNTO 148, SIMPONI)
Sponsor : Centocor

Date of Review : February 19, 2009

Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of golimumab is well controlled, leading to a product that is pure and potent. The product is free from endogenous or adventitious infectious agents sufficient to meet 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). Please refer to concluding section for other product quality-related statements to be included in the potential approval letter.

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

The current assay for detection of adventitious virus contamination in the unprocessed bulk harvest performed at _____ is a sub-optimal legacy assay dating from the 1980's and has an unacceptable percentage of false positives, which may be attributable to subtleties in assay performance. As a temporary safety measure, testing has been transferred to a second contract testing organization, _____ where this assay has not been susceptible to matrix effects. As a permanent solution and a post-marketing commitment, the Sponsor will be requested to optimize the existing assay or develop an improved assay for detecting adventitious virus contamination in the unprocessed bulk harvest. b(4)

II. Summary of Quality Assessments

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

- Golimumab (CNTO148, SIMPONI) is a human IgG₁κ monoclonal antibody directed against human tumor necrosis factor alpha (TNF-α). The submission includes the complete sequence of both the heavy chain and light chain, two of each composing the complete IgG₁κ molecule. Each heavy chain contains _____ intrachain disulfide bridges, whereas each light chain contains _____ intrachain disulfide bridges. Each heavy chain is linked to the other, and to one of two light chains, through interchain disulfide bonds. Golimumab has a β-pleated sheet structure. The carbohydrate structure is typical of that for other monoclonal antibodies. _____ b(4)

_____ Golimumab displays an N-linked glycan structure as expected for a human IgG₁; there is no evidence for O-glycosylation. _____

_____ Golimumab is a complex biomolecule that displays microheterogeneity. This heterogeneity results primarily from heavy chain deamidation, terminal galactosylation,

and _____ The mass weight of golimumab is 150-151 kDa. b(4)

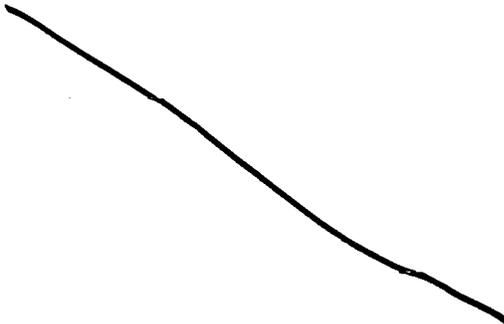
- Drug substance manufacture occurs at Centocor B.V., Einsteinweg 101, 2333 CB Leiden, The Netherlands.
- The mechanism of action for golimumab is to neutralize the activity of human TNF- α . Abnormally high levels of soluble TNF- α have been implicated in the pathophysiology of rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. Binding of soluble TNF- α by golimumab prevents this cytokine from binding to cell surface TNF- α receptors, consequently preventing the initiation of downstream signaling cascades. Golimumab is also capable of binding to TNF- α expressed on the surface of cells. In addition, the Fc region functions to bind FcRn and Fc γ R1. The binding affinity to FcRn was evaluated by an FcRn competition assay (IC₅₀: 15-17 μ g/mL), whereas the binding affinity to Fc γ R1 was assessed by ELISA (EC₅₀: 0.8 μ g/mL). Golimumab has been shown to be capable of binding complement and mediating complement-dependent cytotoxicity (CDC) of mTNF^{hi} transfectomas. However, mTNF^{lo} cells (LPS-stimulated monocytes), which are more representative of leukocytes from patients with activated inflammatory disease, are not susceptible to golimumab-mediated CDC.
- The clinical indications for golimumab include adult rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis. No clinical studies of golimumab have been conducted in pediatric populations.
- Golimumab is administered at a 50 mg dose given as a SC injection once per month, _____ After proper training in SC injection technique, a patient may self-administer the injections. For patients with rheumatoid arthritis, golimumab is administered in combination with methotrexate; for patients with psoriatic arthritis or ankylosing spondylitis, co-administration of methotrexate is optional. b(4)
- Golimumab is provided in 1 mL pre-filled syringes that are assembled with a Centocor Autoinjector _____ It is intended for single use. b(4)
Golimumab is supplied in two dosage formats (100 mg/1 mL and 50 mg/0.5 mL). Each dosage format contains 100 mg/mL golimumab, 4.1% (w/v) sorbitol, 5.6 mM l-histidine, and 0.015% polysorbate 80 dissolved in Water for Injection. The excipients used are of compendial grade as follows: L-histidine [United States Pharmacopoeia (USP)/European Pharmacopoeia (EP)], L-histidine monohydrochloride monohydrate (EP), sorbitol [National Pharmacopoeia (NF)], polysorbate 80 (NF/EP), and Water for Injection (USP/EP).
_____ b(4)
- Excipients were chosen based on known formulations for proteins and stability studies as follows:
 - Sorbitol- _____
 - Histidine _____ b(4)

- Polysorbate 80 (PS 80)- _____

b(4)

- The primary container closure is a _____ mL long syringe barrel with a 27 G fixed needle, along with a _____
There are two secondary packaging modes as follows: _____
(2) Centocor Autoinjector (DMF under review at CDRH as a consult review). **Note: The needle shield contains latex; this should be reflected in the labeling.**
- PFS and autoinjectors are packaged in individual cardboard carton boxes, protecting the product from light.
- Golimumab is expressed in _____ with expression plasmids _____
The variable regions were constructed based on the human framework and CDRs from an anti-TNF- α monoclonal antibody isolated from a TNF- α -immunized xenomouse. Post-transfection, there were _____
_____ prior to establishment of the Master Cell Bank, _____ MCB;02NOV01. The current system of cell banks also includes the Working Cell Banks _____ WCB;29MAY02 and _____ WCB;29NOV05. These cell banks have been tested for viability upon thaw, identity, sterility, mycoplasma and adventitious agents. Post-production cells were tested for genetic stability; this investigation supports a _____ culture period for these cells.
- Manufacture of the golimumab Drug Substance is divided into _____ steps that are grouped into three main areas as follows:

b(4)



b(4)

- The golimumab Drug Substance manufacturing process is based on Centocor's monoclonal antibody platform process. This process has undergone several modifications, including changes to site, scale, cell line and unit operations. Process parameters were subjected to a risk assessment to identify critical process parameters

3 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

**II. REVIEW OF COMMON TECHNICAL DOCUMENT-QUALITY (CTD-Q)
MODULE 1**

**A. ENVIRONMENTAL ASSESSMENT OR CLAIM OF CATEGORICAL
EXCLUSION**

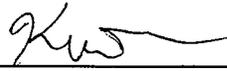
Golimumab meets the criteria for a categorical exclusion defined in the regulations 21 CFR 25.31(c).

III. LIST OF DEFICIENCIES TO BE COMMUNICATED

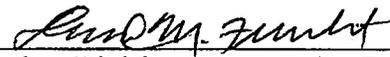
There are no CMC-related deficiencies precluding approval of this BLA.

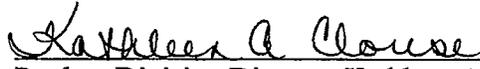
IV. ADMINISTRATIVE

A. Reviewer's Signature

 2/26/09
Product Quality Reviewer: Kurt Brorson, Ph.D.

B. Endorsement Block

 2/26/09
Product Division Team Leader: David M. Frucht, M.D.

 02/26/09
Product Division Director: Kathleen A. Clouse, Ph.D.

C. CC Block

OBP Office Director: Steven Kozlowski, M.D.
Clinical Deputy Division Director: Rigoberto Roca, M.D.
Clinical Division Director: Bob Rappaport, M.D.
Division of Monoclonal Antibodies File/BLA STN 125289

2/26/09



PRODUCT QUALITY REVIEW



BLA #125289

**Golimumab
(SIMPONI)**

Centocor Inc.

**Kurt Brorson, Ph.D.
Division of Monoclonal Antibodies**



Product Quality Review Data Sheet

1. BLA 125289

2. REVIEW #: 1

3. REVIEW DATE: 14-Feb-2009

4. REVIEWER: Kurt Brorson, Ph.D.

5. COMMUNICATIONS AND PREVIOUS CMC-RELATED DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>	
End of phase 2 meeting (comparability plan)	4/21/05	
Correspondence regarding dosage form	4/25/06	
Pre-BLA meeting (combined CMC & clinical)	8/21/07	
Pre-BLA meeting correspondence (immunogenicity discussion)	8/29/07	
Telecon to discuss AVA event (Centocor)	10/14/08	b(4)
Telecon to discuss AVA event 	10.21/08	
Telecon to discuss AVA event (Centocor)	10/23/08	
Telecon to discuss AVA event (Centocor)	11/7/08	
Telecon to discuss AVA event (Centocor)	11/20/08	
Telecon to discuss AVA event (Centocor)	12/11/08	

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
0000 (original submission)	6/25/08
0014 (Stability amendment)	12/30/08
00xx (Response to inspection observations)	pending



PRODUCT QUALITY REVIEW TEMPLATE



Chemistry Assessment Section

7. NAME & ADDRESS OF APPLICANT:

Name: Centocor, Inc.
 Address: 200 Great Valley Parkway, Malvern PA 19355
 Representative: Bethany Paxson
 Telephone: 610-651-6000

8. DRUG PRODUCT NAME/TYPE:

- a) Proprietary Name: SIMPONI
- b) Non-Proprietary Name (USAN): Golimumab
- c) Other names: CNTO148, rTNV148B
- d) Submission Priority: Standard

9. PHARMAC. CATEGORY: Anti-TNF- α monoclonal antibody

10. DOSAGE FORM: Prefilled syringe in either a passive delivery system or an autoinjector device with either a 50 mg/syringe (0.5 mL) or a 100 mg/syringe (1.0 mL)

11. STRENGTH/POTENCY: Golimumab is provided in two dosage formats: 50 mg and 100 mg deliverable.

Table 1. Quantitative and Qualitative Composition

<u>Component</u>	<u>100 mg Dose Amount per dose (mg)</u>	<u>50 mg Dose Amount per dose (mg)</u>	<u>Concentration</u>
CNTO 148	100	50	100 mg/mL
Sorbitol	41.0	20.5	4.1% (w/v)
L-Histidine	0.87	0.44	5.6 mM
PS 80	0.15	0.075	0.015% (w/v)
Water for injection (mL)	1	0.5	NA ^a

Note: PS 80 is polysorbate 80,

b(4)

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

Chemistry Assessment Section

15. RELATED/SUPPORTING DOCUMENTS:

Drug Master File (DMF) and Master File for Devices (MAF):

- _____
- _____

b(4)

16. STATUS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	Complete	Q4 2008	Patricia Hughes
Carton and Vial Labeling	Pending		Kimberly Rains
Environmental Assessment	Approve	2/13/09	Kurt Brorson
BMT-Centocor BV DS facility inspection	EIR complete	2/20/09	Kurt Brorson, Patricia Hughes & Kalavarti Suvarna
BMT- _____ DS safety testing facility inspection	EIRcomplete	2/20/09	Kurt Brorson, Patricia Hughes & Kalavarti Suvarna
BMT-DP & autoinjector facilities	Inspections waived	Q3 2008	Patricia Hughes
Trade name review	Pending		

b(4)

17. CMC Inspectional Activities:

Two inspections were performed:

1. **Centocor BV, Leiden Holland.** This is the drug substance manufacturer and the main testing site for DS and DP release and stability. The site was inspected Jan 28- Feb 3, 2009 by Kurt Brorson (DMA), Patricia Hughes (DMPQ) and Kalavarti Suvarna (DMPQ). A form 483 with five items was issued; responses are pending.
2. _____ This is testing site for drug substance microbial safety (i.e., mycoplasma and adventitious viruses). The site was inspected Feb 4-6, 2009 by Kurt Brorson (DMA), Patricia Hughes (DMPQ) and Kalavarti Suvarna (DMPQ). A form 483 with four items was issued; responses are pending.

b(4)

Inspections for other sites (i.e., Drug Product fill, cell bank testing, autoinjector assembly) were waived, as they are frequently inspected by ORA.

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Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)

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Product Goli mumar

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

CTD Module 2 Contents	Present?	If not, justification, action & status
Overall CTD Table of Contents [2.1]	<input checked="" type="checkbox"/> Y N	
Introduction to the summary documents (1 page) [2.2]	<input checked="" type="checkbox"/> Y N	
Quality overall summary [2.3]	<input checked="" type="checkbox"/> Y N	} N/A This information is submitted in module 3
<input type="checkbox"/> Drug Substance	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Drug Product	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Facilities and Equipment	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> Adventitious Agents Safety Evaluation	<input checked="" type="checkbox"/> 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]	<input checked="" type="checkbox"/> Y N	
Drug Substance [3.2.S]	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> general info	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> nomenclature		
<input type="checkbox"/> structure (e.g. sequence, glycosylation sites)		
<input type="checkbox"/> properties	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> manufacturers (names, locations, and responsibilities of all sites involved)		
<input type="checkbox"/> description of manufacturing process		
<input type="checkbox"/> batch numbering and pooling scheme		
<input type="checkbox"/> cell culture and harvest	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> purification		
<input type="checkbox"/> filling, storage and shipping		
<input type="checkbox"/> control of materials		
<input type="checkbox"/> raw materials and reagents	<input checked="" type="checkbox"/> Y N	
<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	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> justification of specifications		
<input type="checkbox"/> analytical method validation		
<input type="checkbox"/> reference standards		
<input type="checkbox"/> stability	<input checked="" type="checkbox"/> Y N	
<input type="checkbox"/> process validation (prospective		

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Product

Part B Page 2

CTD Module 3 Contents	Present?	If not, justification, action & status
plan, results, analysis, and conclusions) <input type="checkbox"/> manufacturing process development (describe changes during non-clinical and clinical development; justification for changes) <input type="checkbox"/> characterization of drug substance <input type="checkbox"/> control of drug substance <ul style="list-style-type: none"> ○ specification <ul style="list-style-type: none"> ○ justification of specs. ○ analytical procedures ○ analytical method validation ○ batch analyses <ul style="list-style-type: none"> ○ consistency (3 consecutive lots) ○ justification of specs. <input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <input type="checkbox"/> stability <ul style="list-style-type: none"> □ summary □ post-approval protocol and commitment □ pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	(Y) N (Y) N (Y) N (Y) N (Y) N (Y) N	
Drug Product [3.2.P] <input type="checkbox"/> description and composition <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"> ○ 3 consecutive lots ○ other needed validation data <input type="checkbox"/> control of excipients (justification of specifications; analytical method	(Y) N (Y) N (Y) N (Y) N (Y) N (Y) N (Y) N (Y) N	

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Product

Part B Page 3

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"> ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity ○ administration device(s) <input type="checkbox"/> stability <ul style="list-style-type: none"> □ summary □ post-approval protocol and commitment □ pre-approval <ul style="list-style-type: none"> ○ protocol ○ results ○ method validation 	(Y) N (Y) N (Y) N	
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"> ○ 3 consecutive lots ○ other needed validation data <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)	Y N Y N Y N Y N Y N Y N Y N Y N Y N	Not Applicable, liquid dosage form

STN 125289

Product _____

CTD Module 3 Contents	Present?	If not, justification, action & status
<input type="checkbox"/> reference standards <input type="checkbox"/> container closure system <ul style="list-style-type: none"> ○ specifications (vial, elastomer, drawings) ○ availability of DMF ○ closure integrity <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"> ○ protocol ○ results 	Y N Y N Y N	<i>N/A</i>
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)	<input checked="" type="checkbox"/> N <input checked="" type="checkbox"/> N	
Appendices for Biotech Products [3.2.A] <input type="checkbox"/> facilities and equipment <ul style="list-style-type: none"> ○ manufacturing flow; adjacent areas ○ other products in facility ○ equipment dedication, preparation and storage ○ sterilization of equipment and materials ○ procedures and design features to prevent contamination and cross-contamination <input type="checkbox"/> adventitious agents safety evaluation (viral and non-viral) e.g.: <ul style="list-style-type: none"> ○ avoidance and control procedures ○ cell line qualification ○ other materials of biological origin ○ viral testing of unprocessed bulk ○ viral clearance studies ○ testing at appropriate stages of production <input type="checkbox"/> novel excipients	<input checked="" type="checkbox"/> N <input checked="" type="checkbox"/> N Y N	<i>N/A, there are none</i>
USA Regional Information [3.2.R] <input type="checkbox"/> executed batch records <input type="checkbox"/> method validation package	<input checked="" type="checkbox"/> N <input checked="" type="checkbox"/> N	

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

Examples of Filing Issues	Yes?	If not, justification, action & status
content, presentation, and organization sufficient to permit substantive review?	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> legible	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> English (or translated into English)	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> compatible file formats	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> navigable hyper-links	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> interpretable data tabulations (line listings) & graphical displays	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> summary reports reference the location of individual data and records	<input checked="" type="checkbox"/> N	
<input type="checkbox"/> all electronic submission components usable	<input checked="" type="checkbox"/> N	
includes appropriate process validation data for the manufacturing process at the commercial production facility?	<input checked="" type="checkbox"/> 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="checkbox"/> N	
includes data demonstrating consistency of manufacture	<input checked="" type="checkbox"/> N	
includes complete description of product lots and manufacturing process utilized for clinical studies	<input checked="" type="checkbox"/> N	
describes changes in the manufacturing process, from material used in clinical trial to commercial production lots	<input checked="" type="checkbox"/> 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="checkbox"/> N	
certification that all facilities are ready for inspection	<input checked="" type="checkbox"/> N	
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.	<input checked="" type="checkbox"/> N	
if not using a test or process specified by regulation, data is provided to show the	Y N	N/A, these are none

STN 125289 Product _____

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 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	<input checked="" type="radio"/> 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	<input checked="" type="radio"/> Y N	
information and data supporting validity of sterilization processes for sterile products and aseptic manufacturing operations	<input checked="" type="radio"/> Y N	
if this is a supplement for post-approval manufacturing changes, is animal or clinical data needed? Was it submitted?	Y N	N/A

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

Recommendation (circle one): File RTF

Reviewer: KWS 8-5-08 Type (circle one): Product (Chair) Facility (DMPQ)
 (signature/ date)

Concurrence:

Branch/Lab Chief: Andrew M. Zumbly
 (signature/ date) 8/05/08

Division Director: Kathleen Clouse
 (signature/ date) 08/05/08

1 CATEGORICAL EXCLUSION

Centocor, Inc., Horsham, PA, certifies that the above referenced action meets the criteria for a categorical exclusion defined in the regulations 21 CFR 25.31(c), and that to the knowledge of Centocor, Inc., no extraordinary circumstances exist. Thus, no environmental assessment needs to be performed.

**Appears This Way
On Original**

2 Page(s) Withheld

Trade Secret / Confidential (b4)

Draft Labeling (b4)

Draft Labeling (b5)

Deliberative Process (b5)