

**CENTER FOR DRUG EVALUATION AND  
RESEARCH**

*APPLICATION NUMBER:*

**BLA 125160/0**

**CHEMISTRY REVIEW(S)**

**BLA 125160**

**Cimzia™  
(Certolizumab pegol, CDP870)**

**UCB, Inc.**

**Gurpreet Gill-Sangha, Ph.D.  
Division Of Monoclonal Antibodies (DMA)  
Review of Chemistry, Manufacturing, and Controls  
For Complete Response to FDA CR Letter of 12/21/06**

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# PRODUCT REVIEW



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ON ORIGINAL**



# Product Review Data Sheet

- 1. BLA 125160
- 2. REVIEW #: 2
- 3. REVIEW DATE: September 5, 2007
- 4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.
- 5. PREVIOUS DOCUMENTS: None

<u>Previous Documents</u>	<u>Document Date</u>
Original BLA submission	01-March-2006
Amendment	13-November-2006
Amendment (via email)	4-December-2006
Amendment (via email)	6-December-2006
Original Review for PEG and Immunogenicity	7-December-2006

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Response to CR letter	30-April-2007
UCB response via email 8/2/07	02-August-2007

7. NAME & ADDRESS OF APPLICANT:

Name:	UCB, Inc.
Address:	1950 Lake Park Drive Smyrna, GA 30080
Representative:	Patricia Fritz, Vice President, Global Regulatory Affairs
Telephone:	(585) 273-5630

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cimzia
- b) Non-Proprietary Name (USAN): Certolizumab pegol
- c) Code Name/# (OBP only): CDP870
- d) Chem. Type/Submission Priority (OBP only):
  - Submission Priority: S

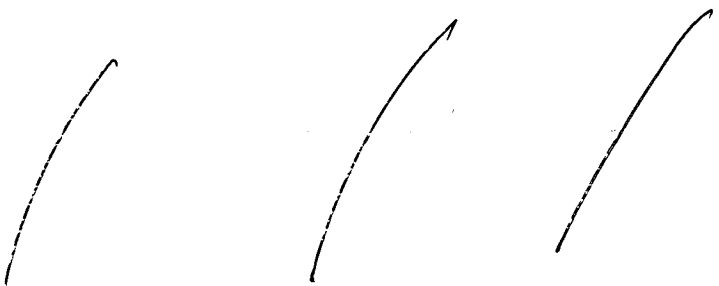
9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

**PRODUCT REVIEW**

Product Review Data Sheet

10. PHARMACOL. CATEGORY: Crohn's Disease
11. DOSAGE FORM: Lyophilized powder reconstituted with sterile water for injection
12. STRENGTH/POTENCY: 200 mg/mL
13. ROUTE OF ADMINISTRATION: Subcutaneous (thigh or abdomen)
14. Rx/OTC DISPENSED:  Rx  OTC
15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):  
 SPOTS product – Form Completed  
 Not a SPOTS product
16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA,  
 MOLECULAR WEIGHT:

INN: Certolizumab pegol  
 USAN Name: Certolizumab pegol  
 Chemical Name: gHTNF40 Fab' – 40KPEG,  
 Company Code Name: CDP870, CDP870 Fab', PHA738144  
 CAS registry #: 428863-50-7  
 Laboratory Code: NA  
 Structure:



17. RELATED/SUPPORTING DOCUMENTS:

**A. DMFs: Refer to CMC review #1 by Gurpreet Gill-Sangha, Ph.D,**

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT

# PRODUCT REVIEW

## Product Review Data Sheet

<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)

### B. Other Documents: None

DOCUMENT	APPLICATION NUMBER.	DESCRIPTION

**APPEARS THIS WAY  
ON ORIGINAL**

# The Chemistry Executive Summary

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of Cimzia leads to a product that is pure and potent. The product is free from \_\_\_\_\_ in a way that meets or exceeds the parameters recommended by FDA. The manufacturing process results in a consistent product as evidenced by results from different production runs including the validation campaign.

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

None

## II. Summary of Chemistry Assessments

### A. Drug Product and Drug Substance

- CIMZIA (certolizumab pegol; CDP870) is supplied as a sterile, white, lyophilized powder for reconstitution and then subcutaneous administration. After reconstitution with 1 mL of sterile Water for Injection, USP, the resulting pH is approximately 5.2. Each single-use vial contains approximately 200 mg certolizumab pegol, 100 mg sucrose, 0.9 mg lactic acid, and 0.1 mg polysorbate. No preservatives are present.
- The drug product is supplied as 200 mg lyophilized certolizumab pegol in a sterile, single-use \_\_\_\_\_ vial, closed with a \_\_\_\_\_ gray rubber stopper, and sealed with an aluminum overseal and tamper proof snap off white plastic cap.
- The drug product is filled and lyophilized using \_\_\_\_\_ at \_\_\_\_\_ Water for Injection (produced at \_\_\_\_\_) is supplied with the drug product. \_\_\_\_\_ assures sterility of the diluent.
- Stability of the drug product has been established for \_\_\_\_\_ months at 2°C - 8°C for commercial scale product and for \_\_\_\_\_ months with clinical product. These results currently support an 18-month expiry. The drug product stability protocol in the BLA is appropriate.



# PRODUCT REVIEW

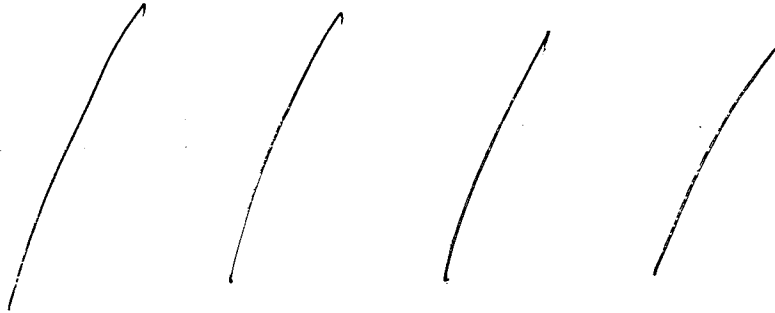
## Executive Summary Section

- Certolizumab pegol is a recombinant, humanized Fab' antibody fragment directed against TNF $\alpha$ , \_\_\_\_\_ to PEG2MAL40K, \_\_\_\_\_

\_\_\_\_\_ The experimentally determined molecular mass of the Fab' fragment is approximately \_\_\_\_\_. The experimentally determined molecular mass of certolizumab pegol is approximately 90.8 kDa, which is consistent with \_\_\_\_\_

- The Fab' fragment is manufactured in *Escherichia coli*. The Drug Substance is produced during \_\_\_\_\_ manufacturing campaigns carried out \_\_\_\_\_, in which the Fab' is \_\_\_\_\_, purified, and pegylated in a process referred to as the "\_\_\_\_\_ process".

- 



- The proposed expiration dating period for storage of Drug Substance based on the data is 18 months from the date of manufacture. The Drug Substance stability protocol in the BLA is appropriate.

- Raw material testing and control is adequate. The only animal derived raw material, \_\_\_\_\_ is derived from \_\_\_\_\_. Based on information available to date, \_\_\_\_\_ has been deemed to pose a minimal risk for \_\_\_\_\_

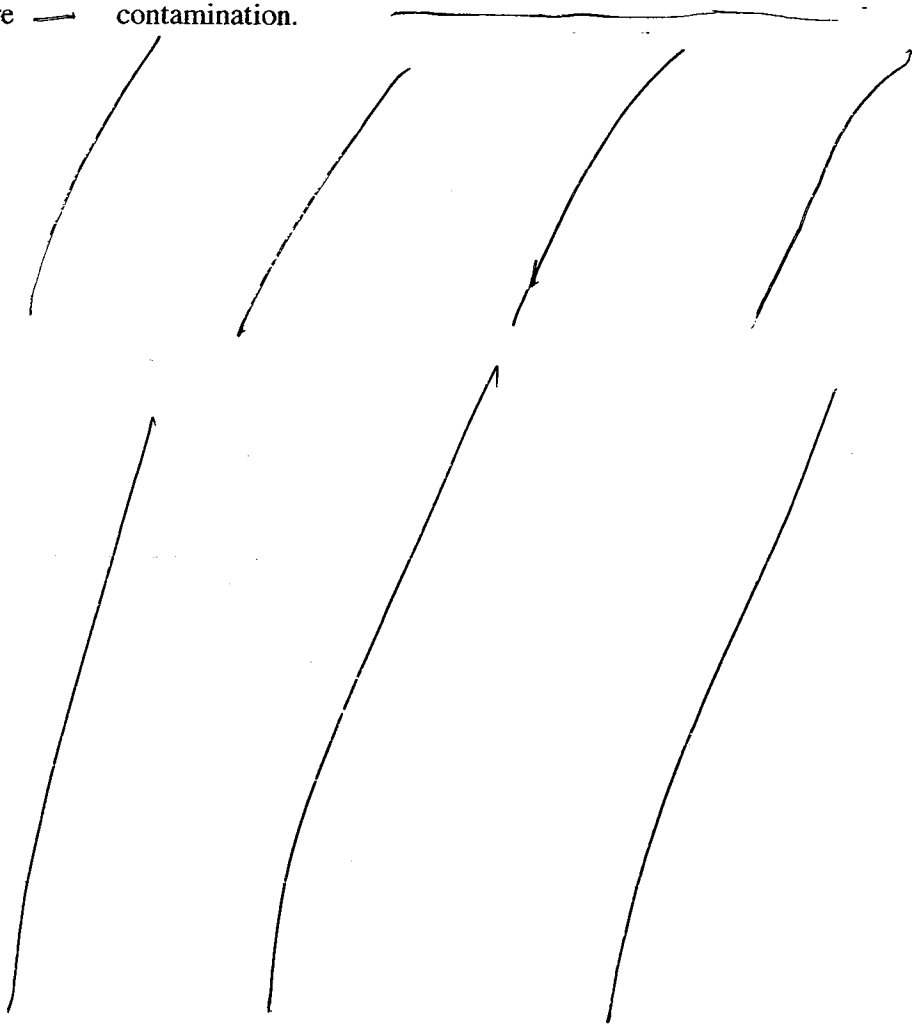
- On 8/25/05, UCB informed FDA that certain batches of drug substance used in the phase III trials (process - contained measurable levels of \_\_\_\_\_

\_\_\_\_\_ These \_\_\_\_\_ were probably introduced \_\_\_\_\_  
The \_\_\_\_\_ INDs, 11197 \_\_\_\_\_ were briefly placed on clinical hold while UCB investigated the levels of the \_\_\_\_\_, in the drug products. Root cause analysis and corrective actions have been proposed and are appropriate. The \_\_\_\_\_ contamination issue did not represent a safety issue (limits with \_\_\_\_\_ criteria) and did not impact process validation. The \_\_\_\_\_ changes \_\_\_\_\_ are likely to remove the possibility of \_\_\_\_\_



Executive Summary Section

future → contamination.



Executive Summary Section

[Redacted content consisting of multiple lines of diagonal slashes]

- CDP870 binds to TNF- $\alpha$  with a binding constant of  $89.0 \pm 4.9$  pM. Potency of the Drug Product is determined by a bioassay. The assay utilizes [Redacted]

[Redacted content consisting of multiple lines of diagonal slashes]

**B. Description of How the Drug Product is Intended to be Used**

Cimzia is intended to be marketed for treatment of Crohn's disease.

Cimzia is supplied as a sterile, white, lyophilized powder for reconstitution with 1 mL sterile Water for Injection (WFI), USP; the resulting pH is approximately 5.2. Each lyophilized vial of Cimzia is reconstituted with 1 mL sterile WFI using a syringe with a 20 gauge needle. The sample is gently swirled with sterile WFI without shaking and left undisturbed for 30 minutes for reconstitution to result in clear or opalescent colorless to pale yellow liquid with no visible particulates. Upon reconstitution, the vials can be refrigerated (not frozen) for up to 24 hours prior to injection. Stability data was provided in the submission to demonstrate that storage of reconstituted Cimzia at refrigerated conditions for 24 hours resulted in stable product. Cimzia should be at room temperature at the time of administration of injection. Using two new 20 gauge needles for each vial, the reconstituted solution is withdrawn, resulting in two syringes each containing 1 mL Cimzia (200 mg). The 20 gauge needles are switched to 23 gauge and the full contents of each syringe are injected subcutaneously into separate sites on abdomen or thigh.

Cimzia pack contents include two \_\_\_\_\_ Type I glass vial with rubber stopper overseals each containing 200 mg lyophilized Cimzia for reconstitution, two 2 mL Type I glass vials containing 1 mL sterile WFI, two 3 mL plastic syringes, four 20 gauge luer-lok needles (1 inch), two 23 gauge luer-lok needles (1 inch) and eight alcohol swabs.

The proposed recommended adult dose for Cimzia is an induction regimen of 400 mg given as two subcutaneous injections at week 0, 2, and 4, followed by a maintenance regimen of 400 mg every 4 weeks. Refer to the clinical review for further changes to the dosing regimen for induction and maintenance.

Cimzia vials should be refrigerated at 2-8 °C. The recommended expiration dating period is 18 months under these storage conditions. The expiry could be extended as additional stability data is provided.

**C. Basis for Approvability or Not-Approval Recommendation**

- Cimzia is manufactured by a robust process with precautions for \_\_\_\_\_  
\_\_\_\_\_. i. Cimzia is manufactured consistently, resulting in a safe and effective product. Two CMC issues raised in the original CR letter have been addressed and adequately resolved in this review.

**PRODUCT REVIEW**

Executive Summary Section

**III. Administrative**

**A. Reviewers' Signature**

Product Reviewer: Gurpreet Gill-Sangha, Ph.D.

*Gurpreet Gill-Sangha*  
9/26/07

**B. Endorsement Block**

Product Team Leader: Patrick Swann, Ph.D.

*Patrick Swann* 9-26-07

Product Acting Division Director: Kathleen Clouse, Ph.D.

*Kathleen Clouse*

**C. CC Block**

Office Director: Steve Kozlowski, M.D.

Division of Monoclonal Antibodies File/BLA STN 125160

4 Page(s) Withheld

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Deliberative Process



**BLA 125160**

**Cimzia™  
(Certolizumab pegol, CDP870)**

**UCB, Inc.**

**Gurpreet Gill-Sangha, Ph.D.  
Division Of Monoclonal Antibodies (DMA)  
Review of Chemistry, Manufacturing, and Controls  
For Sections Related to PEG-linker and Immunogenicity  
Assay**



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# Product Review Data Sheet

- 1. BLA 125160
- 2. REVIEW #: 1
- 3. REVIEW DATE: December 7, 2006
- 4. REVIEWER: Gurpreet Gill-Sangha, Ph.D.
- 5. PREVIOUS DOCUMENTS: None

<u>Previous Documents</u>	:	<u>Document Date</u>
---------------------------	---	----------------------

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Original BLA submission	01-March-2006
Amendment	13-November-2006
Amendment (via email)	4-December-2006
Amendment (via email)	6-December-2006

7. NAME & ADDRESS OF APPLICANT:

Name:	UCB, Inc.
Address:	1950 Lake Park Drive Smyrna, GA 30080
Representative:	Patricia Fritz, Vice President, Global Regulatory Affairs
Telephone:	(585) 273-5630

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Cimzia
- b) Non-Proprietary Name (USAN): Certolizumab pegol
- c) Code Name/# (OBP only): CDP870
- d) Chem. Type/Submission Priority (OBP only):
  - Submission Priority: S

9. LEGAL BASIS FOR SUBMISSION: 505 (b) (1)

10. PHARMACOL. CATEGORY: Crohn's Disease



# PRODUCT REVIEW



## Product Review Data Sheet

11. DOSAGE FORM: Lyophilized powder reconstituted with sterile water for injection

12. STRENGTH/POTENCY: 200 mg/mL

13. ROUTE OF ADMINISTRATION: Subcutaneous (thigh or abdomen)

14. Rx/OTC DISPENSED:  Rx  OTC

15. SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):

SPOTS product – Form Completed

Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

INN: Certolizumab pegol  
 USAN Name: Certolizumab pegol  
 Chemical Name: gHTNF40 Fab' – 40KPEG,  
 Company Code Name: CDP870, CDP870 Fab', PHA738144  
 CAS registry #: 428863-50-7  
 Laboratory Code: NA  
 Structure:

Four large diagonal slashes indicating redacted information.

17. RELATED/SUPPORTING DOCUMENTS:

### A. DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS <sup>2</sup>	DATE REVIEW COMPLETED	COMMENT
—	II	/	/	I	Adequate	November 29, 2006 by Gurpreet Gill-Sangha, Ph.D.	
—	II	/	/	I	Adequate	November 29, 2006 by Gurpreet Gill-Sangha, Ph.D.	



# PRODUCT REVIEW



## Product Review Data Sheet

<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

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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)

**B. Other Documents: None**

DOCUMENT	APPLICATION NUMBER	DESCRIPTION

**APPEARS THIS WAY  
ON ORIGINAL**



# The Product Review for BLA 125160

## The Executive Summary

Please refer to a separate document for Executive summary.

### I. Recommendations

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

### II. Summary of Chemistry Assessments

- A. Description of the Drug Product(s) and Drug Substance(s)
- B. Description of How the Drug Product is Intended to be Used
- C. Basis for Approvability or Not-Approval Recommendation

### III. Administrative

#### A. Reviewer's Signature

Gurpreet Gill-Sangha

Gurpreet Gill-Sangha, Ph.D.  
Product Reviewer, DMA/OBP/OPS/CDER, HFD-123

12-7-06

Date

#### B. Endorsement Block

Patrick G. Swann

Patrick G. Swann, Ph.D.  
Deputy Director, DMA/OBP/OPS/CDER, HFD-123

12-7-06

Date

#### C. CC Block

67 Page(s) Withheld

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# Review Memo

**Ref:** 125160/0, Response to Sandoz 483 item #1b

**Prepared by:** Kurt Brorson, Ph.D., Staff Scientist, DMA *9/13*

**Through:** Kathleen A. Clouse, Ph.D., Chief, *K. Clouse 11/20/06*  
Lab of Cell Biology; Acting Director DMA

**CSO:** Marlene Swider, ODE3/DGP  
**cc.:** Gil Salud, TFRB

**Sponsor:** UCB

**Product:** Certolizumab pegol

**Date of submission:** Sept 25, 2006  
**Date of Review:** Nov 17, 2006

## Background

Certolizumab pegol (CDP870) is a humanized anti-TNF Fab' antibody fragment  
\_\_\_\_\_ to PEG2MAL40K, \_\_\_\_\_

\_\_\_\_\_ The Fab is  
expressed in E. coli, purified by \_\_\_\_\_ chemically conjugated to  
PEG2MAL40K and \_\_\_\_\_. The product is  
supplied in a kit as a sterile lyophilized dosage form in vials for reconstitution with  
sterile WFI.

Drug substance manufacture occurs at \_\_\_\_\_ Drug  
product manufacture occurs at \_\_\_\_\_ Release  
testing is shared between \_\_\_\_\_, UCB Rochester, NY, and some contract sites.

Certolizumab pegol (CDP870) is currently under BLA review for Crohn's disease.  
As part of an initial BLA review, an inspection was performed on the drug  
substance manufacturing facility, \_\_\_\_\_ on July 17-21,  
2006. A three item 483 was issued to the firm.

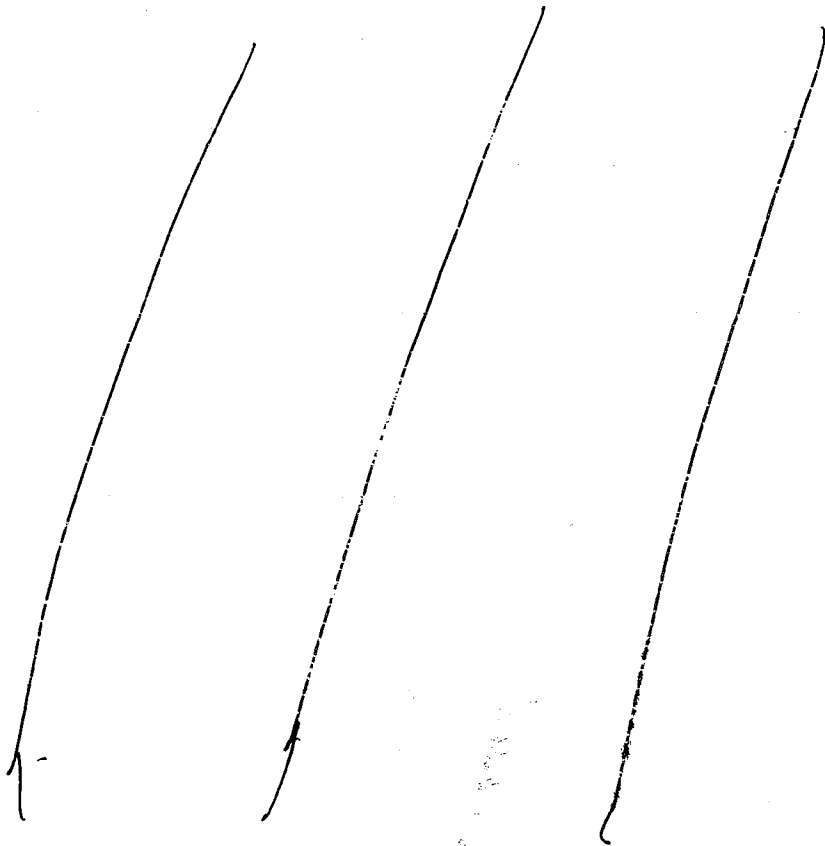
Item #1b was: "The assay for \_\_\_\_\_ ) is performed at a  
contract site, \_\_\_\_\_ ). Robustness testing of the \_\_\_\_\_ test  
method has not been performed \_\_\_\_\_ have  
resulted in multiple \_\_\_\_\_ failures \_\_\_\_\_



In this amendment, they report modifications to the assay and revalidation of the modified assay.

**Contents**

- The assay is performed at a contractor, [redacted] UCB and [redacted] performed an audit of [redacted] in March/April 2006. They also conducted joint [redacted] testing at the three sites to determine if site specific differences could be identified that lead to the [redacted] / failures at [redacted]. No glaring procedural differences were found. The audit and investigation concluded that the failures were caused by [redacted]
- The assay was modified by [redacted]



**Recommendation.** The new [redacted] assay format has been revalidated and is acceptable. The 483 item has been resolved.

# Review Memo

**Ref:** 125160/0, Response to Sandoz 483 item #1a

**Prepared by:** Kurt Brorson, Ph.D., Staff Scientist, DMA *KB*

**Through:** Kathleen A. Clouse, Ph.D., Chief, *Kathleen Clouse*  
Lab of Cell Biology; Acting Director DMA

**CSO:** Marlene Swider, ODE3/DGP

**cc.:** Gil Salud, TFRB

**Sponsor:** UCB

**Product:** Certolizumab pegol

**Date of submission:** Sept 15, 2006

**Date of Review:** Nov 17, 2006

## Background

Certolizumab pegol (CDP870) is a humanized anti-TNF Fab' antibody fragment  
to PEG2MAL40K,

The Fab is expressed in E. coli, purified by \_\_\_\_\_, chemically conjugated to PEG2MAL40K and \_\_\_\_\_  
The product is supplied in a kit as a sterile lyophilized dosage form in vials for reconstitution with sterile WFI.

Drug substance manufacture occurs at \_\_\_\_\_ Drug  
product manufacture occurs at \_\_\_\_\_ Release  
testing is shared between \_\_\_\_\_ UCB Rochester, NY, and some contract sites.

Certolizumab pegol (CDP870) is currently under BLA review for Crohn's disease. As part of an initial BLA review, an inspection was performed on the drug substance manufacturing facility, \_\_\_\_\_, on July 17-21, 2006. A three item 483 was issued to the firm.

Item #1a was: " \_\_\_\_\_  
/ / / / /

— for release of drug substance. The suitability of these assays for testing bulk drug substance was established in a lab at UCB-Rochester. The suitability of these assays as implemented at — has not been demonstrated by means of interlaboratory trials between UCB-Rochester and —

### Contents

— and UCB identified all assays common between the two facilities and performed an inter-laboratory bridging study for each. These assays include those cited in the 483 form as well as the — purity assay / —

The test articles for the inter-lab comparison included three drug substance batches and some stressed samples —

—. The acceptance criteria for assay comparability was equivalent results at the two sites within a proscribed error (between — depending on the assay).

All acceptance criteria for the bridging study were met.

**Recommendation.** Inter-laboratory precision has been established for the cited assays. The 483 item has been resolved.

# Review Memo

Ref: 125160/0, Response to Sandoz 483 item #2

Prepared by: Kurt Brorson, Ph.D., Staff Scientist, DMA *KB*

Through: Kathleen A. Clouse, Ph.D., Chief, *Kathleen Clouse*  
Lab of Cell Biology; Acting Director DMA

CSO: Marlene Swider, ODE3/DGP  
cc.: Gil Salud, TFRB

Sponsor: UCB

Product: Certolizumab pegol

Date of submission: Sept 25, 2006  
Date of Review: Nov 17, 2006

## Background

Certolizumab pegol (CDP870) is a humanized anti-TNF Fab' antibody fragment to PEG2MAL40K,

The Fab is expressed in E. coli, purified by \_\_\_\_\_ chemically conjugated to PEG2MAL40K and \_\_\_\_\_. The product is supplied in a kit as a sterile lyophilized dosage form in vials for reconstitution with sterile WFI.

Drug substance manufacture occurs at \_\_\_\_\_ Drug product manufacture occurs at \_\_\_\_\_ Release testing is shared between \_\_\_\_\_, UCB Rochester, NY, and some contract sites.

Certolizumab pegol (CDP870) is currently under BLA review for Crohn's disease. As part of an initial BLA review, an inspection was performed on the drug substance manufacturing facility, \_\_\_\_\_ ) on July 17-21, 2006. A three item 483 was issued to the firm.

Item #2 was: "Written production and process control procedures are not followed in the execution of production and process control functions. Specifically, " \_\_\_\_\_

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In this amendment, they report the new operating \_\_\_\_\_  
\_\_\_\_\_ and justify it with a small scale study.

**Contents**



**Recommendation.** The new operating range is acceptable. The 483 item has been resolved.

# Review Memo

**Ref:** 125160/0, Response to Sandoz 483 item #3

**Prepared by:** Kurt Brorson, Ph.D., Staff Scientist, DMA *K.B.*

**Through:** Kathleen A. Clouse, Ph.D., Chief, *Kathleen Clouse*  
Lab of Cell Biology; Acting Director DMA

**CSO:** Marlene Swider, ODE3/DGP  
**cc.:** Gil Salud, TFRB

**Sponsor:** UCB

**Product:** Certolizumab pegol

**Date of submission:** July 27, 2006  
**Date of Review:** Nov 17, 2006

## Background

Certolizumab pegol (CDP870) is a humanized anti-TNF Fab' antibody fragment to PEG2MAL40K,

The Fab is expressed in E. coli, purified by \_\_\_\_\_, chemically conjugated to PEG2MAL40K and \_\_\_\_\_. The product is supplied in a kit as a sterile lyophilized dosage form in vials for reconstitution with sterile WFI.

Drug substance manufacture occurs at \_\_\_\_\_ Drug product manufacture occurs at \_\_\_\_\_ Release testing is shared between \_\_\_\_\_, UCB Rochester, NY, and some contract sites.

Certolizumab pegol (CDP870) is currently under BLA review for Crohn's disease. As part of an initial BLA review, an inspection was performed on the drug substance manufacturing facility, \_\_\_\_\_, on July 17-21, 2006. A three item 483 was issued to the firm.

Item #3 was: "Control procedures are not established which monitor the output of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process material and the drug product. Specifically,

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**Contents**

/

/

/

**Recommendation.** The new action limit is acceptable. The 483 item has been resolved.

# Review Memo

**Ref:** 125160/0, immunogenicity assay review

**Prepared by:** Kurt Brorson, Ph.D., Staff Scientist, DMA *KB*

**Through:** Kathleen A. Clouse, Ph.D., Chief, *K. Clouse*  
Lab of Cell Biology; Acting Director DMA

**CSO:** Marlene Swider, ODE3/DGP

**Cc:** John Hyde, MD., Medical Officer, ODE3/DGP

**Sponsor:** UCB

**Product:** Certolizumab pegol

**Date of submission:** Mar 1, 2006

**Date of Review:** Oct 12, 2006

## Background

Certolizumab pegol (CDP870) is a humanized anti-TNF Fab' antibody fragment  
\_\_\_\_\_ to PEG2MAL40K, \_\_\_\_\_

\_\_\_\_\_ The Fab is  
expressed in E. coli, purified by \_\_\_\_\_, chemically conjugated to  
PEG2MAL40K and \_\_\_\_\_ The product is  
supplied in a kit as a sterile lyophilized dosage form in vials for reconstitution with  
sterile WFI.

Drug substance manufacture occurs at \_\_\_\_\_ Drug  
product manufacture occurs at \_\_\_\_\_ Release  
testing is shared between \_\_\_\_\_ UCB Rochester, NY, and some contract sites.

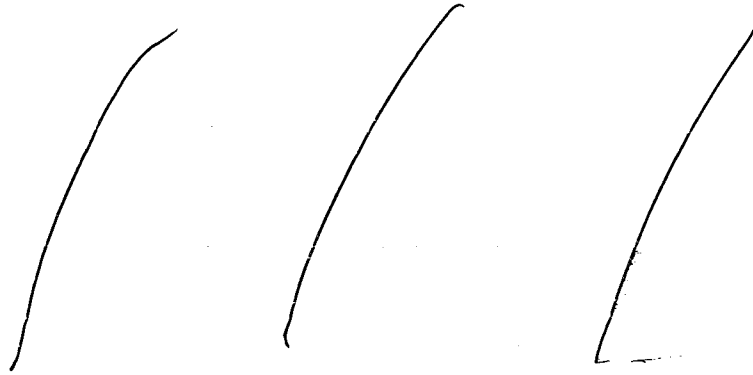
Certolizumab pegol (CDP870) is currently under BLA review for Crohn's disease. As part of an initial BLA review, OBP normally reviews the adequacy of the assay used to detect anti-product antibodies, the product immunogenicity assessment and CMC information related to surrogate API forms used in animal studies. All of this information is in section 4 (non-clinical pharm/tox) of the BLA.



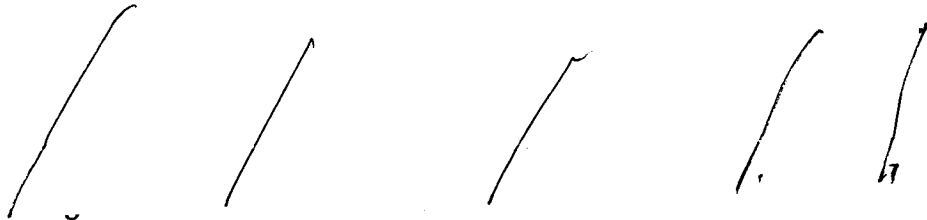
**Anti-API antibody assay.**

The assay was initially developed by Celltech in 1998 and subsequently re-qualified as sponsorship of the product changed during development:

- ARLE05M0604 – 40001265 “Validation of ELISA for the detection of antibodies to CDP870”. This is the original immunogenicity assay qualification performed by Celltech in 1998. The assay is a \_\_\_\_\_  
\_\_\_\_\_ The assay was validated using \_\_\_\_\_  
\_\_\_\_\_ or precision, accuracy, range, LOD, specificity, and freeze/thaw sensitivity. \_\_\_\_\_



- ARLE05M0506 – 40001087 “Evaluation of the suitability of the \_\_\_\_\_



- ARLE05M1305 – 40001557 “Antibodies to CDP870 in nonclinical studies - impact of the change in lower limit of quantification for the screening ELISA”. The LOQ was reset to \_\_\_\_\_
- ARLE05M0606 – 40001527 “Validation report for the enzyme-linked immunosorbant assay (ELISA) for the determination of anti- CDP870 antibody”. The assay was revalidated in 2002 to rule out \_\_\_\_\_
- ARLE05M0708 – 40001528 “Cross-site comparison of the enzyme-linked immunosorbant assay (ELISA) for the determination of anti- CDP870 antibody in clinical samples”. In 2003, the assay was cross-validated between Pharmacia and Celltech with : \_\_\_\_\_  
\_\_\_\_\_ This was to rule out discordant data as the product was transferred between firms.
- ARLE05M0707-40001529 “Validation of Pharmacia's ELISA for the detection of antibodies to CDP870 in human \_\_\_\_\_ plasma”. In

2003, the assay was re-validated by Pharmacia. It was re-validated for precision, accuracy, range, LOD/Q, specificity, reagent stability, serum stability and freeze/thaw sensitivity.

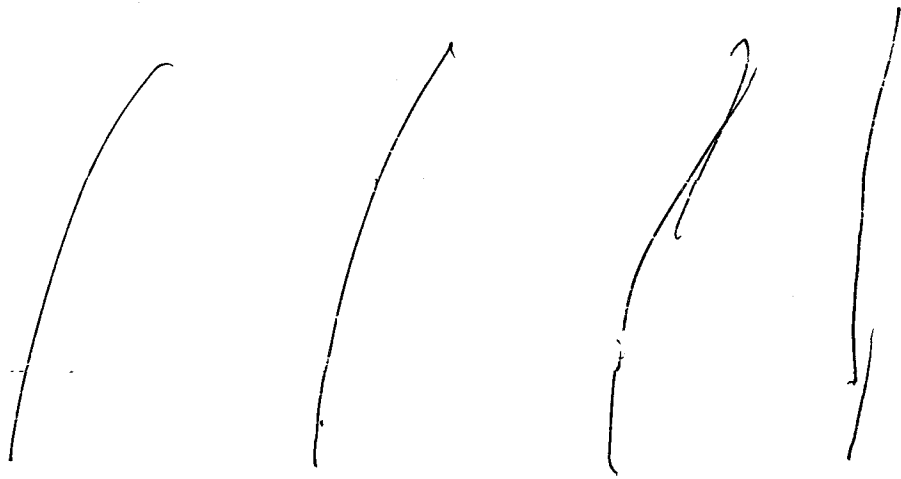
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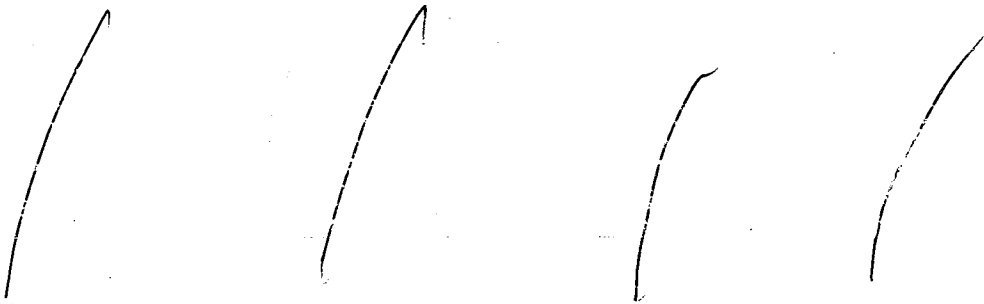
- ARLE05M0615 – 40001384 “Cross-site comparison of ELISA assays for the detection of antibodies to CDP870 in clinical samples”. In 2004, the product was transferred back to Celltech, so they performed another cross-site validation study t
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**Other assays used in the immunogenicity assessment**

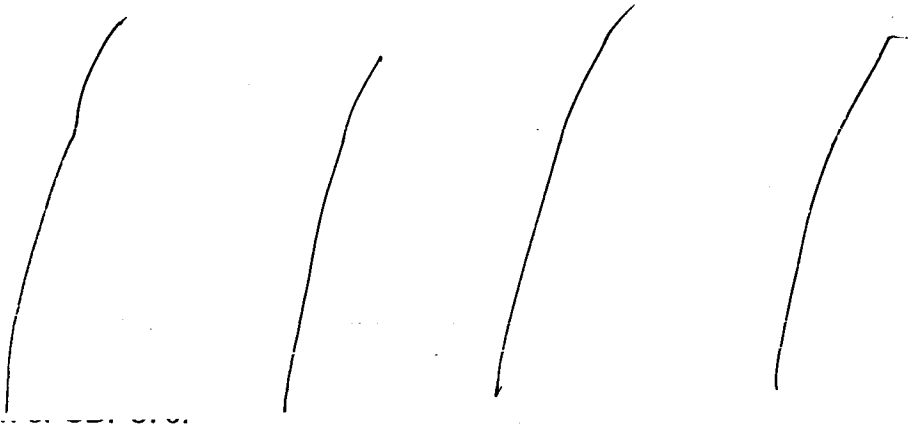
- ARLE05M0704 – 40001485 “Evaluation of the performance characteristics of an analytical method for the determination of anti-CDP870 antibody titers in human plasma using a ELISA”.
- 
-



- ARLE05M0618 – 40001445 “Validation of ELISA for the detection of antibodies to CDP870”. An indirect ELISA was developed



- ARLE05M0705 – 40001530 “Validation of the ELISA for the detection of antibodies to CDP870”



### Product immunogenicity

Additional relevant studies were performed to qualify the overall approach to assessing product immunogenicity:

- ARLE05M1306 – 40001556 “Analysis of samples positive for antibodies to infliximab in the anti- CDP870 assay to test for cross-reactivity”. Twenty patient samples with anti-Remicade HACA do not contain CDP870

- ARLE05K2705 – 40000941 “Characterisation of the antibody response to CDP870: Supplementary research report”. This report evaluates the immunology of the anti-CDP870 response in single dose studies of 30 cynomolgous monkeys and 12 human volunteers. One of the thirty monkeys developed significant ( $>$   $\text{————}$ ) antibody and eight of twelve human volunteers had antibodies ranging from  $\text{————}$ . In general:
  - Volunteers given higher doses of CDP870 (3-10 mg/kg) had lower rates and responses than lower dose volunteers (0.3-1 mg/kg).
  - Antibodies were specific against the  $\text{————}$  of CDP870
  - $\text{————}$
  - $\text{————}$
  - **Note:** All of these observations are consistent with current understandings of antibody responses to proteins.
- ARLE05M0622 – 40001531 “Final Report of CDP870 antibody subgroup on CDP870 immunogenicity”. This is a summary circa 2003 of the immunological observations concerning antibody responses to CDP870. It was prepared by an internal Pfizer/Celltech committee. The major conclusions were:
  - About 40% of patients chronically dosed s.c. develop HAHA.
  - HAHA increases clearance of CDP870
  - Lower doses (0.3 mg/kg) result in higher rates of HAHA than higher doses (3-10 mg/kg)
  - CDP870 is more immunogenic in RA patients than Crohn’s disease patients.
  - CDP870 is more immunogenic when administered s.c. than i.v.
  - There is no consistent trend towards increases in adverse events in HAHA<sup>+</sup> patients.
  - **Note:** All of these observations are consistent with current understandings of antibody responses to proteins.

**API forms and immunogenicity assays used in animal studies.**

Surrogate forms of CDP870 (PEGylated  $\text{————}$  antibody Fab fragment that has specificity for mouse and rat TNF) were developed for rat tox studies. This was necessary because CDP870 doesn’t bind rat TNF.

- ARLE05M0613 – 40001275 “Development report for the production of cTN3  $\text{————}$ , and testing of cross-reactivity with mouse and rat TNF $\alpha$  using

a cell-based bioassay binding assay". This antibody (cTN3) is a antibody that has specificity for mouse and rat TNF. The  $K_D$  for mouse TNF is 1.2 nM; for rat TNF, 6.2 nM. The antibody expression construct contains

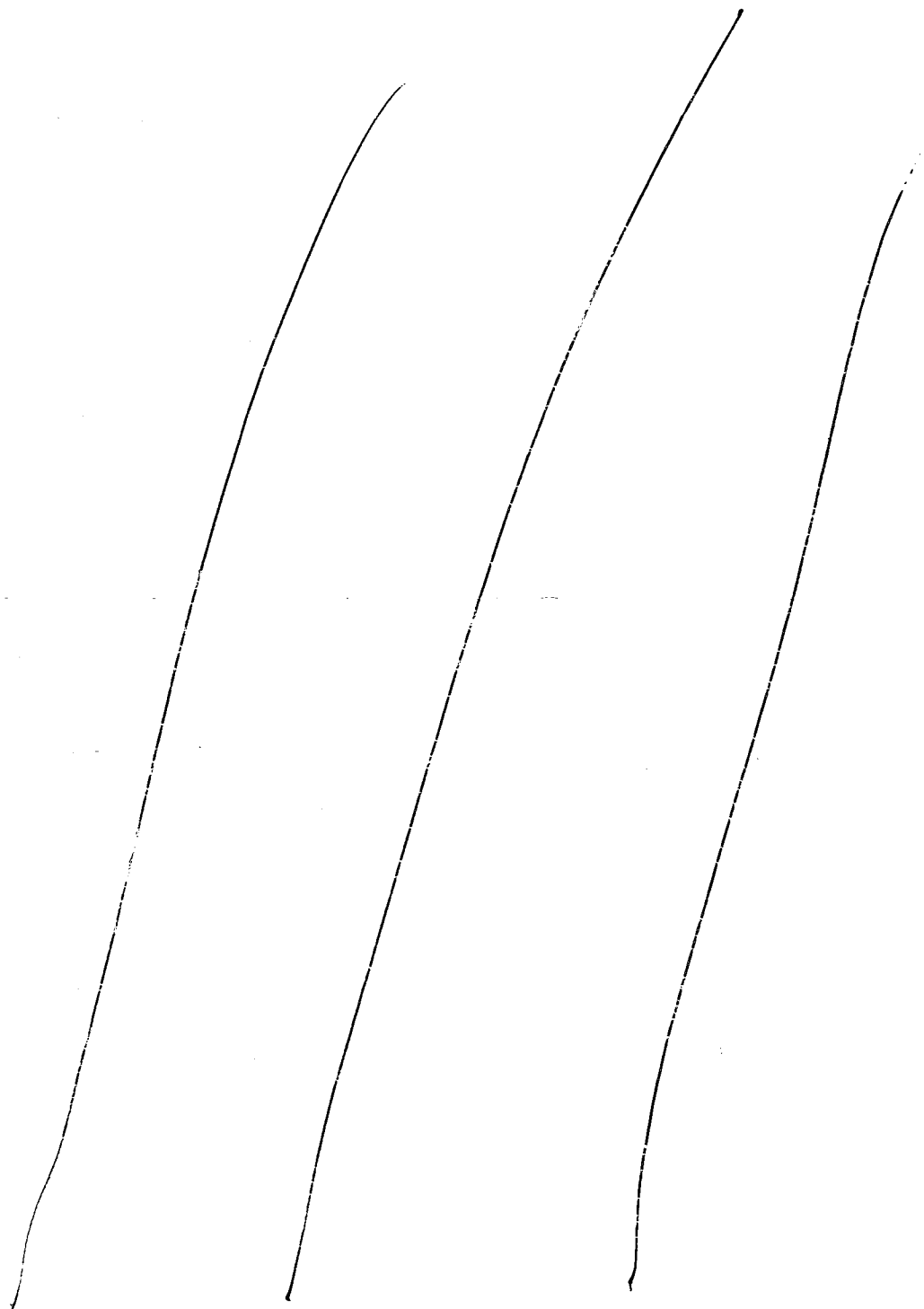
The Ab is tested by . It has neutralizing activity for both rat and mouse TNF in an L929 assay.

- ARLE05J1415 – 40001277 "Development report for the production of cTN3 PF (cTN3 PEG-Fab'), testing of crossreactivity with mouse and rat TNF $\alpha$  using a assay, and neutralisation of rat TNF $\alpha$  using a cell-based bioassay". This molecule is a PEGylated antibody Fab fragment that has specificity for mouse and rat TNF. The  $K_D$  for mouse TNF is 1.2 nM; for rat TNF, 6.7 nM. The antibody expression construct c

It has neutralizing activity for both rat and mouse TNF in an L929 assay, although the potency for mouse TNF is ~2-fold higher.

- ARLE05M0717 - 40001522 "Analysis of TN3 PEGylated Fab' (cTN3 PF) to support reproductive toxicology studies associated with the CDP870 programme". This report contains CMC information related to the cTN3 PF used in rat studies. Four batches of the product were produced over the duration of the tox studies (10014129/19, 4166/75, 4367/53, 6740/05). Each was assessed for . They were also tested for room temperature stability for 24 hours. In general each lot complied with the acceptance criteria; they were . They were stable for at least 24 hours using the above battery of tests. All of the batches were also compared side-by-side in an L929 bioassay and found to have equivalent activity.
- ARLE05M0521 – 40001124 "Validation of ELISA for the detection of antibodies to cTN3 – in rat plasma and milk samples (GLP- . The anti-mouse TNF antibody assay was validated for precision, accuracy, range, LOD/LOQ, specificity, freeze/thaw stability. The range was determined to be

Misc. CMC reports from section 4



**Recommendation.** UCB has performed critical supportive activities for their clinical and toxicological program:

- Surrogate CDP870 forms used in rat studies are well characterized and have substantial anti-TNF activity. They are adequate models for CDP870.
- The immunology of CDP870 has been adequately characterized. Like other antibody products, modest levels of anti-CDP870 antibodies develop in a subset of patients, are directed to the \_\_\_\_\_ and mostly impact product clearance rather than safety.
- The immunogenicity assay is adequate and has been qualified for its intended use.
- An algorithm has been developed where patients are \_\_\_\_\_

\_\_\_\_\_ This is consistent with industry practice.



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
5515 Security Lane  
Rockville MD 20852-1448

**Date:** November 14, 2006

**To:** Administrative File, STN 125160/0

**From:** Gilbert Salud, CMC Reviewer, CDER/OC/DMPQ TFRB, HFD-328

*11/14/06*

**Through:** Brenda Uratani PhD, Acting Branch Chief, CDER/OC/DMPQ/TRFB, HFD-328

*B. Uratani  
11/14/06*

**Subject:** Review Memo: Biologic License Application: Original Application for treatment of Crohns disease.

**US License** #1736

**Applicant** UCB Inc.  
1950 Lake Park Drive  
Smyrna, GA 30080

**Facility**

*11*

**Product** CDP870® (Certolizumb Pegol)

**Indication**

\_\_\_\_\_

**Due date:** December 30, 2006



**Recommendation:** The drug substance section of this application has been reviewed and the submission is recommended for approval.

---

**Summary**

- UCB Inc. submitted this BLA in support of the manufacturing of CDP 870(Certolizumab Pegol). The CDP870 drug substance is a recombinant, humanized antibody fragment directed against TNF alpha, which is \_\_\_\_\_ to PEG@MAL40K, \_\_\_\_\_
- The CDP870 drug substance is produced: \_\_\_\_\_  
\_\_\_\_\_
- The Drug substance is manufactured at \_\_\_\_\_
- The CMC sections related to manufacturing in the BLA were evaluated only from microbiology perspective. Drug product quality related to product specifications, process specifications, and analytical methods were deferred to the Product Office (OPS/OBP/DMA/DTP).

**Review Narrative**

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_

5 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process

**Conclusion**

- I. The drug substance section of the application as it relates to microbiology product quality is deemed acceptable. This application is recommended for approval.
- II. Review of product specifications, process specifications, and analytical methods were not part of this review. These sections were deferred to the product office (OPS/OBP/DMA/DTP).
- III. No additional inspectional follow-up items were identified.

Cc: HFD-328, Uratani  
HFD-180, Swider  
HFD-328, Harper-Velasquez  
HFD-328, TFRB Blue Files (STN125160)

Archived File: S:\archive\BLA\125160\125160.0.rev.mem.BLA.November 14, 2006.doc



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Public Health Service

Food and Drug Administration  
Center for Drug Evaluation and Research  
5515 Security Lane  
Rockville MD 20852-1448

**Date:** November 13, 2006  
**To:** Administrative File, STN BL 125160/0  
**From:** Janet Barletta, Ph.D. CDER/OC/DMPQ/TFRB, HFD-328  
**Through:** Brenda Uratani, Ph.D., Branch Chief, CDER/OC/DMPQ/TFRB, HFD-328 *Brenda 11/13/06*  
**Subject:** Review Memo (BLA): To provide for the manufacture of Certolizumab drug product at  
\_\_\_\_\_ ). A separate review of the  
drug substance will be provided by another reviewer in TFRB and DMA.  
**US License:** 1736  
**Applicant:** UCB, Inc.  
1950 Lake Park Drive  
Smyrna, GA 30080  
**Manufacturing Facility:** \_\_\_\_\_  
**FEI:** \_\_\_\_\_  
**Product:** CIMZIA™ (Certolizumab pegol)  
**Indication:** \_\_\_\_\_  
**Due date:** December 30, 2006

**Recommendation:** The submission, as amended, is recommended for approval.

### Review Summary

**P.1. Description of the Composition of the Drug Product:** Certolizumab (CDP870) is a lyophilized formulation (200 mg/vial) for subcutaneous injection. The reconstitution diluent is sterile WFI.

- 200 mg CDP870 drug substance/vial
- 100 mg sucrose
- 0.1 mg polysorbate 20

**P.2. Pharmaceutical Development:** is a recombinant, humanized, antibody Fab fragment with specificity for human TNF $\alpha$ . The Fab fragment is manufactured in *E. coli*, purified, and conjugated to polyethylene glycol (PEG) to extend the plasma half life.

14 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process



# Review Cover Sheet

**BLA STN 125160**

**Cimzia (certolizumab pegol)**

**UCB, Inc**

**Kurt Brorson, Ph.D. HFD-123  
Division of Monoclonal Antibodies**



# CMC Review Data Sheet

- 1. **BLA#** STN 125160
- 2. **REVIEW #:** 1
- 3. **REVIEW DATE:** 10-Oct-2006
- 4. **REVIEWERS:** Kurt Brorson, Ph.D.
- 5. **COMMUNICATIONS AND PREVIOUS DOCUMENTS<sup>1</sup>:**

<u>Previous Documents</u>	<u>Document Date<sup>2</sup></u>
Pre-BLA Meeting	5-Dec-2005
Filing Review.	21-April-2006
CMC FAXed IR	6-July-2006

<sup>1</sup> Chronology of previous CMC communications between CDER and the firm and/or reviews  
<sup>2</sup> Applicant's letter date or date of review and/or communication with applicant

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

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
STN 125160/0 Original Submission (Fab protein)	23-June-2006
STN 125160/0.004 Stability information	10-Aug-2006
STN 125160/0.005 Response to CMC IR	11-AUG-2006
STN 125160/0 Immunogenicity Assay	10-Oct-2006

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

**Name:** UCB Pharma, Inc.  
**Address:** 1950 Lake Park Dr.  
 Smyrna GA 30080  
**Representative:** Shannon Helms  
**Telephone:** 770-970-8592

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

- a) Proprietary Name: Cimzia
- b) Non-Proprietary Name: Certolizumab pegol
- c) Code name: CDP870
- d) Common name: anti-TNF Fab: PEG2MAL40K conjugate
- e) Drug Review Status: Non-Fast Track
- f) Chemical Type: Recombinant humanized Fab: PEG2MAL40K conjugate

- 9. **PHARMACOL. CATEGORY:** Therapeutic Fab: PEG2MAL40K conjugate to TNF.



## PRODUCT REVIEW



10. **DOSAGE FORM:** Sterile parenteral lyophilizate in stoppered glass vials.

**Composition of drug product:**

Names of Ingredient	Unit Quantity	Function	Reference to Quality Standards
CDP870 Drug Substance <sup>a</sup>	200.0 mg	Active Ingredient	Company Standard
Sucrose	100.0 mg		NF
Polysorbate	0.10 mg		NF
			NF

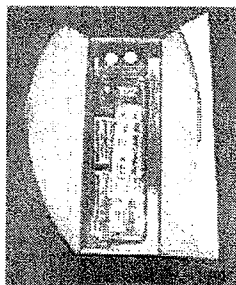
<sup>a</sup> Polysorbate

11. **STRENGTH/POTENCY:**

- (i) The concentration of Cimzia Drug Product upon reconstitution in WFI is 180-215 mg/ml.
- (ii) Potency is measured using a proprietary \_\_\_\_\_ bioassay. The IC<sub>90</sub> for CDP870 using this assay is 3 ng/ml
- (iii) The affinity of CDP870 for TNF $\alpha$  was measured using a \_\_\_\_\_ instrument; it is ~90 pM.

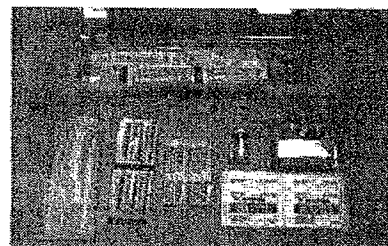
12. **ROUTE OF ADMINISTRATION:** Subcutaneous injection after reconstitution with Water for Injection, USP

**Components in commercial pack:**



Full Commercial Pack Configuration

Each Pack Contains 2 single dose trays and 2 vials of Cimzia Product



Each Tray Contains:  
1- 23G needle  
2- 20G needles  
1- 3mL syringe  
4- alcohol swabs  
1 vial 1mL WFI

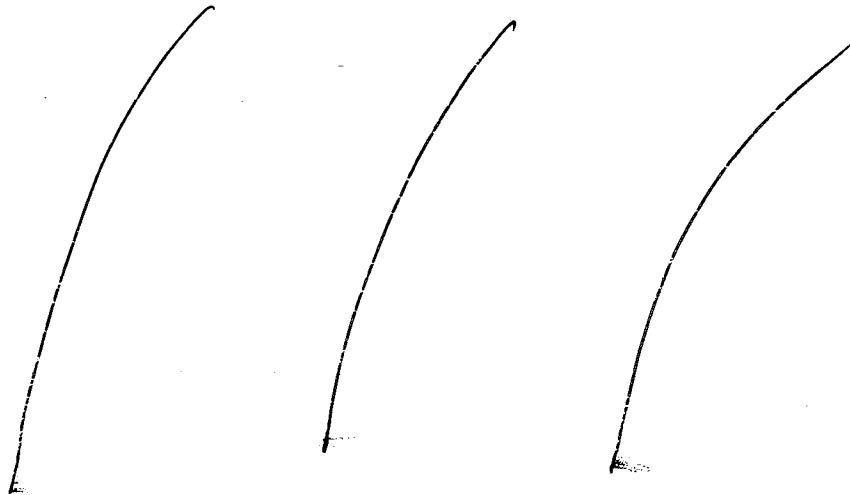




13. ANIMAL- AND HUMAN-DERIVED RAW MATERIALS

The only animal-derived raw materials used in cell culture is

\_\_\_\_\_

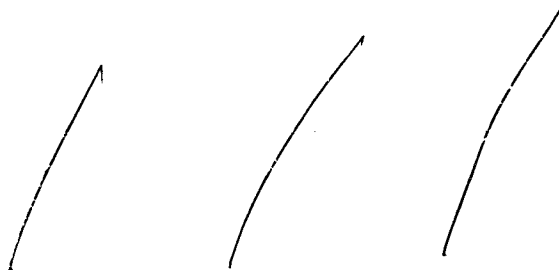


14. PRIMARY STRUCTURE, HOST SOURCE:

Certolizumab pegol (CDP870) is a humanized anti-TNF Fab' antibody fragment  
\_\_\_\_\_ to PEG2MAL40K. \_\_\_\_\_

\_\_\_\_\_ The Fab is expressed in E. coli, purified by \_\_\_\_\_  
chemically conjugated to PEG2MAL40K \_\_\_\_\_ The  
product is supplied in a kit as a sterile lyophilized dosage form in vials for reconstitution with  
WFI.

Diagram of active ingredient:



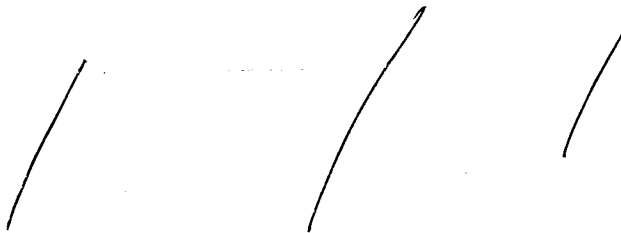


# PRODUCT REVIEW

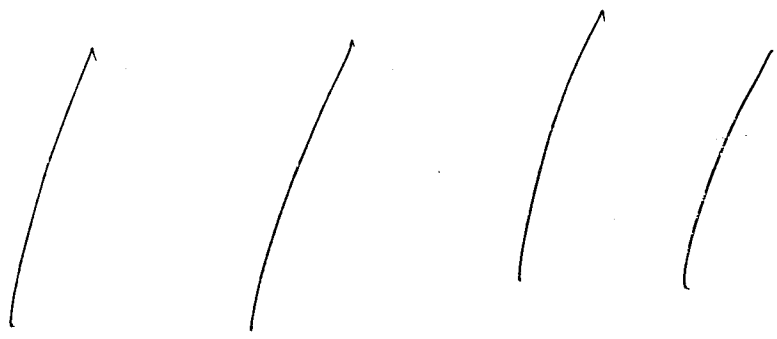


## Sequence of Fab'

Light Chains:



Heavy Chains:



### 15. RELATED/SUPPORTING DOCUMENTS; DMFs:

DMF #	TYPE	HOLDER	ITEM REFERENCED	CODE <sup>1</sup>	STATUS	REVIEW DATE	COMMENTS
✓	III	/	/	4	N/A		Meets USP <661> and As requirements
✓	V			4	N/A		Site was inspected as part of this application
✓	III			4	N/A		Meets USP <381>

<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

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



# PRODUCT REVIEW



OBP:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Establishment Status	Approval		Gil Salud
Labeling Nomenclature Committee	N/A	N/A	N/A
OPDRA <sup>1</sup>	Tradename under review		
Microbiology review			Janet Barletta
Environmental Assessment	Approval <sup>2</sup>	10/10/06	Kurt Brorson

1. Review trade name for medical error avoidance.
2. Cimizia is well characterized and consists of \_\_\_\_\_ ; and polyethylene glycol. PEGs are reported to be practically non-toxic, with no adverse effects observed in rats at levels of 2% in the diet (approximately equivalent to 1000mg/kg bw/day). The maximum amount of PEG2MAL expected to be used in the manufacture of CDP870 drug substance per year is \_\_\_\_\_. The proposed action is not expected to significantly alter the concentration or distribution of these substances, their metabolites, or degradation products, in the environment. It meets the criteria for exclusion under 21 CFR 25.31(c).

## 17. CMC Inspectional Activities

1. \_\_\_\_\_ (07/17/06 to 07/21/06): This facility is the site of drug substance manufacture. Product reviewer Kurt Brorson along with TFRB Inspector Gilbert Salud participated in this inspection. A three-item FDA Form 483 was issued to the firm. Adequate responses to the 483 were received by the agency. The facility was found to be in compliance with cGMPs and capable of manufacturing certolizumab pegol drug substance in a consistent manner.
2. \_\_\_\_\_ (7/23 & 24/06): Bioassay (potency) testing of drug substance and drug product release is completed at this site. Product reviewer Kurt Brorson along with TFRB Inspector Gilbert Salud participated in this inspection. No FDA Form 483 was issued to the firm. The facility was found to be in compliance with cGMPs and capable of adequately testing certolizumab pegol drug substance and drug product.
3. Inspections for all other sites involved with certolizumab pegol production or testing were waived by TFRB based on a risk analysis of previous inspections.

# The Chemistry Executive Summary

## I. Recommendations

### A. Recommendation and Conclusion on Approvability

The data submitted in this application support the conclusion that the manufacture of Cimzia leads to a product that is pure and potent. The product is free from \_\_\_\_\_ in a way that meets or exceeds the parameters recommended by FDA. The manufacturing process results in a consistent product as evidenced by results from different production runs including the validation campaign.

The CMC review team has communicated comments and questions to the sponsor throughout the review period in an attempt to resolve concerns. Our most recent communication with the sponsor was on November 29, 2006. Replies to this inquiry were received on December 4 and December 6. Unfortunately, two minor issues which were raised in our communication on November 29 were unresolved by the recent amendments and the following two comments should be conveyed to sponsor:

1. In your submission received December 6, 2006, you propose to submit a report in February 2007 to support the establishment of \_\_\_\_\_ in-process control at \_\_\_\_\_ at the \_\_\_\_\_. The study report should contain data for \_\_\_\_\_ levels for all batches manufactured to support the proposed in-process control. Also, please provide an updated table for in-process controls to include for \_\_\_\_\_ monitoring at \_\_\_\_\_.
2. Your submission received December 4, 2006, describes an amended comparability protocol to support PEG2MAL40K scale up to \_\_\_\_\_. However, it appears from Table 1 in this submission that campaign \_\_\_\_\_ (validation campaign) used PEG2MAL40K manufactured at the \_\_\_\_\_ scale. Since campaign \_\_\_\_\_ batches used the same process as the proposed commercial manufacturing process, there is no manufacturing change and there is no need for this comparability protocol. Therefore, please provide a statement for removal of the comparability protocol from the BLA. However, if there are differences between the manufacturing process as used during the validation campaign and proposed commercial manufacturing process, please highlight them in detail and submit a revised comparability protocol.

## II. Summary of Chemistry Assessments

### A. Drug Product and Drug Substance

- CIMZIA (certolizumab pegol; CDP870) is supplied as a sterile, white, lyophilized powder for reconstitution and then subcutaneous administration. After

reconstitution with 1 mL of sterile Water for Injection, USP, the resulting pH is approximately 5.2. Each single-use vial contains approximately 200 mg certolizumab pegol, 100 mg sucrose, 0.9 mg lactic acid, and 0.1 mg polysorbate. No preservatives are present.

- The drug product is supplied as 200 mg lyophilized certolizumab pegol in a sterile, single-use \_\_\_\_\_ vial, closed with a \_\_\_\_\_ gray rubber stopper, and sealed with an aluminum overseal and tamper proof snap off white plastic cap.
- The drug product is filled and lyophilized using \_\_\_\_\_ at \_\_\_\_\_ Water for Injection (produced at \_\_\_\_\_ is supplied with the drug product. \_\_\_\_\_ assures sterility of the diluent.
- Stability of the drug product has been established for \_\_\_\_\_ months at 2°C - 8°C for commercial scale product and for \_\_\_\_\_ months with clinical product. These results currently support an 18-month expiry. The drug product stability protocol in the BLA is appropriate.
- Certolizumab pegol is a recombinant, humanized Fab' antibody fragment directed against TNF $\alpha$ , \_\_\_\_\_ to PEG2MAL40K, \_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_ The experimentally determined molecular mass of the Fab' fragment is approximately \_\_\_\_\_ The experimentally determined molecular mass of certolizumab pegol is approximately 90.8 kDa, which is consistent with \_\_\_\_\_
- The Fab' fragment is manufactured in *Escherichia coli*. The Drug Substance is produced during \_\_\_\_\_ manufacturing campaigns carried out at \_\_\_\_\_ in which the Fab' \_\_\_\_\_, purified, and pegylated in a process referred to as the \_\_\_\_\_ process".



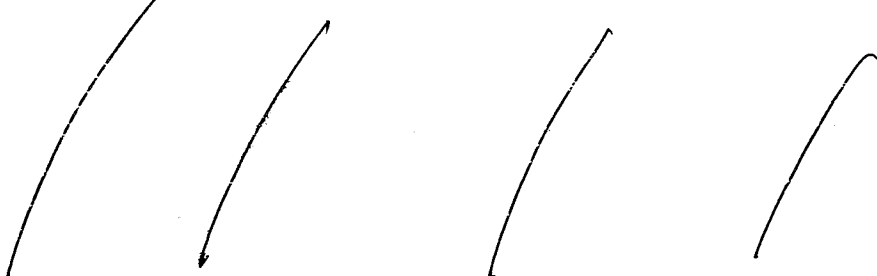


# SUMMARY



- The proposed expiration dating period for storage of Drug Substance based on the data is 18 months from the date of manufacture. The Drug Substance stability protocol in the BLA is appropriate.
- Raw material testing and control is adequate. The only animal derived raw material \_\_\_\_\_ is derived from \_\_\_\_\_. Based on information available to date, \_\_\_\_\_ has been deemed to pose a minimal risk for \_\_\_\_\_.
- On 8/25/05, UCB informed FDA that certain batches of drug substance used in the phase III trials (process \_\_\_\_\_) contained measurable levels of \_\_\_\_\_.

\_\_\_\_\_ . These \_\_\_\_\_ were probably introduced \_\_\_\_\_ .  
 \_\_\_\_\_ The \_\_\_\_\_ CDP-870 INDs, 11197 \_\_\_\_\_ were briefly placed on clinical hold while UCB investigated the levels of the \_\_\_\_\_ , in the drug products. Root cause analysis and corrective actions have been proposed and are appropriate. The \_\_\_\_\_ contamination issue did not represent a safety issue (limits within \_\_\_\_\_ criteria) and did not impact process validation. The \_\_\_\_\_ changes at \_\_\_\_\_ are likely to remove the possibility of future \_\_\_\_\_ contamination.





# SUMMARY



- CDP870 binds to TNF- $\alpha$  with a binding constant of  $89.0 \pm 4.9$  pM. Potency of the Drug Product is determined by a ~~bioassay. The assay utilizes~~



**B. Description of How the Drug Product is Intended to be Used**

Cimzia is intended to be marketed for treatment of Crohn's disease.

Cimzia is supplied as a sterile, white, lyophilized powder for reconstitution with 1 mL sterile Water for Injection (WFI), USP; the resulting pH is approximately 5.2. Each lyophilized vial of Cimzia is reconstituted with 1 mL sterile WFI using a syringe with a 20 gauge needle. The sample is gently swirled with sterile WFI without shaking and left undisturbed for 30 minutes for reconstitution to result in clear or opalescent colorless to pale yellow liquid with no visible particulates. Upon reconstitution, the vials can be refrigerated (not frozen) for up to 24 hours prior to injection. Stability data was provided in the submission to demonstrate that storage of reconstituted Cimzia at refrigerated conditions for 24 hours resulted in stable product. Cimzia should be at room temperature at the time of administration of injection. Using two new 20 gauge needles for each vial, the reconstituted solution is withdrawn, resulting in two syringes each containing 1 mL Cimzia (200 mg). The 20 gauge needles are switched to 23 gauge and the full contents of each syringe are injected subcutaneously into separate sites on abdomen or thigh.

Cimzia pack contents include two \_\_\_\_\_ Type I glass vial with rubber stopper overseals each containing 200 mg lyophilized Cimzia for reconstitution, two 2 mL Type I glass vials containing 1 mL sterile WFI, two 3 mL plastic syringes, four 20 gauge luer-lok needles (1 inch), two 23 gauge luer-lok needles (1 inch) and eight alcohol swabs.

The proposed recommended adult dose for Cimzia is an induction regimen of 400 mg given as two subcutaneous injections at week 0, 2, and 4, followed by a maintenance regimen of 400 mg every 4 weeks. Refer to the clinical review for further changes to the dosing regimen for induction and maintenance.

Cimzia vials should be refrigerated at 2-8 °C. The recommended expiration dating period is 18 months under these storage conditions. The expiry could be extended as additional stability data is provided.

**C. Basis for Approvability or Not-Approval Recommendation**

- Cimzia is manufactured by a robust process with precautions for \_\_\_\_\_  
\_\_\_\_\_ Cimzia is manufactured consistently, resulting in a safe and effective product. Two minor CMC issues remain to be addressed.





**III. Administrative**

**A. Reviewers' Signature**

Product Reviewer: Kurt Brorson, Ph.D.

Product Reviewer: Gurpreet Gill-Sangha, Ph.D.

**B. Endorsement Block**

Product Team Leader: Patrick Swann, Ph.D.

Product Acting Division Director: Kathleen Clouse, Ph.D.

**C. CC Block**

Office Director: Steve Kozlowski, M.D.

Division of Monoclonal Antibodies File/BLA STN 125160

# Review Memo

**Ref:** 125160/0/5

**Prepared by:** Kurt Brorson, Ph.D., Staff Scientist, DMA *KB*

**Through:** Kathleen A. Clouse, Ph.D., Chief, *K. Clouse*  
Lab of Cell Biology; Acting Director DMA

**CSO:** Marlene Swider

**Sponsor:** UCB

**Product:** Certolizumab pegol

**Date of submission:** July 27, 2006  
**Date of Review:** Aug 11, 2006

## Background

Certolizumab pegol (CDP870) is a humanized anti-TNF Fab' antibody fragment  
\_\_\_\_\_ to PEG2MAL40K.

\_\_\_\_\_ The Fab is  
expressed in E. coli, purified by \_\_\_\_\_, chemically conjugated to  
PEG2MAL40K and \_\_\_\_\_. The product is  
supplied in a kit as a sterile lyophilized dosage form in vials for reconstitution with  
sterile WFI.

Drug substance manufacture occurs at \_\_\_\_\_ Drug  
product manufacture occurs at \_\_\_\_\_ Release  
testing is shared between — UCB Rochester, NY, and some contract sites.

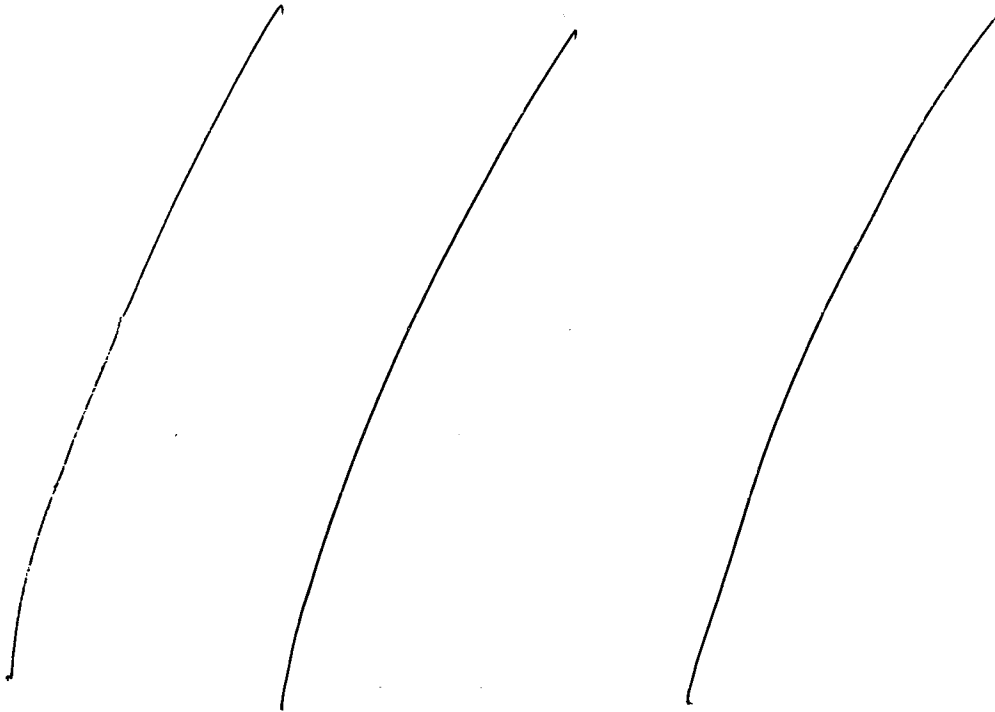
Certolizumab pegol (CDP870) is currently under BLA review for Crohn's disease.  
As part of the initial BLA review, the following questions and requests for  
information were conveyed to the sponsor on July 6:

*(Three large handwritten slashes indicating redacted content)*



**Amendment contents**

In this amendment, UCB addresses each question.



**Recommendation.** UCB has adequately addressed the CMC questions conveyed on July 6, 2006.

# Review Memo

Ref: 125160/0/4

Prepared by: Kurt Brorson, Ph.D., Staff Scientist, DMA 913

Through: Kathleen A. Clouse, Ph.D., Chief, *K. Clouse*  
Lab of Cell Biology; Acting Director DMA

CSO: Marlene Swider

Sponsor: UCB

Product: Certolizumab pegol

Date of submission: July 17, 2006  
Date of Review: Aug 10, 2006

## Background

Certolizumab pegol (CDP870) is a humanized anti-TNF Fab' antibody fragment to PEG2MAL40K

expressed in E. coli, purified by \_\_\_\_\_ The Fab is chemically conjugated to PEG2MAL40K and \_\_\_\_\_ The product is supplied in a kit as a sterile lyophilized dosage form in vials for reconstitution with sterile WFI.

Drug substance manufacture occurs at \_\_\_\_\_ Drug product manufacture occurs at \_\_\_\_\_ Release testing is shared between \_\_\_\_\_ UCB Rochester, NY, and some contract sites.

Certolizumab pegol (CDP870) is currently under BLA review for Crohn's disease.

### \_\_\_\_\_ issue

On 8/25/05, UBC informed CDER that certain batches of drug substance used in the phase III trials (process \_\_\_\_\_ contained measurable levels of \_\_\_\_\_

— These \_\_\_\_\_ were thought to have been introduced \_\_\_\_\_

The CDP-870 INDs, 11197 were briefly placed on clinical hold while UCB investigated the levels of in the drug products. The investigation concluded that:

- The contamination was traced to
- levels in DS batches made during campaigns were within the permissible levels stipulated by . The highest levels were: . **Note:** These are likely to be further removed by that is used to manufacture drug product.
- The DS lots were within other release criteria.

As follow-up, UCB and made several commitments:

- A method for detecting these was implemented. UCB committed to FDA to test all future batches of CDP-870 for . This will continue until a mutual agreement is made with the agency indicating that the testing can be terminated. They will not use any batch that exceeds the limits.
- will also test used in isolation & purification of CDP-870.
- UCB performed a GMP status review of on Feb 7 & 8, 2006.
- has eliminated
- has conducted a review of their . This activity is a long-term project. **Note:** During the July 2006 inspection, FDA verified that the

#### Amendment content

UCB also committed to perform an evaluation of drug substance stability in the presence of the . The following concentrations were tested: no (negative control),

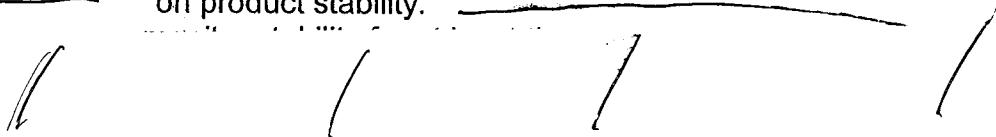
stability samples were stored at -70°C (routine storage), 2-8°C and 25°C (stress condition). The samples were only studied at 25°C. The stability protocol specifies running the study to , with an optional extension to . **Note:** The study should be extended to s for at least those samples stored under the routine storage condition (-70°C). It would also be informative to extent the 2-8°C storage samples to as well.

A report containing results from the stability studies were submitted in this amendment:

- Samples held under routine storage (-70°C) remained within stability specifications. There was no trend indicating any quality attribute change over the

- Samples held at 2-8°C remained within stability specifications. There was a small increase in the level of \_\_\_\_\_ in some samples, but a correlation was not consistent with presence of ppm levels of \_\_\_\_\_ (i.e., the \_\_\_\_\_ sample did not demonstrate this trend).
- Samples held at 25°C were OOS for \_\_\_\_\_ . There was also a marked trend upward in \_\_\_\_\_ This occurred in all samples, including the negative control, and didn't correlate with levels of \_\_\_\_\_

**Recommendation:** The study design is adequate for addressing the impact of \_\_\_\_\_ on product stability. \_\_\_\_\_



**APPEARS THIS WAY  
ON ORIGINAL**

# Review Memo

**Ref:** 125160

**Prepared by:** Kurt Brorson, Ph.D., Staff Scientist, DMA *KB*

**Through:** Kathleen A. Clouse, Ph.D., Chief, *K. Clouse*  
Lab of Cell Biology; Acting Director DMA

**CSO:** Marlene Swider, ODE3/DGP

**Sponsor:** UCB Inc. (Formerly Celltech)

**Product:** Certolizumab pegol (CDP870, Cimzia)

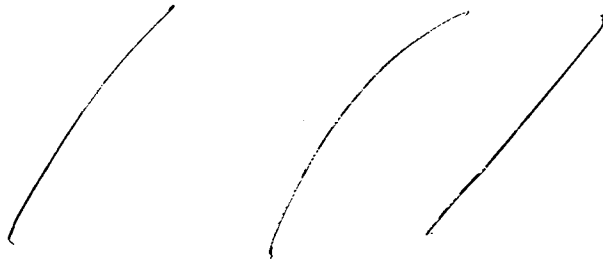
**Date of submission:** 3/1/06  
**Date of Review:** 6/23/06

## Summary

Certolizumab pegol (CDP870) is a humanized anti-TNF Fab' antibody fragment  
to PEG2MAL40K,

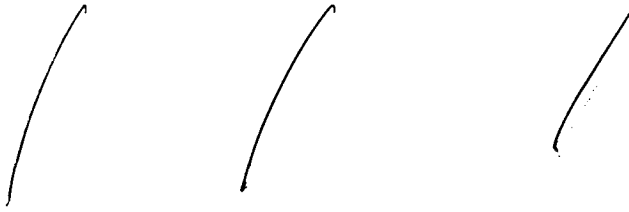
expressed in E. coli, purified by \_\_\_\_\_, The Fab is  
to PEG2MAL40K and \_\_\_\_\_, chemically conjugated  
supplied in a kit as a sterile lyophilized dosage form in vials for reconstitution with  
WFI. The product is

Diagram of active ingredient:

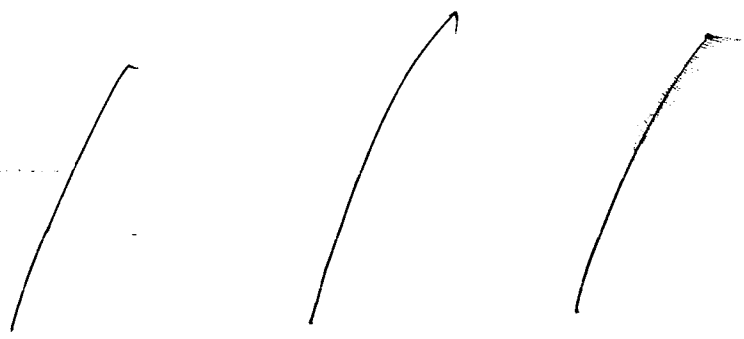


Sequence of Fab'

Light Chains:



Heavy Chains:



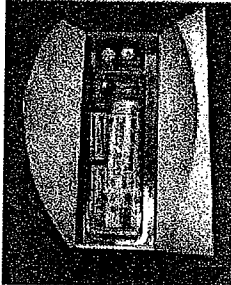
Composition of drug product:

Names of Ingredient	Unit Quantity	Function	Reference to Quality Standards
CDP870 Drug Substance <sup>a</sup>	200.0 mg	Active Ingredient	Company Standard
Sucrose	100.0 mg	_____	NF
Polysorbate	0.10 mg	_____	NF
		_____	NF

**APPEARS THIS WAY  
ON ORIGINAL**

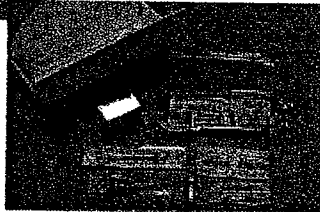


Components in commercial pack:



Full Commercial Pack Configuration

Each Pack Contains 2 single dose trays and 2 vials of Cimzia Product



Each Tray Contains:  
1- 23G needle  
2- 20G needles  
1- 3mL syringe  
4- alcohol swabs  
1 vial 1mL WFI

## Drug Substance

### Facilities:

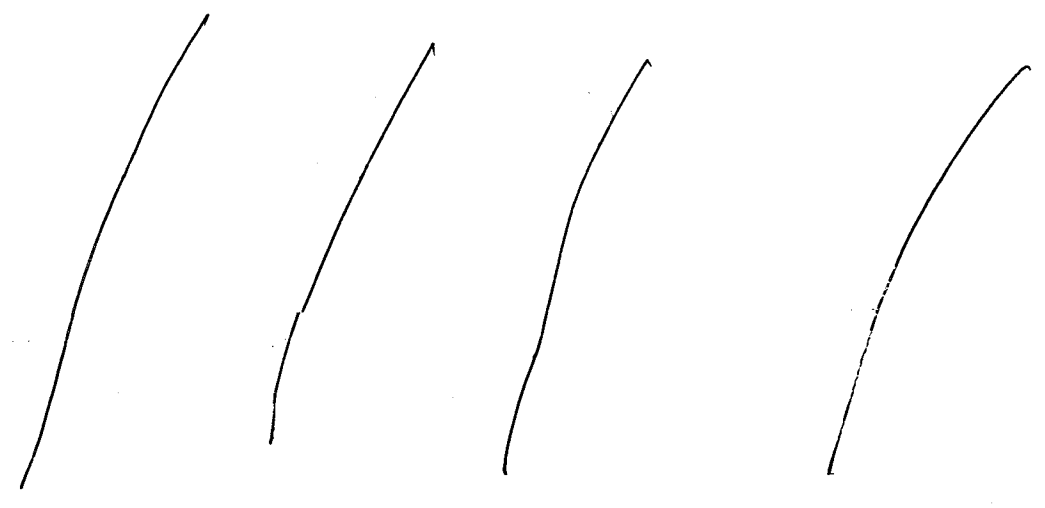
- Drug substance manufacture takes place at \_\_\_\_\_ Several drug substance tests are also performed at this site.
- Drug product release and stability testing occurs at UCB Manufacturing Inc.; 755 Jefferson Road; Rochester, NY 14623; USA
- Specialty testing and storage takes place at contractors and other locations. These include:
  - The bioassay is performed by \_\_\_\_\_
  - \_\_\_\_\_ testing is performed by \_\_\_\_\_
  - Bulk is stored at \_\_\_\_\_ and UCB Pharma Ltd; Unit 11-14 Foster Avenue; Woodside Park; Dunstable; Bedfordshire; LU5 5TA; UK
  - \_\_\_\_\_

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Trade Secret / Confidential

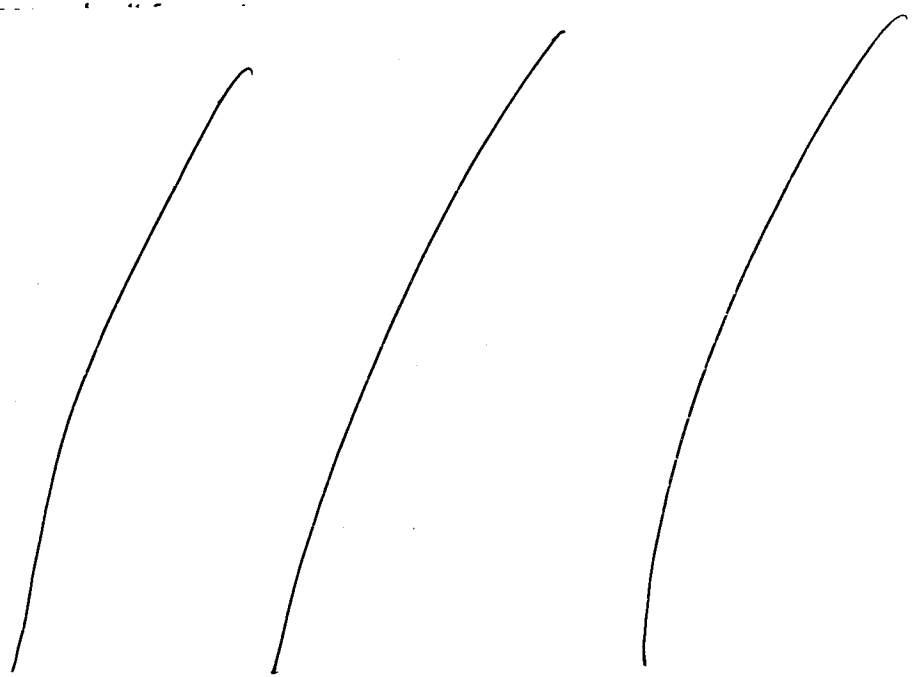
Draft Labeling

Deliberative Process



**Recommendation:** The BLA can be approved pending confirmation by:

- \_\_\_\_\_ inspections (note: these inspections were completed in July 17-25, 2006)
- TFRB microbiology review
- PEG and PEGylation review
- Resolution of the following questions:

- 
- **Note:** responses to these questions were submitted on July 27, 2006; see review of amendment 5.

19 Page(s) Withheld

Trade Secret / Confidential

Draft Labeling

Deliberative Process