

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

125544Orig1s000

OTHER REVIEW(S)

Background and Summary Description:

The Applicant, Celltrion Inc., submitted 351(k) BLA 125544/0 CT-P13* on August 8, 2014 as a proposed biosimilar to US-licensed Remicade (infliximab). The Applicant seeks approval for all the reference product's indications for US-licensed infliximab (Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis¹, Rheumatoid Arthritis in combination with methotrexate, Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis). The Applicant proposes to supply CT-P13* as a 100 mg lyophilized powder in single-dose vials that require reconstitution and dilution prior to intravenous infusion, which is the same as the reference product.

The submitted labels and labeling contain the proposed proprietary name, (b) (4), which the Applicant withdrew during the review cycle. Subsequently, the Applicant submitted a request for proprietary name review for "Inflectra", which was found acceptable by the Division of Medication Error Prevention and Analysis (DMEPA) on February 23, 2015.

Materials Reviewed:

- Vial Container Label
- Carton Labeling, 1-count
- Carton Labeling, 10-count

Start of Sponsor Material



¹ This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at <http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm>.

Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum:

1. name (expressed either as the proper or common name); *conforms*. However the proper name for this biosimilar product is pending.
2. lot number or other lot identification; *conforms*.
3. name of the manufacturer; *conforms*. However OBP recommends revising manufacturer information (b) (4) on the small label.
4. for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *Not applicable*.

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label: *Not applicable*.

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label. *Not applicable*.

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum the name (expressed either as the proper or common name), the lot number or other lot identification and the name of the manufacturer; in addition, for multiple dose containers, the recommended individual dose. Containers bearing partial labels shall be placed in a package which bears all the items required for a package label. *See "Partial Label" above*.

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label. *Not applicable*.

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents. – This conforms to the regulation per CMC visual inspection. Does not conform.

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label [See 21 CFR 207.35]; NDC number not required on a small/partial label. However, OBP recommends relocating NDC to appropriate location on the labels.

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and prominence] *conforms*.

F. 21 CFR 201.15 Drugs; prominence of required label statements; *conforms*.

G. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

H. 21 CFR 201.25 Bar code; does not conform. Although barcode is not required on small label, the Applicant should first label with a linear barcode (b) (4)

I. 21 CFR 201.50 Statement of identity; *conforms*.

J. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

K. 21 CFR 201.55 Statement of dosage; *conforms*.

L. 21 CFR 201.100 Prescription drugs for human use; *conforms*. This is a small label and the required information is listed on the carton labeling.

Start of Sponsor Material

Carton Labeling, 1-count

(b) (4)



Carton Labeling, 10-count

(b) (4)



End of Sponsor Material

III. Carton

A. 21 CFR 610.61 Package Label:

- a) The proper name of the product; [see 21 CFR 600.3 (k) and section 351 of the PHS Act]. *Conforms.* However the proper name for this biosimilar product is pending.
- b) The name, addresses, and license number of manufacturer; does not conform.
- c) The lot number or other lot identification; *conforms.*
- d) The expiration date; *conforms.*
- e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative". *conforms.*
- f) The number of containers, if more than one; *conforms.*
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms.*
- h) The recommended storage temperature; *conforms.*
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms.*
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable, single-dose container.*
- k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms.* However, OBP recommends revising to relocate the route of administration to appear under the strength statement.
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable.*

m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.

n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.

o) The adjuvant, if present; *not applicable*.

p) The source of the product when a factor in safe administration; *not applicable*.

q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.

r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals.

- Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels. *Conforms*. However OBP recommends revising MG statement to standard format.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Infliximab is a monoclonal antibody and is exempt*.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor:

The name and address of the distributor of a product may appear on the label provided that the name, address, and license number of the manufacturer also appears on the label and the name of the distributor is qualified by one of the following phrases:
"Manufactured for _____". "Distributed by _____", "Manufactured

by _____ for _____”, “Manufactured for _____ by _____”, “Distributor: _____”, or “Marketed by _____”. The qualifying phrases may be abbreviated. *Not applicable.*

- E. 21 CFR 610.67 Bar code label requirements:
Biological products must comply with the bar code requirements at §201.25 of this chapter; does not conform.

- F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; does not conform.

- G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*. However, OBP recommends revising statements regarding reconstitution and dilution, infusion. These revisions aim to remove unnecessary words to decrease crowding of the label. (b) (4)
_____.

- H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

- I. 21 CFR 201.10 Drugs; statement of ingredients; [Placement and Prominence]; does not conform.

- J. 21 CFR 201.15 Drugs; prominence of required label statements; does not conform. Route of administration lacks prominence.

- K. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

- L. 21 CFR 201.25 Bar code label requirements; does not conform.

- M. 21 CFR 201.50 Statement of identity; *conforms*

- N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*

- O. 21 CFR 201.55 Statement of dosage; *conforms*.

- P. 21 CFR 201.100 Prescription drugs for human use; *conforms*. However, OBP recommends revising the list of ingredients to comply with USP Official 5/1/2015 –7/31/2015, USP 38/NF 33, <1091> Labeling of Inactive Ingredients.

CDER Labeling Preferences

This section describes additional concerns provided to the Applicant that address CDER Labeling practices.

A. General Comment for the Vial

1. Confirm there is (b) (4) cap overseal of the vials to comply with a revised United States Pharmacopeia (USP) standard [USPC Official 5/1/2015 -7/31/2015, USP 38/NF 33], <1> INJECTIONS, PACKAGING, Labeling on Ferrules and Cap Overseal.

B. Carton Labeling, 1-count

1. Remove the (b) (4) that from (b) (4). The (b) (4) are competing with important information.

C. Vial Container Label

1. We consider the Vial Container Label a partial label due to its small size per 21 CFR 610.60(c). Our recommendations below are intended to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability.
2. Revise the presentation of the proprietary name, nonproprietary name, dosage form and strength that appears in (b) (4) font color (b) (4) so the text on the label is (b) (4).
3. Increase the prominence of the strength "100 mg per vial".
4. Add the statement "For Intravenous Infusion Only" to appear under the strength statement.
5. Revise the statement (b) (4) to "Reconstitute and Dilute Before Intravenous Infusion."
6. Delete the statement, (b) (4).
7. If there is space on the label, a linear barcode should be used (b) (4).

Conclusions

The container label and carton labeling and for Inflectra (CT-P13^{*}) were reviewed and found not to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 200.100 and United States Pharmacopeia, USP 38/NF 33 [5/1/2015-7/31/2015]. Identified labeling deficiencies will be sent to the Applicant.

Comments to the Applicant

Please note that within the following container label and carton labeling comments, FDA refers to Celltrion's proposed product using the descriptor "CT-P13^{*}" in place of the nonproprietary name because the Agency is continuing to consider its approach to nonproprietary naming of your proposed product. "CT-P13^{*}" is not intended to be included on your final printed labels or labeling.

A. General Comments

1. Replace all instances of the proprietary name [REDACTED] (b) (4) with "Inflectra" on all labels and labeling.
2. Confirm there is [REDACTED] (b) (4) cap overseal of the vials to comply with a revised United States Pharmacopeia (USP) Official 05/1/2015 – 7/31/2015, USP 38/NF 33, General Chapters: <1> Injections, Packaging, Labeling on Ferrules and Cap Overseals.
3. Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e).

B. Carton Labeling, 10 vials

1. Add the NDC to the top one-third portion of the carton labeling to comply with 21 CFR 201.2.
2. Ensure the font size of "CT-P13^{*}" is at least half the size font size of the proprietary name "Inflectra" per 21 CFR 201.10.

^{*} FDA is using the descriptor "CT-P13^{*}" in place of the nonproprietary name because the Agency is continuing to consider its approach to nonproprietary naming of your product. CT-P13 is not intended to be included in your final printed labels and labeling.

3. Revise the strength statement [REDACTED] (b) (4) that appears in the [REDACTED] (b) (4) to read "100 mg per vial" or "100 mg/vial"².
4. Relocate the strength statement "100 mg per vial" from alongside the dosage form, For Injection, to appear below the dosage form.
5. Add the route of administration "For Intravenous Infusion Only" to appear below the strength. For example:

Inflectra
(CT-P13*)
For Injection
100 mg per vial
For Intravenous Infusion Only

6. Revise the statement [REDACTED] (b) (4) to "Reconstitute and Dilute Before Intravenous Infusion."
7. Revise the statement [REDACTED] (b) (4) to "Infuse over at least 2 hours with an in-line filter."
8. Revise medication guide to read read "Dispense the enclosed Medication Guide to each patient."
9. Revise the reconstitution and dilution instructions to read as follows:

Reconstitute each vial with 10 mL Sterile Water for Injections, USP. The resulting concentration is 10 mg/mL. Do NOT shake reconstituted solution. Further dilute with 0.9% Sodium Chloride Injection, USP. See insert for full preparation instructions.
10. Delete the statement [REDACTED] (b) (4)

² FDA Guidance for Industry: Safety Considerations for Container Labels and Carton Labeling Design to Minimize Medication Errors. April 2013. Draft Guidance.
<http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm349009.pdf>

11. Revise the manufacturer information to comply with per 21 CFR 600.3(t) and 21 CFR 610.61(b). The manufacturer is the "Applicant" or licensee that appears on your submitted 356h form. For example:

"Manufacturer:" or "Manufactured by:" (Licensee or Applicant on the 356h form)

Celltrion, Inc.

23, Academy-ro

Yeonsu-gu, Incheon, 406-840, Republic of Korea

US License No. 1996

12. Add a linear bar coder to comply with 21 CFR 610.67. If using QR codes, ensure they appear on the side or back panel, away from the linear bar code and in a size that does not compete with, distract from the presentation of other required or recommended information on the labeling.¹

13. Ensure the carton labeling and prescribing information list all the inactive ingredients. Currently, the list of inactive ingredients and their respective amounts in both the proposed prescribing information and carton labeling differ. Additionally, revise the list of ingredients to comply with 21 CFR 201.100(b)(iii) and USP Official 5/1/2015 – 8/1/2015, USP 38/NF 33, <1091> Labeling of Inactive Ingredients, by listing the names of the inactive ingredients in alphabetical order in the following format: inactive ingredient (amount). For example:

Once reconstituted, each mL contains 10 mg CT-P13*, di-sodium hydrogen phosphate dihydrate (x mg), polysorbate 80 (x mg), sodium dihydrogen phosphate monohydrate (x mg), and (b) (4) sucrose (x mg).

C. Carton Labeling, 1 vial

1. See comments B2, B5, B6, B7, B8, B9, B10, B11, B12, and B13.
2. Remove the (b) (4) from (b) (4). The (b) (4) are competing with important information.¹

D. Vial Container Label

1. See comments B2, B5, and C2.
2. We consider the Vial Container Label a partial label due to its small size per 21 CFR 610.60(c). Our recommendations below are intended to preserve the required and recommended information on the label and remove less important information to provide more white space and improve readability.
3. Revise the presentation of the NDC, proprietary name, nonproprietary name, dosage form, and strength on the PDP [REDACTED] (b) (4) [REDACTED] so the text on the label is [REDACTED] (b) (4) [REDACTED].¹
4. Increase the prominence of the strength "100 mg per vial".
5. Revise the statement [REDACTED] (b) (4) [REDACTED] to "Reconstitute and Dilute Before Intravenous Infusion."
6. Delete the statement, [REDACTED] (b) (4) [REDACTED]
7. Revise the statement [REDACTED] (b) (4) [REDACTED] to read "See insert".
8. Revise the manufacturer information to read:
Mfd by: Celltrion, Inc.
US Lic. No. 1996
[REDACTED] (b) (4) [REDACTED]
Additionally, delete [REDACTED]
9. If there is space on the label, add a linear barcode should be used [REDACTED] (b) (4) [REDACTED].

LABEL AND LABELING MEMORANDUM

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*****This document contains proprietary information that cannot be released to the public*****

Date of This Review:	April 4, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 125544
Product Name and Strength:	Inflectra (infliximab-dyyb) For Injection 100 mg per vial
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Celltrion
Submission Dates:	April 1, 2016
Panorama #:	2015-2265-2
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader (Acting):	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that DMEPA review the revised carton labeling and container labels for Inflectra (infliximab-dyyb), BLA 125544, to determine if the labels and labeling are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous labels and labeling review¹.

2 CONCLUSIONS

The revised carton labeling and container labels for Inflectra (infliximab-dyyb), BLA 125544 are acceptable from a medication error perspective. We have no further recommendations at this time.

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

¹ McMillan T. Label and Labeling Review for Inflectra (BLA 125544). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 30. RCM No. 2015-2265-1.

APPENDIX A LABELS AND LABELING

1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Inflectra labels and labeling submitted via email in advance of the official submission by Celltrion on April 1, 2016.

- Container label
- Carton labeling

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
04/04/2016

LUBNA A MERCHANT on behalf of MISHALE P MISTRY
04/04/2016

LUBNA A MERCHANT
04/04/2016

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

******Pre-decisional Agency Information******

Memorandum

Date: April 4, 2016

To: Nina Ton, Pharm.D., Senior Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer,
Office of Prescription Drug Promotion (OPDP)

Subject: BLA # 125544 – INFLECTRA (infliximab-dyyb) for injection, for
intravenous use

Reference is made to DPARP's consult request dated October 14, 2016, requesting review of the proposed Package Insert (PI), Carton/Container Labeling, and Medication Guide MG) for INFLECTRA (infliximab) for injection, for intravenous use (Inflectra).

OPDP has reviewed the proposed PI entitled, "BLA 125544 draft labeling to Applicant 3.18.2016.docx" that was sent via e-mail from DPARP to OPDP on March 18, 2016. OPDP's comments on the proposed PI are provided on the attached marked-up copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling entitled:

- "draft-carton-container-labels.pdf"
- "draft-primary-container-labels.pdf"
- "draft-semi-carton-container-labels.pdf"

that was submitted by sponsor on February 23, 2016. OPDP has no comments at this time on the proposed Carton/Container labeling.

Please note that comments on the proposed MG were provided on April 1, 2016, under separate cover as a collaborative review between OPDP and the Division of Medical Policy Programs (DMPP).

Thank you for your consult. If you have any questions please contact me at (240) 402-5039 or adewale.adeleye@fda.hhs.gov

61 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

ADEWALE A ADELEYE
04/04/2016



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

FINAL LABEL AND LABELING MEMO

Date:	April 4, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products (OBP) Jibril Abdus-samad -S <small>Digitally signed by Jibril Abdus-samad-S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad-S Date: 2016.04.04 09:58:03 -04'00'</small>
Through:	Kurt Brorson, PhD, Lab Chief Division of Biotechnology Review and Research II Kurt A. Brorson -A <small>Digitally signed by Kurt A. Brorson -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300078163, cn=Kurt A. Brorson -A Date: 2016.04.04 11:17:08 -04'00'</small>
Application:	BLA 125544/0
Product:	Inflectra (infliximab-dyyb*)
Applicant:	Celltrion, Inc.
Submission Dates:	April 4, 2016

Introduction

The container label and carton labeling were previously reviewed by OBP on March 29, 2016¹ and found to be acceptable. However on April 1, 2016, we requested the Applicant revise the package type term from "[REDACTED] (b) (4)" to "single-use" for consistency with the reference product US-licensed Remicade (infliximab). This memo evaluates the revised container label and carton labeling submitted via email on April 1, 2016 in advance of the official submission.

Conclusion

The container label and carton labeling submitted via email on April 1, 2016 in advance of the official submission are acceptable (see below).

* Inflectra has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Subsequent to submission of the 351(k) BLA, the nonproprietary name for Inflectra was determined to be infliximab-dyyb.

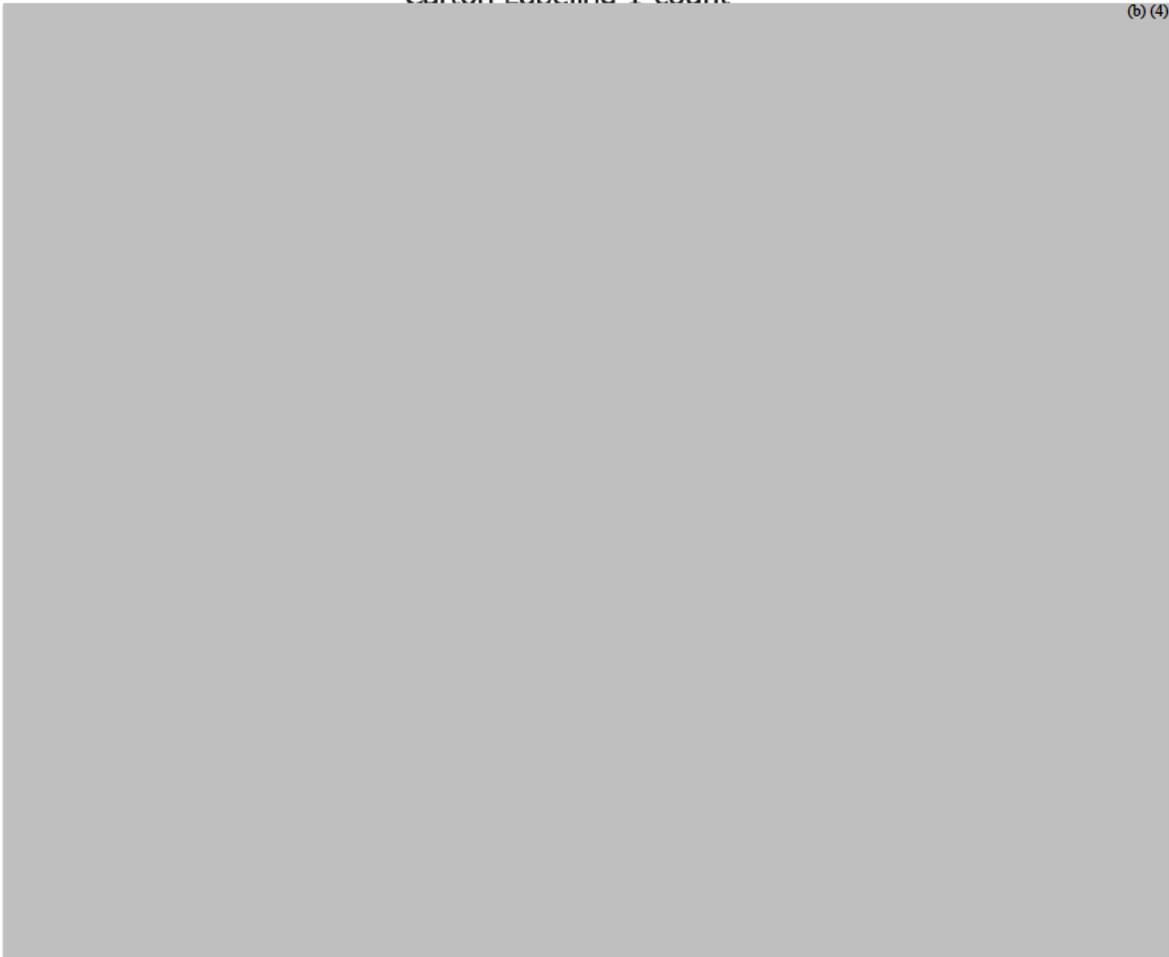
¹ Abdus-Samad, J. STN 125544/0-1 Labeling Review. Silver Spring MD: Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Office of Biotechnology Products; 2016 MARCH 29.

Container Label



(b) (4)

Carton Labeling 1-count



(b) (4)

Carton Labeling 10-count

(b) (4)



**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy**

PATIENT LABELING REVIEW

Date: April 1, 2016

To: Badrul A. Chowdhury, M.D.
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)

Shawna Hutchins, MPH, BSN, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Adewale Adeleye, Pharm.D, MBA
Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

Subject: Review of Patient Labeling: Medication Guide (MG)

Drug Name (established name): INFLECTRA (infliximab-dyyb)

Dosage Form and Route: Injection, for Intravenous Use

Application Type/Number: BLA 125544

Applicant: Celltrion, Inc.

1 INTRODUCTION

On August 8, 2014, Celltrion Inc. submitted for the Agency's review a 351(k) Biologics License Application (BLA) for a proposed biosimilar to the US-licensed Remicade (infliximab) lyophilized concentrate for injection for intravenous use. The Division of Medication Error Prevention and Analysis (DMEPA) issued a conditionally acceptable letter for the the tradename INFLECTRA on February 23, 2015. A complete response letter was issued by the Agency on June 8, 2015. The Applicant resubmitted the BLA on October 5, 2015. Celltrion requested licensure of INFLECTRA (infliximab-dyyb) for injection, for intravenous use for the following indications¹:

- Crohn's Disease for reducing signs and symptoms and inducing and maintaining clinical remission in adult patients with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy and for reducing the number of draining enterocutaneous and rectovaginal fistulas and maintaining fistula closure in adult patients with fistulizing Crohn's disease.
- Pediatric Crohn's Disease for reducing signs and symptoms and inducing and maintaining clinical remission in pediatric patients 6 years of age and older with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy.
- Ulcerative Colitis for reducing signs and symptoms, inducing and maintaining clinical remission and mucosal healing, and eliminating corticosteroid use in adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy.
- Rheumatoid Arthritis in combination with methotrexate, for reducing signs and symptoms, inhibiting the progression of structural damage, and improving physical function in patients with moderately to severely active rheumatoid arthritis.
- Ankylosing Spondylitis for reducing signs and symptoms in patients with active ankylosing spondylitis.
- Psoriatic Arthritis for reducing signs and symptoms of active arthritis, inhibiting the progression of structural damage, and improving physical function in patients with psoriatic arthritis.
- Plaque Psoriasis for the treatment of adult patients with chronic severe (i.e.,

¹ Celltrion also requested licensure of INFLECTRA for pediatric ulcerative colitis. REMICADE's indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on Sept. 23, 2018. Accordingly, FDA will not be able to license a proposed biosimilar product for this indication until the orphan exclusivity expires.

extensive and/or disabling) plaque psoriasis who are candidates for systemic therapy and when other systemic therapies are medically less appropriate.

This collaborative review is written by the Division of Medical Policy Programs (DMPP) and the Office of Prescription Drug Promotion (OPDP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on October 14, 2015 DMPP and OPDP to review the Applicant's proposed Medication Guide (MG) for INFLECTRA (infliximab-dyyb) for injection, for intravenous use.

2 MATERIAL REVIEWED

- Draft INFLECTRA (infliximab-dyyb) for injection, for intravenous use MG received on October 5, 2015, revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 18, 2016.
- Draft INFLECTRA (infliximab-dyyb) for injection, for intravenous use Prescribing Information (PI) received on October 5, 2015 revised by the Review Division throughout the review cycle, and received by DMPP and OPDP on March 18, 2016.
- Approved REMICADE (infliximab-dyyb) for injection, for intravenous use comparator labeling dated October 2, 2015.

3 REVIEW METHODS

To enhance patient comprehension, materials should be written at a 6th to 8th grade reading level, and have a reading ease score of at least 60%. A reading ease score of 60% corresponds to an 8th grade reading level.

Additionally, in 2008 the American Society of Consultant Pharmacists Foundation (ASCP) in collaboration with the American Foundation for the Blind (AFB) published *Guidelines for Prescription Labeling and Consumer Medication Information for People with Vision Loss*. The ASCP and AFB recommended using fonts such as Verdana, Arial or APFont to make medical information more accessible for patients with vision loss. We reformatted the MG document using the Arial, size 10.

In our collaborative review of the MG we:

- ensured that the MG is consistent with the Prescribing Information (PI)
- ensured that the MG is free of promotional language or suggested revisions to ensure that it is free of promotional language
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG meets the criteria as specified in FDA's Guidance for Useful Written Consumer Medication Information (published July 2006)
- ensured that the presentation of information in the MG is consistent with the format of the approved MG for the reference product where applicable.

4 CONCLUSIONS

The MG is acceptable with our recommended changes.

5 RECOMMENDATIONS

- Please send these comments to the Applicant and copy DMPP and OPDP on the correspondence.
- Our collaborative review of the MG is appended to this memorandum. Consult DMPP and OPDP regarding any additional revisions made to the PI to determine if corresponding revisions need to be made to the MG.

Please let us know if you have any questions.

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/s/

SHARON W WILLIAMS
04/01/2016

SHAWNA L HUTCHINS
04/01/2016

LASHAWN M GRIFFITHS
04/01/2016

LABEL AND LABELING MEMORANDUM

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*****This document contains proprietary information that cannot be released to the public*****

Date of This Review:	March 30, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 125544
Product Name and Strength:	Inflectra (infliximab-dyyb) For Injection 100 mg per vial
Product Type:	Single ingredient product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Celltrion
Submission Dates:	February 23, 2016
Panorama #:	2015-2265-1
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Team Leader (Acting):	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that DMEPA review the revised carton labeling and container labels for Inflectra (infliximab-dyyb), BLA 125544, for areas of vulnerability that could lead to medication errors. The revisions are in response to recommendations that we made during a previous labels and labeling review¹. We note that in addition to other revisions, Celltrion has incorporated the proprietary name, Inflectra, on the labels and labeling. We provide recommendations for the newly designed labels and labeling in Section 2.1 below.

2 CONCLUSIONS AND RECOMMENDATIONS

We concur with the label and labeling comments from the Office of Biotechnology Products (OBP). We also defer to CMC for the determination of the appropriate package type term on labels and labeling. In addition, we recommend the following be implemented prior to approval of this BLA:

2.1 RECOMMENDATIONS FOR CELLTRION

A. All container labels and carton labeling

1. If space permits, revise and bold the storage statement to the following to increase the prominence of this important information and to minimize the risk of the storage information being overlooked:

Must be refrigerated, Store at 2-8°C (36°-46°F).

B. All carton labeling

1. Revise the “Dispense the enclosed Medication Guide to each patient. (b) (4) ” statement to the following to reduce clutter on the Principal Display Panel:

Dispense the enclosed Medication Guide to each patient.

2. Revise the spacing on the side panel that contains the Usual Dosage to reduce clutter.

C. Carton labeling (1-count vial)

Place the “Rx Only” statement after the “Infuse over at least 2 hours with an in-line filter” statement on the PDP.

¹ McMillan T. Label and Labeling Review for Inflectra (BLA 125544). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2016 MAR 08. RCM No. 2015-2265.

APPENDIX A LABELS AND LABELING

1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,² along with postmarket medication error data, we reviewed the following Inflectra labels and labeling submitted by Celltrion on February 23, 2016.

- Container label
- Carton labeling

2 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

² Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

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/s/

TERESA S MCMILLAN
03/30/2016

MISHALE P MISTRY
03/30/2016

LUBNA A MERCHANT
03/30/2016



Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Biotechnology Products

FINAL LABEL AND LABELING REVIEW

Date:	March 29, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products Jibril Abdus-samad -S <small>Digitally signed by Jibril Abdus-samad -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300433429, cn=Jibril Abdus-samad -S Date: 2016.03.29 14:43:59 -0400</small>
Through:	Kurt Brorson, PhD, Lab Chief Division of Biotechnology Review and Research II Kurt A. Brorson -A <small>Digitally signed by Kurt A. Brorson -A DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=1300078163, cn=Kurt A. Brorson -A Date: 2016.03.29 14:56:39 -0400</small>
Application:	BLA 125544/0
Product:	Inflectra (infliximab-dyyb*)
Applicant:	Celltrion, Inc.
Submission Dates:	February 23; March 23, 25 2016

Executive Summary:

The container label and carton labeling for Inflectra (infliximab-dyyb) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100. The revised labeling complies with relevant chapters of the United States Pharmacopeia (USP), USP 38/NF 33 [December 1, 2015 to April 30, 2016]. Three batches of product contain the text (b) (4) on the vial caps. Although this text does not comply with USP, it is not a safety issue and will be discontinued in future batches. Labeling deficiencies were identified and resolved. The container label and carton labeling on March 25, 2016 are acceptable.

* Inflectra has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Subsequent to submission of the 351(k) BLA, the nonproprietary name for Inflectra was determined to be infliximab-dyyb.

Background and Summary Description:

The Applicant, Celltrion Inc., submitted a 351(k) BLA 125544/0 CT-P13** on August 8, 2014 as a proposed biosimilar to US-licensed Remicade (infliximab) which resulted in a Complete Response (CR). Subsequently on October 5, 2015, the Applicant submitted a complete response to the deficiencies outlined in the CR Letter.

During the first review cycle, OBP completed a labeling review dated May 19, 2015¹ that provided container label and carton labeling comments. These comments were not sent to the Applicant because the Agency deferred labeling comments until the application was otherwise adequate. On February 4, 2016 during review of the resubmission, the Agency sent container label and carton labeling comments to the Applicant. This review evaluates the Applicant's revised container label and carton labeling submitted on February 23, 2016.

Table 1: Proposed Product Characteristics of Inflectra (infliximab-dyyb).

Proprietary Name:	Inflectra
Proper Name:	infliximab-dyyb
Indication:	Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Rheumatoid Arthritis in combination with methotrexate, Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis
Dose:	3 mg/kg, 5 mg/kg, and can increase to 10 mg/kg at varying intervals (week 0, 2, 6, then every 6 or 8 weeks) depending on the indication.
Route of Administration:	Intravenous infusion
Dosage Form:	for Injection
Strength and Container-Closure:	100 mg lyophilized powder in single-dose vials
Storage and Handling:	Refrigerate at 2°C to 8°C (36°F to 46°F).

** At the time of the original submission, the Agency generally referred to Celltrion's proposed product by the Celltrion descriptor "CT-P13." Subsequently, the nonproprietary name for Inflectra was determined to be infliximab-dyyb.

¹ Abdus-Samad, J. STN 125544/0 Labeling Review. Silver Spring MD: Food and Drug Administration, Center for Drug Evaluation and Research, Office of Pharmaceutical Quality, Office of Biotechnology Products; 2015 MAY 19.

Materials Reviewed:

Container Label

Carton Labeling (1-count and 10-count)

Start of Applicant Material

Container Label

(b) (4)



End of Applicant Material

Subpart G-Labeling Standards
Subpart A-General Labeling Provisions

I. Container

A. 21 CFR 610.60 Container Label

(a) Full label. The following items shall appear on the label affixed to each container of a product capable of bearing a full label: *This product has a partial label (see below). However, there was space on the label to allow for placement of some of the items recommended for the full label.*

(1) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*. During the review process, the proper name was determined to be "infliximab-dyyb". The February 23, 2016 submission of the product label and labeling did not use the proper name but the Applicant revised as requested after the proper name was determined.

(2) The name, address, and license number of manufacturer; *conforms*.

(3) The lot number or other lot identification; *conforms*.

(4) The expiration date; *conforms*.

- (5) The recommended individual dose, for multiple dose containers; *not applicable*.
- (6) The statement: "Rx only" for prescription biologicals; *conforms*.

(7) If a Medication Guide is required under part 208 of the chapter, the statement required under §208.24(d) of this chapter instructing the authorized dispenser to provide a Medication Guide to each patient to whom the drug is dispensed and stating how the Medication Guide is provided, except where the container label is too small, the required statement may be placed on the package label; *not applicable. The vial container label is considered a partial label and therefore, MG statement is not required.*

(b) Package label information. If the container is not enclosed in a package, all the items required for a package label shall appear on the container label; *not applicable*.

(c) Partial label. If the container is capable of bearing only a partial label, the container shall show as a minimum

- the name (expressed either as the proper or common name); *conforms*.
- the lot number or other lot identification; *conforms*.
- the name of the manufacturer; *conforms*.
- in addition, for multiple dose containers, the recommended individual dose; *not applicable*.
- Containers bearing partial labels shall be placed in a package which bears all the items required for a package label; *conforms*.

Considering this vial container label is a partial label, we provided the following recommendations to preserve the required and recommended information, remove less important information, create more white space, and improve readability.

OBP Requests:

Removing bolding of manufacturer information. *Applicant revised as requested.*

Delete the distributor. *Applicant revised as requested.*

Delete the (b) (4) so that the manufacturer information reads "Mfd by: Celltrion, Inc." *Applicant revised as requested.*

(d) No container label. If the container is incapable of bearing any label, the items required for a container label may be omitted, provided the container is placed in a package which bears all the items required for a package label; *not applicable*.

(e) Visual inspection. When the label has been affixed to the container, a sufficient area of the container shall remain uncovered for its full length or circumference to permit inspection of the contents; *does not conform*.

OBP Request: Indicate how the label is affixed to the vial and where the visual area of inspection is located per 21 CFR 610.60(e). *The Applicant's confirmed there is sufficient space that provides an area of inspection when the label is applied to the vial. Acceptable.*

B. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located at the top of the label. [See 21 CFR 207.35]; *conforms*.

C. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*. However, we request the package type term revision.

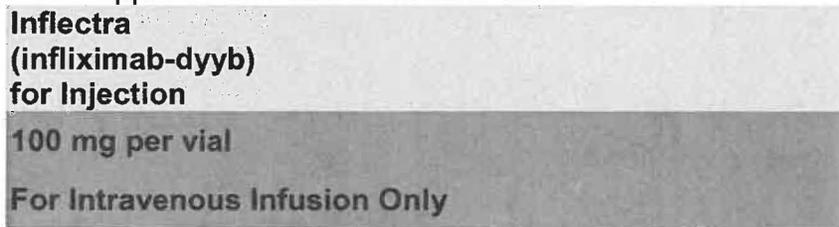
OBP Request: Revise "Single-use vial" to "Single-dose vial."
Applicant revised as requested.

D. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *does not conform*.

OBP Request:

During the 3/23/2016 teleconference with the Applicant, we explained the peach and green background coloring is considered intervening matter between the proprietary name and proper name per 21 CFR 201.10(a). We recommended the peach and green color blocking so that the proprietary name, proper name, and dosage form appear within the same color block.



Inflectra
(infliximab-dyyb)
for Injection
100 mg per vial
For Intravenous Infusion Only

Applicant revised as requested on March 25, 2016 submission.

21 CFR 201.15 Drugs; prominence of required label statements; *does not conform*.

OBP Request:

Bold the storage information. *Applicant revised as requested.*

F. 21 CFR 201.17 Drugs; location of expiration date; *conforms*.

G. 21 CFR 201.25 Bar code; *does not conform*.

OBP Request: Add a linear barcode. We requested this in the previous labeling comments; however your February 22, 2016 submission did not provide a response. *Applicant revised as requested.*

H. 21 CFR 201.50 Statement of identity; *conforms*.

I. 21 CFR 201.51 Declaration of net quantity of contents; *conforms*.

J. 21 CFR 201.55 Statement of dosage; *conforms*.

K. 21 CFR 201.100 Prescription drugs for human use; *conforms*.

Start of Applicant Material

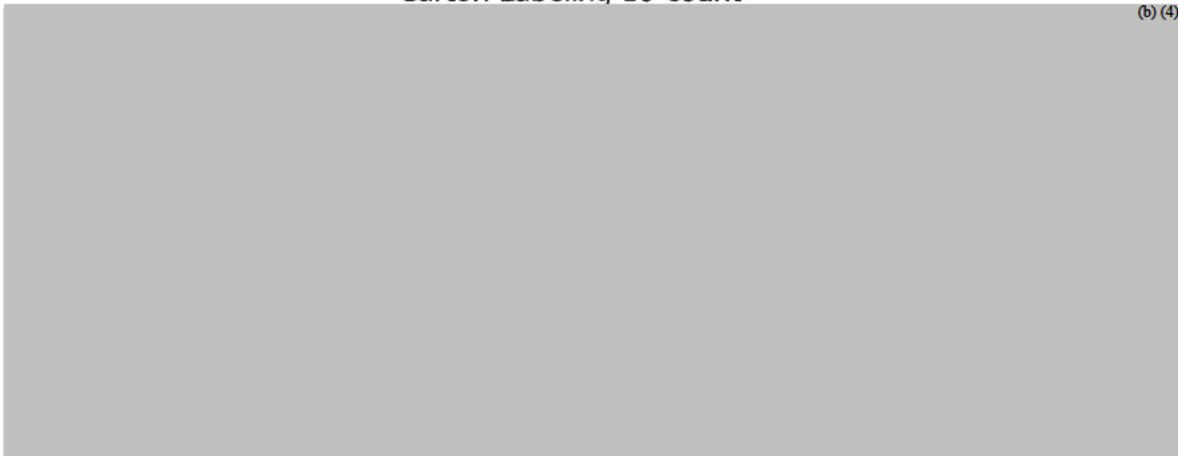
Carton Labeling 1-count

(b) (4)



Carton Labeling 10-count

(b) (4)



End of Applicant Material

II. Carton

A. 21 CFR 610.61 Package Label:

a) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *conforms*. During the review process, the proper name was determined to be "infliximab-dyyb". The February 23, 2016 submission of the product label and labeling did not use the proper name but the Applicant revised as requested after the proper name was determined.

b) The name, addresses, and license number of manufacturer; does not conform.

OBP Request: [REDACTED] (b) (4)

Revise the manufacturer information so that the license number appears with the licensed manufacturer. For example:

Manufactured by:
Celltrion, Inc.
23, Academy-ro
Yeonsu-gu, Incheon,
406-840, Republic of Korea
US License No. 1996

for
Hospira, a Pfizer Company
[insert distributor address]

Applicant revised as requested.

c) The lot number or other lot identification; *does not conform*.

OBP Request: During the 3/23/2016 teleconference with the Applicant, we requested them to add the lot number and expiration date on the 10-count carton labeling.

Applicant revised as requested on March 25, 2016 submission.

d) The expiration date; *does not conform (see above)*.

e) The preservative used and its concentration, if no preservative is used and the absence of a preservative is a safety factor, the words "no preservative"; *conforms*.

- f) The number of containers, if more than one; *conforms*.
- g) The amount of product in the container expressed as (1) the number of doses, (2) the volume, (3) units of potency, (4) weight, (5) equivalent volume (for dried product to be reconstituted), or (6) such combination of the foregoing as needed for an accurate description of the contents, whichever is applicable; *conforms*.
- h) The recommended storage temperature; *conforms*.
- i) The words "Do not Freeze" or the equivalent, as well as other instructions, when indicated by the character of the product; *conforms*.
- j) The recommended individual dose if the enclosed container(s) is a multiple-dose container; *not applicable, this is a single-dose container*.
- k) The route of administration recommended, or reference to such directions in and enclosed circular; *conforms*.
- l) Known sensitizing substances, or reference to enclosed circular containing appropriate information; *not applicable*.
- m) The type and calculated amount of antibiotics added during manufacture; *not applicable*.
- n) The inactive ingredients when a safety factor, or reference to enclosed circular containing appropriate information; *not applicable*.
- o) The adjuvant, if present; *not applicable*.
- p) The source of the product when a factor in safe administration; *not applicable*.
- q) The identity of each microorganism used in manufacture, and, where applicable, the production medium and the method of inactivation, or reference to an enclosed circular containing appropriate information; *not applicable*.
- r) Minimum potency of product expressed in terms of official standard of potency or, if potency is a factor and no U.S. standard of potency has been prescribed, the words "No U.S. standard of potency"; *conforms*.

s) The statement "Rx only" for prescription biologicals; *does not conform*.

OBP Request: Place the "Rx Only" statement after the "Infuse over at least 2 hours with an in-line filter" statement on the principal display panel (PDP) to comply with 21 CFR 610.61(s) and 21 CFR 201.100. *Applicant revised as requested*.

Note: If product has a medication guide, a statement is required on the package label if it is not on the container label (see above). It is recommended on both labels; *conforms*. *The vial container label is considered a partial label and therefore, MG statement is not required*.

B. 21 CFR 610.62 Proper name; package label; legible type [Note: Per 21 CFR 601.2(c)(1), certain regulation including 21 CFR 610.62 do not apply to the four categories of "specified" biological products listed in 21 CFR 601.2(a)]. *Exempt. Inflectra (infliximab-dyyb) is a monoclonal antibody*.

C. 21 CFR 610.63 Divided manufacturing responsibility to be shown; *not applicable*.

D. 21 CFR 610.64 Name and address of distributor; *does not conform*. *The labeling lacks the distributor address*.

OBP Request: If listing a distributor (Hospira, a Pfizer Company), add the distributor address to comply with 21 CFR 610.64. *Applicant revised as requested*.

E. 21 CFR 610.67 Bar code label requirements; *conforms*.

Biological products must comply with the bar code requirements at §201.25 of this chapter;

F. 21 CFR 201.2 Drugs and devices; National Drug Code numbers – The National Drug Code (NDC) number is located on top of the label [See 21 CFR 207.35]; *conforms*.

G. 21 CFR 201.5 Drugs; adequate directions for use; *conforms*. *However, we request the package type term revision*.

OBP Request: Revise "Single-use vial" to "Single-dose vial." *Applicant revised as requested*.

H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.

I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *does not conform.*

OBP Request:

During the 3/23/2016 teleconference with the Applicant, we explained the peach and green background coloring is considered intervening matter between the proprietary name and proper name per 21 CFR 201.10(a). We recommended the peach and green color blocking so that the proprietary name, proper name, and dosage form appear within the same color block.

**Inflectra
(infliximab-dyyb)
for Injection
100 mg per vial
For Intravenous Infusion Only**

Applicant revised as requested on March 25, 2016 submission

J. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform.*

OBP Requests:

If space permits, consider adding some (b) (4) space between the dosage form, strength, and route of administration. For example:

Inflectra
(infliximab-dyyb)
for Injection

100 mg per vial

For Intravenous Infusion Only

Applicant revised as requested.

Revise the "Dispense the enclosed Medication Guide to each patient. (b) (4) statement to the following to reduce clutter on the Principal Display Panel:

Dispense the enclosed Medication Guide to each patient.

Applicant revised as requested.

Consider utilizing the additional space on the side panel that currently contains the barcode to improve the spacing and reduce the cluttered appearance. Consider the following:

- Relocate the storage information from the bottom of the cluttered side panel to the top of the side panel that contains the manufacturer information and barcode.
Applicant revised as requested.
- Relocate the "No U.S. standard of potency" to side panel that contains the manufacturer information and barcode.
Applicant revised as requested.

K. 21 CFR 201.17 Drugs; location of expiration date; *does not conform.*

OBP Request: During the 3/23/2016 teleconference with the Applicant, we requested them to add the lot number and expiration date on the 10-count carton labeling. *Applicant revised as requested on March 25, 2016 submission*

L. 21 CFR 201.25 Bar code label requirements; *conforms.*

M. 21 CFR 201.50 Statement of identity; *conforms.*

N. 21 CFR 201.51 Declaration of net quantity of contents; *conforms.*

O. 21 CFR 201.55 Statement of dosage; *conforms.*

P. 21 CFR 201.100 Prescription drugs for human use; *does not conform.*

OBP Request: Place the "Rx Only" statement after the "Infuse over at least 2 hours with an in-line filter" statement on the principal display panel (PDP) to comply with 21 CFR 610.61(s) and 21 CFR 201.100. *Applicant revised as requested.*

Discussion of Additional Labeling Concerns

Text on Vial Cap

Subsequent to our labeling request to confirm there was (b) (4) cap overseal of the vials to comply with United States Pharmacopeia (USP), General Chapters: <1> Injections, the Applicant noted they used (b) (4) caps that contain the wording (b) (4) on three batches (15B4C01, 15B4C02, and 15B4C03) which comprise (b) (4) vials. All future product and product vialled since August 7, 2015 will comply with the aforementioned USP requirement.

Considering there is no safety issue, we find the Applicant's use of (b) (4) caps with the text (b) (4) is acceptable from a labeling perspective. The Division of Medication Error Prevention and Analysis agrees there is no safety issue. Additionally, the OBP Quality Review team agrees with this assessment.

Conclusions:

The container label and carton labeling for Inflectra (infliximab-dyyb) were reviewed and found to comply with the following regulations: 21 CFR 610.60 through 21 CFR 610.67; 21 CFR 201.2 through 21 CFR 201.25; 21 CFR 201.50 through 21 CFR 201.57, 21 CFR 201.100. The revised labeling complies with relevant chapters of the United States Pharmacopeia (USP), USP 38/NF 33 [December 1, 2015 to April 30, 2016]. Three batches of product contain the text (b) (4) on the vial caps. Although this wording does not comply with USP, it is not a safety issue and will be discontinued in future batches. Labeling deficiencies were identified and resolved. The container label and carton labeling on March 25, 2016 are acceptable (see below).

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LABEL AND LABELING MEMORANDUM

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

*****This document contains proprietary information that cannot be released to the public*****

Date of This Review: March 08, 2016

Requesting Office or Division: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

Application Type and Number: BLA 125544

Product Name and Strength: Inflectra (infliximab-dyyb)
For Injection
100 mg per vial

Product Type: Single ingredient product

Rx or OTC: Rx

Applicant/Sponsor Name: Celltrion

Submission Dates: August 8, 2014, November 14, 2014
and November 17, 2015

Panorama #: 2015-2265

DMEPA Primary Reviewer: Teresa McMillan, PharmD
Carlos Mena-Grillasca, RPh

DMEPA Team Leader: Kendra Worthy, PharmD

DMEPA Deputy Director: Lubna Merchant, MS, PharmD

OMEPRM Deputy Director: Kellie Taylor, PharmD, MPH

1 PURPOSE OF MEMO

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that DMEPA review the Prescribing Information (PI), carton labeling, and container labels for Inflectra (infliximab-dyyb), BLA 125544, for areas of vulnerability that could lead to medication errors. The proposed labels and labeling for BLA 125544 were reviewed by DMEPA on May 4, 2015¹ and recommendations were provided. However, BLA 125544 received a complete response on June 8, 2015 and our recommendations were not communicated to the Sponsor. Celltrion submitted a response to the complete response on October 5, 2015 and no labels and labeling were submitted at that time. This memorandum is to communicate that DMEPA maintains the recommendations provided on May 4, 2015 and we do not have any additional recommendations at this time.

This memorandum also summarizes our evaluation of the suffix proposed by Celltrion for the nonproprietary name and communicates our recommendation for the nonproprietary name.

2 ASSESSMENT OF THE NONPROPRIETARY NAME

FDA has determined that the use of a distinguishing suffix in the nonproprietary name for Celltrion's Inflectra product is necessary to distinguish this proposed product from Remicade (infliximab). As explained in FDA's draft Guidance for Industry, Nonproprietary Naming of Biological Products, FDA expects that a nonproprietary name for Inflectra that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance. FDA advised Celltrion to provide proposed suffixes in accordance with the draft guidance².

On November 17, 2015, Celltrion submitted a list of suffixes, in their order of preference, to be used in the nonproprietary name of their product. In addition, Celltrion submitted supporting analyses for each of the suffixes they proposed for the purpose of demonstrating that the proposed suffixes satisfy the factors described in section V of the draft guidance. We evaluated the suffixes and determined that Celltrion's preferred suffix, -dyyb, is unlikely to be a source of error: the suffix does not suggest any drug substance name or core name designated by USAN council, is not too similar to any other products' suffix designation, does not look similar to the names of other currently marketed products, and does not include any abbreviations commonly used in clinical practice in a manner that may lead the suffix to be misinterpreted as

¹ McMillan T. Label and Labeling Review for Inflectra (BLA 125544). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 MAY 4. Panorama No. 2014-17283.

² See the FDA draft guidance for industry on Nonproprietary Naming of Biological Products (August 2015). When final, this guidance will represent FDA's current thinking on this topic. The guidances referenced in this document are available on the FDA Drugs guidance Web page at <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM459987.pdf>

another element on the prescription or order. In addition, the suffix is devoid of meaning and does not make promotional representations with respect to safety or efficacy of this product.

FDA's determination does not constitute or reflect a decision on a general naming policy for biological products, including biosimilars. FDA issued draft guidance on Nonproprietary Naming of Biological Products in August 2015, and the Agency is carefully considering the comments submitted to the public docket as we move forward in finalizing the draft guidance.³ As a result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biological products established by FDA. Were the name to change, FDA intends to work with Celltrion to minimize the impact this would have to its manufacture and distribution of this product, should it be licensed.

3. CONCLUSIONS AND RECOMMENDATIONS

We maintain our recommendations provided on May 4, 2015 and note that the proposed label and labeling reference the proprietary name (b) (4). On February 10, 2015, the Applicant withdrew the name (b) (4) and informed us that they intend to market this product with the proprietary name Inflectra. The name Inflectra was found acceptable on February 23, 2015 and November 19, 2015.⁴ We concur with the label and labeling comments from the Office of Biotechnology Products (OBP). Additionally, we find that Celltrion's proposed suffix "-dyyb" is acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to infliximab-dyyb. We recommend that our recommendations outlined in section 3.1 and 3.2 be implemented prior to approval of this BLA.

3.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

Remove all instances of the proprietary name (b) (4) and replace with the proprietary name "Inflectra".

³ FDA has received several citizen petitions directed to the nonproprietary naming of biosimilar products. The citizen petition submitted by Johnson & Johnson requests that FDA require biosimilar products to bear nonproprietary names that are similar to, but not the same as, those of their reference products or of other biosimilars (see Docket No. FDA-2014-P-0077). The citizen petitions submitted by the Generic Pharmaceutical Association and Novartis request that FDA require biosimilar products to be identified by the same nonproprietary name as their reference products (see Docket Nos. FDA-2013-P-1153 and FDA-2013-P-1398). Although FDA is designating a proper name that contains a distinguishing suffix for Inflectra, FDA is continuing to consider the issues raised by these citizen petitions, the comments submitted to the corresponding public dockets, and comments submitted to the dockets for the draft guidance for industry Nonproprietary Naming of Biological Products (August 2015) and the proposed rule, Designation of Official Names and Proper Names for Certain Biological Products (80 FR 52224), with respect to establishing a general naming convention for biological products.

⁴ McMillan T. Proprietary Name Review for Inflectra (BLA 125544). Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2015 NOV 19. And 2015 FEB 23 Panorama No. 2015-1649964 and Panorama No. 2014-44603.

3.2 RECOMMENDATIONS FOR CELLTRION

A. Non-proprietary name

1. We find the nonproprietary name, infliximab-dyyb acceptable for your proposed product; revise your proposed labels and labeling accordingly. The nonproprietary name containing the distinguishing suffix will be the proper name designated in the license should your 351(k) BLA be approved.

FDA's comments on the nonproprietary name for this product do not constitute or reflect a decision on a general naming policy for biosimilar products. FDA issued draft guidance on Nonproprietary Naming of Biological Products in August 2015, and the Agency is carefully considering the comments submitted to the public docket as we move forward in finalizing the draft guidance. As result, the nonproprietary name is subject to change to the extent that it is inconsistent with any general naming policy for biosimilar products established by FDA. Were the name to change, we would work with you to minimize the impact this would have to your manufacture and distribution of this product, should it be licensed.

B. All labels and labeling

1. Remove all instances of the proprietary name [REDACTED] ^{(b) (4)} and replace with the proprietary name "Inflectra".
2. Revise the nonproprietary name to infliximab-dyyb wherever it appears in the proposed labels and labeling for your proposed product.

APPENDIX LABELS AND LABELING

1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,⁵ along with postmarket medication error data, we reviewed the following Inflectra labels and labeling submitted by Celltrion on August 8, 2014.

- Container label
- Carton labeling

2 Label and Labeling Images

Carton Labeling (1-count vial)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

⁵ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA S MCMILLAN
03/08/2016

LUBNA A MERCHANT
03/08/2016

KELLIE A TAYLOR
03/08/2016

REVIEW

In document 0040, Celltrion provided an interim analysis of study CT-P13 3.4 in active Crohn's disease patients. Study CT-P13 3.4 is a randomized, double-blind, parallel-group study to assess the safety of CT-P13 compared to Remicade (US & EU) in patients with active Crohn's disease. Study CT-P13 3.4 monitored immunogenicity as part of the safety assessment at Week 0 (Dose 1), Week 14 (Dose 4), Week 30 (Dose 6), Week 54 (Dose 9) and End-of-study visit.

220 patients have been enrolled and randomized into 1 of 4 treatment groups described below. However, as part of this interim analysis, 109 patients who received at least 1 dose of study drug were unblinded and included in the interim immunogenicity analysis.

Reviewer Comment: *The sponsor states that each patient had at least one dose, but does not mention if any patients had less than the three planned doses at the time of analysis. We should verify the sponsor clarifies this remark in the final report.*

In addition to CT-P13/Remicades, the patients may also have been treated with any of the following 5 additional therapies

- 5-aminosalicylates or antibiotics (if the dose remained constant for at least 4 weeks prior to randomization)
- Corticosteroids (prednisone, prednisolone, or budesonide) at the equivalent of 30 mg per day of prednisone or less (stable dose for 2 weeks prior to randomization)
- Azathioprine (stable dose for 8 weeks prior to randomization)
- 6-mercaptopurine (6-MP) (stable dose for 8 weeks prior to randomization)
- Methotrexate (MTX) (stable dose for 6 weeks prior to randomization)

Reviewer Comment: *The breakdown of how many patients, and from which groups, received these additional therapies was not provided. These therapies are all immunosuppressive and could influence immunogenicity results. The sponsor should clarify which patients received which additional treatments.*

A schema of the clinical plan is provided below:



Figure 1 Outline of Study CT-P13 3.4

Reviewer Comments:

- 1. Not indicated is the treatment schedule, where patients received CT-P13 or US/EU Remicade (5 mg/kg) at Weeks 0, 2, 6, and 14, and then every eight weeks through week 54.*
- 2. The immunogenicity sampling in the interim analysis occurred at week 14 (pre-dose), so the patients were exposed to 3 doses of infliximab, and the previous dose was 8 weeks earlier. This is the same time period (8 wks) that was used in CT-P13 1.4.*

ELISA Assay

The sponsor used the same ELISA assay that was used in Study CT-P13 1.4, though the test was performed by a new CRO, (b) (4), for study 3.4 where (b) (4) performed the assay for study 1.4.

The patients in study 3.4 were undergoing repeat dosing of CT-P13/Remicade, so the levels of circulating drugs at 8 weeks after dose 3 (sampling time, week 14) are expected to be higher than 8 weeks after a single dose that was seen in CT-P13 1.4. With that said, the sponsor did not provide PK results that were also tested together with the immunogenicity data. Because there was some concern over the drug tolerance of the ELISA assay in study CT-P13 1.4, and because we expect circulating drug levels to be

higher, the sponsor should provide information discussing the levels of circulating drug at the time of immunogenicity sampling.

The following excerpt from Table 4 of the Study Report shows the free drug tolerance on the ELISA assay performed at (b) (4)

Free drug interference	1000 ng/mL of positive control was tolerable up to 193 µg/mL of US-licensed Remicade® 500 ng/mL of positive control were tolerable up to 137µg/mL of US- licensed Remicade® 250 ng/mL of positive control were tolerable up to 91.0 µg/mL of US- licensed Remicade® 100 ng/mL of positive control were tolerable up to 43.3 µg/mL of US- licensed Remicade® 4.00 ng/mL of positive control was tolerable up to 5.71 µg/mL of US- licensed Remicade®
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Reviewer Comments:

1. The assay was transferred from (b) (4) to (b) (4). The same assay performed at (b) (4) had much worse drug tolerance performance (shown below):

Table 3: Study CT-P13 1.4 Drug Tolerance Level for New ELISA Assay

	Drug Tolerance Level			PK concentration at Day 57 (PK population)	
	LPC (60 ng/mL)	MPC (500 ng/mL)	HPC (1000 ng/mL)	Mean (µg/mL)	Range (µg/mL)
CT-P13	10 µg/mL	20 µg/mL	50 µg/mL	4.243 µg/mL	0 ¹ -19.021 µg/mL
EU-approved Remicade®	5 µg/mL	20 µg/mL	50 µg/mL	4.092 µg/mL	0 ¹ -12.458 µg/mL
US-licensed Remicade®	10 µg/mL	20 µg/mL	50 µg/mL	4.484 µg/mL	0 ¹ -12.859 µg/mL

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Source: Table 12 in the Report on Immunogenicity Results from CT-P13 1.4 Study for 'Drug Tolerance Level'
¹ < 200 µg/mL is regarded as BLOQ and calculated as 0.

Applying the replacement assay resulted in the total number of subjects detected as being antibody positive increasing from 17 (8.1%) to 43 (20.4%) subjects, distributed between the groups as follows:
 17 subjects (24.3%) in the CT-P13 group, 18 subjects (25.4%) in the EU-approved Remicade® group and 8 subjects (11.4%) in the US-licensed Remicade® group.

These results from (b) (4) show the high positive control (1000 ng/mL) is blocked by 50 µg/mL of circulating drug. The assay performed by (b) (4) is 10x better (100 ng/mL is blocked by 43.3 µg/mL of circulating drug), so the issues of circulating drug tolerance are minimized.

2. In study CT-P13 1.4, ~40% (~20/50) of ADA negative subjects treated with CT-P13 had circulating drug levels > 5.7 µg/mL, which was in excess of the LPC (4.00 ng/mL). With the repeat dose nature of Study CT-P13 3.4, we expect higher circulating drug levels, and drug serum levels higher than 5.7 µg/mL. These patients with higher circulating drug levels are 'inconclusive' and represent a gap in the sponsor's analysis. There is value in knowing these low level responses to ADA, though these very low ADA responses likely do not represent clinically meaningful responses. Additionally, this gap in knowledge is tolerable because 100 ng/mL had a tolerance up to 43.3 µg/mL, so 43.3 µg/mL becomes the de facto sensitivity of the assay. A drug tolerance of 43.3 µg/mL is

very good sensitivity, so the overall sensitivity of the assay, in the presence of expected levels of onboard drug, is probably acceptable, but interpretation of the data depends on the levels of circulating drug being below 43 ug/mL.

ELISA METHOD VALIDATION AND PERFORMANCE

The sponsor states that the ELISA method has been validated, but did not provide the validation report.

A summary of the validation report activities is provided below.

Table 3 Validation Acceptance Criteria for ELISA-based ADA Assay

Validation Parameter	Acceptance Criteria
Precision	Inter/intra assay of HPC, MPC, LPC, and PNC samples have to be less than 30.0 %.
Specificity and selectivity	Matrix interference (Hemolyzed and lipemic serum) LPC and HPC have to show the mean responses as follows: HPC > LPC > cut point > blank response
Validation Parameter	Acceptance Criteria
	Matrix selectivity (Crohn's Disease serum) Below the ACP in at least 90 % unspiked matrix samples 90 % of the matrix samples had to have percentage recovery between 70 % and 130 % with LPC and HPC
Stability	F/T, TM, STS (stability in frozen matrix) Within \pm 30 % of a response of the freshly prepared reference controls

Source: Validation Plan RBPR2 (Original)

ACP: Assay cut point, F/T: Freeze-thaw, HPC: High positive control, MPC: Mid positive control, LPC: Low positive control, PNC: pooled negative control, STS: Short-term stability, TM: Thawed matrix

Reviewer Comment: *The summary includes little information other than assurances of moderate precision, acceptable performance in hemolytic or lipemic serum, and acceptable levels of freeze/thaw stability. There is not assessment of the validation of the assay's robustness, sensitivity, or cut-point provided.*

Table 4 Anti-drug Antibody Assay Performance

Validation Parameter	High Positive Control (HPC) (1000 ng/mL)	Mid Positive Control (MPC) (500 ng/mL)	Low Positive Control (LPC) (4.00 ng/mL)	Pooled Negative Control (PNC)
Inter-assay precision (n=20). CV (%)	4.87	6.82	13.8	¹ 11.1
Mean Intra-assay precision (n=6). CV (%)	1.28	2.83	2.26	3.25
Confirmatory cut point. % signal inhibition (3.91 µg/mL Remicade* (US))	11.5 % (NHS serum) 19.0 % (CD serum)			
Screening assay cut point factor	1.113 (NHS serum) 1.30 (CD serum)			
Sensitivity (ng/mL)	0.708 ng/mL			
Hemolysis and Lipemia	LPC and HPC showed no apparent significant effect in Hemolyzed (5 %) and Lipemic serum			
Matrix Interference and Selectivity	² Unacceptable for unspiked samples (14/20 passed) Acceptable with 9 out of 10 sample lots meeting the acceptance criteria (< 30 % at 70-130 %) at each PC level			
Prozone Effect	The absence of a hook effect was demonstrated as the measured OD signals are above the cut point for all dilutions			
Free drug interference	1000 ng/mL of positive control was tolerable up to 193 µg/mL of US-licensed Remicade* 500 ng/mL of positive control were tolerable up to 137 µg/mL of US- licensed Remicade* 250 ng/mL of positive control were tolerable up to 91.0 µg/mL of US- licensed Remicade* 100 ng/mL of positive control were tolerable up to 43.3 µg/mL of US- licensed Remicade* 4.00 ng/mL of positive control was tolerable up to 5.71 µg/mL of US- licensed Remicade*			
Thawed Matrix Stability, RT (hrs) (n = 6). % Difference RLU	24 hours at RT LPC: 0.533 %, HPC: 2.06 %			
Freeze-thaw Stability, -70 °C or colder (cycles) (n = 6). % Difference RLU	5 cycles thawed at RT LPC: -0.533 %, HPC: 2.74 %			
Frozen Matrix Stability (days) (n = 6). % Difference RLU	29 days at -70 °C or colder LPC: 1.06 %, HPC: 2.41 % 47 days at -25 °C LPC: 4.35 %, HPC: -0.64 %			

¹Precision of NC was analyzed in quadruplicate on 10 independent validation runs (n=40).

²Since the unspiked CD selectivity samples did not meet acceptance criteria during the validation, disease specific cut point was determined statistically from the analysis of 50 individual CD serum sample lots and applied to sample analysis.

CD: Crohn's disease. CV: Coefficient of variation. HPC: High positive control. LPC: Low positive control, NHS: Normal Human Subjects, RLU: Relative Light Units. N/A: Not applicable. PNC: Pooled negative control

Reviewer Comment: *The ELISA performance attributes appear to be acceptable, though a full review of the validation is needed.*

ADA INCIDENCE

The sponsor's summary of ADA incidence is provided below.

Table 7 Summary of ADA incidence in Study CT-P13 3.4

	CT-P13 (N=54)	US-licensed Remicade* (N=43)	EU-approved Remicade* (N=12)	Total (N=109)
Number of patients (%)				
Baseline (Week 0)				
Positive	1 (1.9)	0	0	1 (0.9)
Negative	53 (98.1)	43 (100.0)	12 (100.0)	108 (99.1)
		55 (100.0) ¹		
Week 14 (all patients)				
Positive	8 (14.8)	5 (11.6)	4 (33.3)	17 (15.6)
		9 (16.4) ¹		
Negative	46 (85.2)	38 (88.4)	8 (66.7)	92 (84.4)
		46 (83.6) ¹		
Week 14 (excluding patients with pre-dose ADA positive result)				
Positive	7 (13.0)	5 (11.6)	4 (33.3)	17 (15.6)
		9 (16.4) ¹		
Negative	46 (85.2)	38 (88.4)	8 (66.7)	92 (84.4)
		46 (83.6) ¹		

Source: Table 1

¹ US-licensed Remicade* and EU-approved Remicade* were combined.**Reviewer Comments:**

1. There's one patient treated with CT-P13 who was positive at baseline, and the sponsor provided analysis that did and did not include that patient. Without individual titers, or information about developing neutralizing antibodies, it is unclear if that patient should be included or not.

2. The 13%/14.8% ADA incidence in CT-P13 is similar to an ADA incidence of 11.6% for US-Remicade, though the assay was not powered for these sorts of analyses. Similarly, the 33% response rate for EU-Remicade should be disregarded as the group is much too small.

ADA TITER**Table 8 Summary of ADA Titer Results in Study CT-P13 3.4**

	CT-P13 (N=54)	US-licensed Remicade [®] (N=43)	EU-approved Remicade [®] (N=12)	Total (N=109)
Week 0 (Baseline)				
Number of patient with ADA positive (%)	1(1.9) ²	0	0	-
Mean ADA Titer (± SD)	- ²	-	-	-
Median ADA Titer (Min. Max)	- ²	-	-	-
Week 14				
Number of patient with ADA positive (%)	8 (14.8%)	5 (11.6%)	4 (33.3%)	17 (15.6%)
		9 ¹		
Mean ADA Titer (± SD)	2.3 (±1.49)	2.4 (±0.89)	3.5 (±2.08)	2.6 (± 1.50)
		2.9 (±1.54) ¹		
Median ADA Titer (Min, Max)	2.0 (1,5)	3.0 (1,3)	3.5 (1,6)	2.0 (1,6)
		3.0 (1.6) ¹		

Source: Table 2

¹ US-licensed Remicade[®] and EU-approved Remicade[®] were combined.² one patient had a positive baseline ADA result but cannot be further analyzed for titration due to insufficient sample volumeNote: The ADA titer values were transformed using a $[\log_2(x)] + 1$ transformation (where x is the reported titer result)**Reviewer Comments:**

1. The sponsor states they did not have enough sample to perform a titer on the patient who was positive at baseline. That will make it very difficult to accurately determine if the patient should be ruled out or not.
2. No statistical analysis of ADA titers was performed. Individual titers need to be evaluated statistically in order to understand the immunogenic response to the products in this study.
3. The mean (and median) titers between CT-P13 and US-Remicade at this interim analysis are similar.

III. REVIEWER CONCLUSIONS

The sponsor's interim analysis shows that a portion of the patients treated in study 3.4 had similar immunogenicity incidence if they were treated with CT-P13 or US-Remicade. The patients with a high ADA incidence with EU-Remicade should be temporarily ignored because so few patients treated with EU-Remicade were analyzed. The ELISA test's move to (b) (4) resulted in much better assay performance, though the validation report was not provided. There are several issues to go over in the validation report, primarily the cut point determination for this patient population, and the circulating drug levels following three doses of study drug or comparator. It is premature to make conclusions based on these results due to the incompleteness of the study, though the data do indicate a similar rate of ADA incidence between US-Remicade and CT-P13 at this time.

**FOOD AND DRUG ADMINISTRATION
Center for Drug Evaluation and Research
Office of Prescription Drug Promotion**

*****Pre-decisional Agency Information*****

Memorandum

Date: June 10, 2015

To: Nina Ton, Pharm.D., Regulatory Project Manager
Division of Pulmonary, Allergy, and Rheumatology Products
(DPARP)

From: Adewale Adeleye, Pharm.D., MBA, Regulatory Review Officer
Office of Prescription Drug Promotion (OPDP)

CC: Katie Klemm, Pharm.D., RAC, Team Leader, OPDP

Subject: BLA 125544
CT-P13 (infliximab) Powder, for Injection Solution

OPDP acknowledges receipt of DPARP's August 19, 2014, consult request to review the proposed product labeling (package insert, carton/container labeling, and medication guide) for CT-P13 (infliximab) Powder, for Injection Solution. Reference is made to DPARP's email to OPDP on June 8, 2015, conveying that a Complete Response action will be taken and labeling will be deferred until the next cycle. Therefore, OPDP will provide comments regarding labeling for this application during a subsequent review cycle. OPDP requests that DPARP submit a new consult request during the subsequent review cycle.

Thank you for the opportunity to comment on the proposed labeling.

If you have any questions, please contact Adewale Adeleye at 240-402-5039 or adewale.adeleye@fda.hhs.gov.

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/s/

ADEWALE A ADELEYE
06/10/2015



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Office of New Drugs/
Office of Drug Evaluation IV
Division of Pediatric and Maternal Health
Silver Spring, MD 20993
Telephone 301-796-2200
FAX 301-796-9744

M E M O R A N D U M

From: Erica Radden, M.D., Medical Officer
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

Through: Hari Cheryl Sachs, M.D., Team Leader
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

Lynne Yao, M.D., Acting Associate Director
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

To: Division of Pulmonary, Allergy and Rheumatology
Products (DPARP)

Drug: CT-P13 (proposed biosimilar to Remicade [infliximab])

Application Number: IND 118135/BLA 125544

Re: Review of the initial Pediatric Study Plan (iPSP) and PSP

Sponsor: Celltrion, Inc.

Proposed Indications: Treatment of:

- Crohn's Disease
- Pediatric Crohn's Disease
- Ulcerative Colitis
- Pediatric Ulcerative Colitis
- Rheumatoid Arthritis
- Ankylosing Spondylitis
- Psoriatic Arthritis

- Plaque Psoriasis

Proposed dosage forms

& route of administration: 100 mg of lyophilized CT-P13 in a 20 mL vial for intravenous infusion

Proposed Pediatric Dosing Regimen:

Crohn's Disease

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response.

Pediatric Crohn's Disease

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Ulcerative Colitis

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Pediatric Ulcerative Colitis

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Rheumatoid Arthritis

- In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.

Ankylosing Spondylitis

- 5 mg/kg at 0, 2 and 6 weeks, then every 6 weeks.

Psoriatic Arthritis and Plaque Psoriasis

- 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks.

Consult Request: DPARP requests assistance in evaluating the sponsor's Pediatric Study Plan and preparing for the Pediatric Review Committee (PeRC) meeting.

Materials Reviewed:

- CT-P13 initial Pediatric Study Plan (April 24, 2014; October 2, 2014; and November 25, 2014)
- Division of Pediatric Maternal Health Staff (DPMH) consult request
- Current Remicade (infliximab) labeling (January 2, 2015)
- Pediatric Review Committee (PeRC) Meeting Minutes (July 15, 2014 and November 5, 2014)
- FDA Advice Letter (July 18, 2014 and October 31, 2014)

Consult and Regulatory Background:

Celltrion, Inc. is developing CT-P13 as a proposed biosimilar to Remicade (infliximab) which is currently licensed by Janssen Biotech, Inc. and was first approved in 1998. Infliximab is a chimeric monoclonal antibody that neutralizes the biological activity of tumor necrosis factor alpha (TNF α) by binding with high affinity to the soluble and transmembrane forms of TNF α and inhibits binding of TNF α with its receptors.¹ TNF is

¹ Current Remicade (infliximab) labeling (January 2, 2015)

a cytokine involved in inflammatory and immune responses, and elevated TNF levels also play a role in pathology of anti-inflammatory diseases.

Remicade has the following indications for which Celltrion plans to seek approval: Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Plaque Psoriasis (PsO), Crohn's Disease (CD), Pediatric CD, Ulcerative Colitis (UC), and Pediatric UC. Pediatric study requirements for Remicade for AS and PsA were fully waived because studies were determined to be impossible or highly impracticable due to the low prevalence of these conditions in the pediatric population. Remicade was approved for CD in August, 1998 prior to the enactment of the Pediatric Rule or the Pediatric Research and Equity Act (PREA). However, the sponsor agreed to a Postmarketing Commitment (PMC), and completed studies in patients 6 years and older for which they were granted approval in May, 2006. Upon approval of the RA indication, in November, 1999, the sponsor was issued a required PMC to conduct a juvenile rheumatoid arthritis clinical study, though the age requirements were not specified. The sponsor completed a study of juvenile RA (JRA) (currently referred to as juvenile idiopathic arthritis or JIA) in patients 4 years and older which was found to be negative, and labeling information regarding this negative study was added into the Pediatric Use subsection of labeling in April, 2007. The sponsor was granted orphan designation for pediatric UC and CD in November, 2003. Subsequently, the treatment of UC was approved in September, 2005, and although requirements under PREA were exempted as a result of the orphan status for this indication, the sponsor agreed to a PMC to study the treatment of moderately to severely active ulcerative colitis in pediatric patients. Again, the required age groups for study were not specified in the approval letter. Of note, the maintenance of UC was approved in October, 2006, and the previously issued pediatric PMC for UC was referenced. The sponsor conducted a study of UC in patients 6 years and older and also received approval for Pediatric UC in September, 2011. (See the discussion below regarding the effect of orphan exclusivity for Pediatric UC and CD recent on the proposed biosimilar application.) Finally, Remicade was approved for plaque psoriasis in September, 2006 at which time pediatric study requirements were fully waived (likely due to safety concerns associated with infections and malignancies), though the approval letter does not specify the rationale for the waiver.

Orphan designations were also granted for JRA (11/23/02) and CD (11/14/95). However, for JRA, the designation was granted after the approval. Therefore, the designation did not impact pediatric study requirements for JRA. Additionally, the CD indication was approved prior to the effective date of both PREA and the Pediatric Rule; therefore, the orphan designation could not impact PREA requirements for CD.

Under the Pediatric Research and Equity Act (PREA), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable. Because non-interchangeable biosimilar products, such as CT-P13, are considered new active ingredients, these products are subject to

PREA. Applicants must submit an iPSP within 60 days of an End-of-Phase 2 (EOP2) meeting as required by the Food and Drug Administration Safety and Innovation Act of 2012 (FDASIA). However, given that CT-P13 is a proposed biosimilar product, no phase 2 or phase 3 studies are planned, and thus, an EOP2 meeting will not take place for this product. Under FDASIA, in the absence of an EOP2 meeting, and if a phase 3 study, or a combined phase 2 and phase 3 study, will not be conducted, an initial Pediatric Study Plan (iPSP) should be submitted as soon as feasible, including as early as the pre-IND phase. However, the iPSP must be submitted no later than 210 days prior to the submission of the NDA/BLA, and an agreed iPSP must be submitted with the NDA/BLA. Failure to include an agreed iPSP in an NDA/BLA or efficacy supplement may be considered grounds for a Refuse to File Action. The sponsor submitted their iPSP on April 24, 2014 with plans to file their BLA in July, 2014 acknowledging that not having an agreed iPSP may be problematic. The sponsor submitted the BLA on August 8, 2014, without an agreed iPSP. However, DPARP agreed to file the application and negotiate the iPSP concurrently with the review, because of the potential benefit of the approval this biosimilar product for public health. DPARP consulted DPMH for assistance in reviewing the sponsor's iPSP and preparing for the Pediatric Review Committee (PeRC) meeting.

Pediatric Study Plan and Biosimilar Extrapolation:

DPMH reviewed the iPSP submitted on April 24, 2014, and determined that the sponsor did not address PREA for all the proposed indications, namely AS, PsA and PsO. The sponsor proposed a partial waiver for JIA in patients <4 years of age and for pediatric CD in patients <6 years of age citing (1) studies would be impossible or highly impracticable and (2) there is evidence suggesting that the drug would be ineffective or unsafe. The sponsor also proposed a partial waiver for JIA in patients 4 to 17 years of age because the drug would be ineffective based on the labeling of the negative study conducted with Remicade in this population. The sponsor proposed to demonstrate biosimilarity to Remicade and extrapolate pediatric data from Remicade based on their biosimilar development program for pediatric CD for patients 6 years and older.

Discussion:

A waiver can be granted for the following reasons:

- (1) necessary studies are impossible or highly impracticable;
- (2) evidence suggests the drug or biologic would be ineffective or unsafe (Note: If this is the reason the studies are being waived, this information MUST be included in the pediatric use section of labeling.);
- (3) the drug or biologic does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients; or
- (4) reasonable attempts to produce a pediatric formulation necessary for that age group have failed.

Generally, for products approved for the treatment of RA, the Agency has required studies in patients 2 to 17 years of age for JIA because JIA is considered the pediatric manifestation of adult RA. The pediatric assessment is complete for Remicade for JIA

for patients 4 to 17 years of age. Furthermore, because other products are approved for JIA (i.e., Humira (adalimumab) and Enbrel (etanercept) in patients 2 years and older), a partial waiver would be reasonable for patients 2 to <4 years of age for infliximab based on the criteria that the product does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients with the condition. However, the sponsor would need to provide data supporting this rationale such as the use of infliximab relative to the use of other TNF inhibitors in the respective pediatric population and age group.

The Agency has also previously required pediatric studies for CD in patients 6 to 17 years of age, (b) (4). The Division of Gastroenterology and Inborn Errors Products (DGIEP) determined that Remicade was adequately labeled for CD (b) (4)

Full waivers for the PsA, AS, and PsO indications based on the same rationale as those granted for the reference product are reasonable. (See the table below with specific recommendations to address PREA for the proposed indications.) If a full waiver is granted for PsO based on a safety concern, labeling will need to reflect that safety concern. Labeling currently contains a boxed warning describing the concern for malignancies and increased infections in pediatric patients. DPMH has recommended inclusion of language in the Pediatric Use section stating that TNF- α blockers, such as Remicade (infliximab), “are not recommended for use in pediatric psoriasis” because of the risk of malignancy and infection.

Conclusion/Recommendations:

The iPSP was reviewed by the Pediatric Review Committee (PeRC) on July 2, 2014, and with their concurrence, FDA advised the sponsor to address PREA for all proposed indications for which they seek licensure. Feedback and recommendations regarding proposed waiver rationale, in addition to potential supporting data was also provided. Additionally, the sponsor was advised to revise the iPSP using the recommended template available on FDA’s website² and to refer to the Guidance for Industry- Pediatric Study Plans: Content of and Process for Submitting Initial Pediatric Study Plans and Amended Pediatric Study Plans. The following advice regarding the approach to the pediatric study plan for each proposed indication was conveyed to the sponsor in correspondence dated July 18, 2014, and is summarized in the table below:

Approved Indications	Pediatric Information in Package Insert Labeling for Remicade	Recommendations for the Pediatric Study Plan	Notes
RA	Remicade is not indicated in pediatric patients for the treatment of JRA	The pediatric assessment is complete for patients 4 years and older. Demonstrate biosimilarity and extrapolate pediatric data from the reference product based on the	The reference product’s orphan drug exclusivity for pediatric JRA has expired. Labeling includes

² <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867.htm>

Approved Indications	Pediatric Information in Package Insert Labeling for Remicade	Recommendations for the Pediatric Study Plan	Notes
		<p>biosimilar development program to fulfill PREA for patients 4 years and older.</p> <p>Request a partial waiver for patients 2 to <4 because infliximab does not represent a meaningful therapeutic benefit over existing therapies and is not likely to be used in a substantial number of pediatric patients with the condition.</p> <p>Request a partial waiver for patients <2 years of age because the condition is rare in this age group and such studies would be highly impracticable.</p>	<p>information on the negative study conducted in patients 4 to 17 years of age.</p>
AS/PsA	Remicade is not indicated for AS/PsA in pediatric patients	Request a full waiver because studies would be impossible or highly impracticable due to the difficulty of making specific diagnoses of juvenile PsA or juvenile AS in the pediatric age range.	
CD	Remicade is indicated for CD for patients 6 years of age and older	<p>The pediatric assessment is complete. Demonstrate biosimilarity and extrapolate pediatric data from the reference product based on the biosimilar development program to fulfill PREA for patients 6 years and older.</p> <p>Request a partial waiver for patients <6 years of age because such studies would be highly impracticable.</p>	The reference product's orphan drug exclusivity for CD and pediatric CD has expired.

(b) (4)

Approved Indications	Pediatric Information in Package Insert Labeling for Remicade	Recommendations for the Pediatric Study Plan	Notes
(b) (4)			
PsO	Remicade is not indicated for PsO in pediatric patients	Request a full waiver based on evidence strongly suggesting that this product would be unsafe in this age group.	FDA previously waived submission of pediatric studies by the BLA holder for Remicade likely due to safety concerns. Postmarketing requirements for other TNF α products, such as Humira, were subsequently waived completely based on safety concerns related to malignancy potential identified in an Agency Drug Safety Communication in 2008.

Accordingly, the sponsor resubmitted an iPSP on October 2, 2014, which was reviewed by PeRC on October 22, 2014. An agreed iPSP letter was issued on October 31, 2014, in which general agreement with the proposed plan was conveyed. However, sponsor was advised to revise their request for full waiver for PsO to a rationale based on evidence strongly suggesting that this product would be unsafe in this age group given the safety concerns related to malignancy potential associated with TNF inhibitors identified in an Agency Drug Safety Communication in 2008. The sponsor submitted the final revised iPSP on November 25, 2104.

Since the review and agreement with this pediatric study plan, DGIEP determined that due to increased incidence of Inflammatory Bowel Disease (IBD) in patients 2 to 6 years of age, the design of IBD clinical trials in children should include patients down to 2 years of age. The change in the proposed pediatric study plan was discussed at PeRC on April 29, 2015. While the division agrees that clinical trials in IBD should include patients down to 2 years of age, in this case, the studies in patients greater than 6 years of age have already been completed. Therefore, a dedicated trial in patients only between 2 to 6 years of age would be impossible or highly impracticable because of the low incidence of IBD in this subgroup. However, the division agrees that moving forward, when a new development program for an IBD product is initiated, including patients from 2 to 17 years of age in pediatric studies would likely be required under PREA.

DPMH agrees with the proposed pediatric development plans as outlined above. DPMH participated in the internal meetings from May, 2014 to May, 2015, assisted in PeRC preparation, and provided comments on the iPSPs and the Advice Letters to the sponsor. Our input is reflected in the written comments in the iPSPs and the Advice Letters dated July 18, 2014, October 31, 2014 (DARRTS Reference IDs: 3595613 and 3652093). DPMH will continue to participate in the PSP review process for the BLA.

Of note, DPARP plans to issue a Complete Response for this BLA due to Chemistry, Manufacturing and Controls issues that preclude a determination of sufficient similarity of CT-P13 to Remicade.

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/s/

ERICA D RADDEN
05/26/2015

HARI C SACHS
05/26/2015

LYNNE P YAO
05/27/2015

**Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Medical Policy Initiatives
Division of Medical Policy Programs**

REVIEW DEFERRAL MEMORANDUM

Date: May 27, 2015

To: Badrul Chowdhury, M.D.
Director
**Division of Pulmonary, Allergy, and Rheumatology
Products (DPARP)**

Through: LaShawn Griffiths, MSHS-PH, BSN, RN
Associate Director for Patient Labeling
Division of Medical Policy Programs (DMPP)
Melissa Hulett, MSBA, MSN, FNP-BC, RN
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Sharon W. Williams, MSN, BSN, RN
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review Deferred: Medication Guide (MG)

Drug Name (established name): CT-P13 (infliximab)

Dosage Form and Route: Lyophilized Concentrate for Injection, for Intravenous Use

Application Type/Number: BLA 125544

Applicant: CELLTRION, Inc.

1 INTRODUCTION

On August 8, 2014, CELLTRION, Inc. submitted for the Agency's review an initial filing for a Biosimilar Biologics License Application for CT-P13. CT-P13 is a proposed biosimilar product to US-licensed Remicaide (infliximab), which was approved by the FDA in 1998. On August 19, 2014, the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested that the Division of Medical Policy Programs (DMPP) review the Applicant's proposed Medication Guide (MG) for CT-P13 (infliximab).

This memorandum documents the DMPP review deferral of the Applicant's proposed Medication Guide (MG) for CT-P13 (infliximab).

2 CONCLUSIONS

Due to outstanding chemistry, manufacturing, and control (CMC) deficiencies, DPARP plans to issue a Complete Response (CR) letter. Therefore, DMPP defers comment on the Applicant's patient labeling at this time. A final review will be performed after the Applicant submits a complete response to the Complete Response (CR) letter. Please send us a new consult request at such time.

Please notify us if you have any questions.

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/s/

SHARON W WILLIAMS
05/27/2015

MELISSA I HULETT
05/27/2015

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: May 19, 2015

TO: Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II

FROM: Kara Scheibner, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Sam H. Haidar, Ph.D., R.Ph.
Acting Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Inspection of PAREXEL International GmbH, Early Phase
Clinical Unit, covering BLA 125544 (CT-P13) sponsored by
Celltrion Inc.

Summary:

At the request of the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP), the Office of Study Integrity and Surveillance (OSIS) conducted inspections of the clinical and analytical portions of the following study:

Study CT-P13 1.4: A Randomized, Double-blind, Three-arm, Parallel Group, Single dose Study to Compare the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Three Formulations of Infliximab (CT-P13, EU Sourced Remicade and US Sourced Remicade) in Healthy Subjects

Clinical Site: PAREXEL International GmbH, Early Phase Clinical Unit, Berlin, Germany

Analytical Site:  (b) (4)

This memo provides a review of the clinical inspection done at PAREXEL only. Inspection of the bioanalytical site (b)(4) was done from (b)(4), and the review by Drs. (b)(4) from this inspection has been posted in DARRTS.

Inspection of the clinical portions of the study was conducted by ORA investigator Sharon Matson from April 13-17, 2015. The audit included a thorough review and examination of facilities and equipment, personnel records, specimen handling and integrity, protocols, SOPs, subject consents, electronic records, IRB documentation, all enrolled subject records, test article accountability, and record retention, as well as interviews and discussions with PAREXEL's management and staff.

At the conclusion of the inspection, Form FDA-483 was issued (**Attachment 1**). OSIS received written responses from PAREXEL on May 8, 2015 and on May 11, 2015 (**Attachments 2 and 3**). The Form FDA-483 observations, PAREXEL's responses, and our evaluations of the observations and responses follow.

FDA-483 observation:

1. **Data in the Clinical Study Report "Listing 16.2.5.1 Exposure to Study Drug (All Randomized Subjects)" and "Table 14.1.7 Study Drug Exposure (All Randomized Subjects)" are incorrect. Specifically, the listing "Total Dose Amount (mg)" and "Weight (kg)" reported for the 213 subjects does not match source records in that:**
 - a. **The weights reported were pulled from screening, but the weights used to prepare doses are from Day -1; and**
 - b. **The procedure for reporting "Total Dose Amount" appears to be based on using the planned dose versus actual.**

In their response (dated May 8, 2015), PAREXEL acknowledges and agrees with this observation. PAREXEL feels that the closeness between actual dosing values and calculated dosing values contributed to the discrepancy. Parexel also acknowledges failure of quality control and the medical writer to detect the discrepancy.

PAREXEL has taken the following actions to assess the impact of the discrepancy, and make the appropriate corrections. The sponsor, Celltrion, Inc., was notified. A corrected version of Listing 16.2.5.1 (**Attachment 4**) and Table 14.1.7 (**Attachment 5**) were submitted to Celltrion that now list the actual medication

dose and the correct body weight (Day -1). They investigated whether use of incorrect body weights or calculated doses impacted study data, and which dosing values were used in the PK analysis.

PAREXEL concluded that no additional statistics were affected. Their PK analysis confirmed that the actual (correct) dosing values were used throughout the study.

We find PAREXEL's response to be acceptable.

In a second response (dated May 11, 2015, **Attachment 3**), PAREXEL informed OSIS of two additional errors in the study report. Subjects 1124 and 3199 were not included in the primary endpoint analysis due to deviations in dose preparations.

1. A calculation error in drug preparation caused Subject 1124 to receive a dose of 356.9 mg instead of 413 mg
2. A transcription error in the pharmacy caused Subject 3199 to receive a dose of 337.9 mg instead of 339 mg.

In the case of Subject 3199, the discrepancy was within manufacturing range (0.03% difference), and this subjects' data were included in PK analysis. Corrective and preventative actions have been put into place in the pharmacy.

PAREXEL assessed the impact of including/excluding Subject 1124 from PK analysis in the updated PK population (now including Subject 3199). Reanalysis confirmed that exclusion of Subject 1124 from the PK population has a negligible effect on overall bioequivalence and study outcome (**Attachment 6**).

We acknowledge PAREXEL's identification of these errors, and the negligible effect on the study data and final outcome.

PAREXEL put measures in place to prevent future discrepancies. The Biostatistics study team, and the Early Phase Biostatistics and Pharmacokinetics/Pharmacodynamics staff will be retrained to be aware of key parameter derivations during development of SAPs (Statistical Analysis Plans) and statistical analyses. In addition, SOP-EP.BS-WW-002: Statistical Analysis Plan will be updated to include comprehensive guidelines for the development of SAPs and quality control.

Conclusion:

Following review and evaluation of the Form FDA-483 observation, the response received from PAREXEL, and the additional error notification and resolution received from PAREXEL, we find that the study data (with included revisions) are acceptable for further review.

Kara Scheibner, Ph.D.
DGDBE, OSIS

Final Classification:

VAI: PAREXEL International GmbH, Early Phase Clinical Unit,
Berlin, Germany

CC:

OTS/OSIS/DNDBE/Bonapace/Dasgupta/Cho

OTS/OSIS/DGDBE/Haidar/Choi/Skelly/Scheibner

OTS/OSIS/Taylor/Fenty-Stewart/Nkah/Dejernett/Johnson

CDER/OND/DPARP/Ton/Chowdhury

Draft: KS 5/18/2015

Edit: MFS 5/18/2015; SHH 5/18/2015

OSI: BE 6766

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/PAREXEL, Berlin, Germany

FACTS: **11487680**

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/s/

KARA A SCHEIBNER
05/22/2015

SAM H HAIDAR
05/22/2015



Center for Drug Evaluation and Research - Food and Drug Administration
DBRRII, Office of Biotechnology Products, Office of Pharmaceutical Science
Bldg. 71, 10903 New Hampshire Ave., Silver Spring, MD 20993

BLA: 125544
 START DATE: 5/20/2015
 FINISH DATE: 5/21/2015
 FROM: William Hallett, Ph.D.
 THROUGH: Harold Dickensheets, Ph.D.
 Kurt Brorson, Ph.D.
 PRODUCT: CT-P13, a proposed biosimilar for Remicade
 INDICATION: Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Rheumatoid Arthritis (RA) in combination with methotrexate, Ankylosing Spondylitis (AS), Psoriatic Arthritis, Plaque Psoriasis i.v.
 ROUTE OF ADMIN. DOSE REGIMEN: RA: 3mg/kg at 0, 2, and 6 weeks, then every 8 weeks increasing up to 10 mg/kg or treating every 4 weeks.
 AS: 5mg/kg at 0, 2, and 6 weeks, then every 6 weeks
 All other indications: 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks with provision in CD adult patients that dose may be increased up to 10mg/kg if they initial respond but later lose response.
 SPONSOR: Celltrion
 CLINICAL DIVISION: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

William H. Hallett - S

Digitally signed by William H. Hallett - S
DN: cn=William H. Hallett - S, o=FDA, ou=CDER, email=William.H.Hallett@FDA.HHS.gov, c=US, serial=114757, Date: 2015.05.22 11:13:58 -0400

Harold L. Dickensheets - S

Digitally signed by Harold L. Dickensheets - S
DN: cn=Harold L. Dickensheets - S, o=FDA, ou=CDER, email=Harold.L.Dickensheets@FDA.HHS.gov, c=US, serial=114757, Date: 2015.05.22 11:13:58 -0400

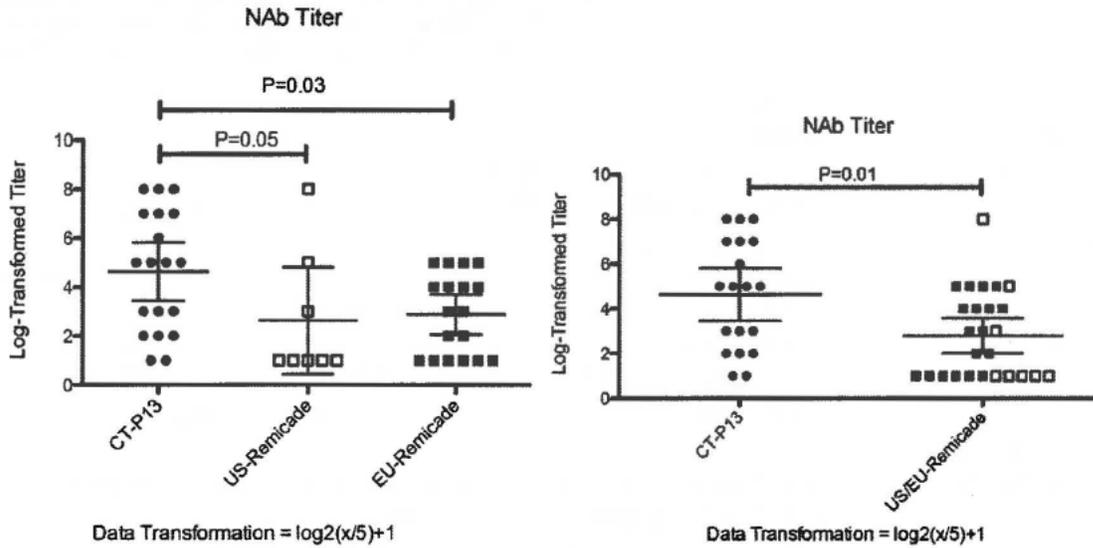
Kurt A. Brorson - A

Digitally signed by Kurt A. Brorson - A
DN: cn=Kurt A. Brorson - A, o=FDA, ou=CDER, email=Kurt.A.Brorson@FDA.HHS.gov, c=US, serial=114757, Date: 2015.05.22 11:13:58 -0400

Amendment to Immunogenicity Review

The immunogenicity review team is correcting a transcription error prior to the analysis of the sponsor's neutralizing antibody titer data resulting in incorrect analysis being performed. Ten of the subjects CT-P13 log-transformed values for screening ADA titers were transposed during posthoc analysis as neutralizing antibody titers. The primary reviewer has subsequently performed an audit of the data used in the analysis and did not identify additional occurrences of incorrect data entry for any data used in the review.

The previous (incorrect) data in the review regarding NAb titers are below.



The two figures above show significant differences (using a Mann-Whitney Rank test) comparing the biosimilar to either US-licensed Remicade, EU-approved infliximab, or the combination of US/EU-Remicade.

The error consisted of the incorrect copying of Screening ADA titer (log scale) values for subjects 1010, 1024, 1043, 1071, 1098, 1136, 1160, 1165, 3189, and 3210 when NAb titers (log scale) should have been used. The table below shows the ADA titers that were incorrectly used in the analysis as well as the NAb titers that should have been used for analysis.

Subject	1010	1024	1043	1071	1098	1136	1160	1165	3189	3210
ADA Titer	2944	1472	1472	1472	2944	368	2944	736	368	368
ADA Titer (log scale ¹)	8	7	7	7	8	5	8	6	5	5
NAb Titer	80	80	80	80	40	20	80	40	40	20
NAb Titer (log scale ²)	5	5	5	5	4	3	5	4	4	3

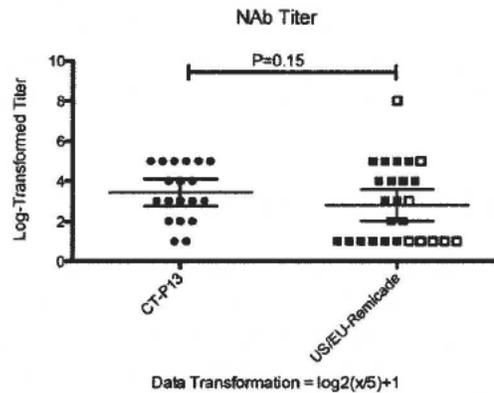
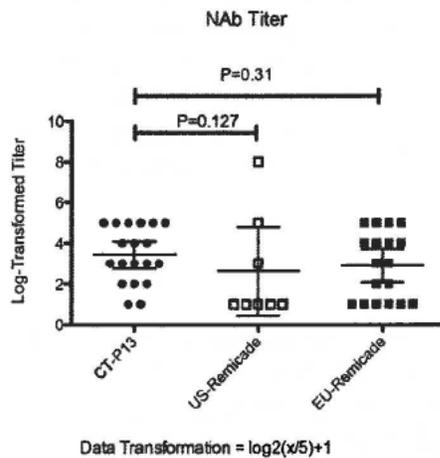
¹ ADA: $[\log_2(x/23)] + 1$

² NAb: $[\log_2(x/5)] + 1$

This error also changes the following mean calculation:

NAb Titers	CT-P13		US-licensed Remicade		EU-approved infliximab		US/EU-Remicade	
	Mean	StDev	Mean	StDev	Mean	StDev	Mean	StDev
Incorrect Data	4.63	2.45	2.63	2.63	2.89	1.64	2.81	1.94
Corrected Data	3.42	1.39	2.63	2.63	2.89	1.64	2.81	1.94

The graphs below incorporate the corrected NAb titers. The resulting p values for the posthoc Mann Whitney analysis performed by the primary immunogenicity reviewer have changed, resulting in a loss of statistical significance. The data do however still indicate a trend towards higher neutralizing antibodies in CT-P13 when compared to US-Remicade (P=0.127) or to combined US/EU-Remicade (P=0.15).



Additionally, if the analysis is performed by confidence interval, as suggested by the clinical statistics reviewer, the following analyses are updated:

CT-P13 versus US-Remicade:

Means: 3.42, 2.63

Mean difference: +0.80 (90% CI: -1.00, +2.60); p=0.44

CT-P13 versus combined US- and EU-Remicade:

Means: 3.42, 2.81

Mean difference: +0.61 (90% CI: -0.22, +1.45); p=0.22

These analyses do not indicate that there is statistically meaningful difference in NAb titers.

Comments to Sponsor

This error also alters the following comment that the review team previously planned to send to the Sponsor as additional comments.

Additional Comments:

Previous version of comment:

You conducted comparative clinical study CT-P13 1.4 to assess the immunogenicity of CT-P13 and US-licensed Remicade. Even if you confirm an analytical bridge is between US-licensed Remicade and EU-approved Remicade (additional subvisible particulate data requested, see above), this study demonstrates a potential trend toward increased neutralizing immunogenic responses in CT-P13-treated subjects compared to the pooled group of subjects receiving either U.S.-licensed Remicade or EU-approved Remicade [27% vs. 19%, respectively (90% confidence Interval: -2.5%, +20%)]. This result is accompanied by differences in binding antibody titers (mean transformed titers 4.74 vs 3.63 in CT-P13 and US-Remicade samples, respectively) and neutralizing antibody titers (mean transformed titers 4.63 vs 2.63, respectively). To address these differences, provide a rationale for why the results from study CT-P13 1.4 are in alignment with the conclusion that the immunogenicity profiles of CT-P13 and US-licensed Remicade are similar.

The proposed corrected comment is below:

You conducted comparative clinical study CT-P13 1.4 to assess the immunogenicity of CT-P13 and US-licensed Remicade. Even if you confirm an analytical bridge is between US-licensed Remicade and EU-approved Remicade (additional subvisible particulate data requested, see above), this study demonstrates a potential trend toward increased neutralizing immunogenic responses in CT-P13-treated subjects compared to the pooled group of subjects receiving either U.S.-licensed Remicade or EU-approved Remicade [27% vs. 19%, respectively (90% confidence Interval: -2.5%, +20%)]. This result is accompanied by differences in binding antibody titers (mean transformed titers 4.74 vs 3.63 in CT-P13 and US-Remicade samples, respectively) and neutralizing antibody titers (mean transformed titers 3.42 vs 2.63, respectively). To address these differences, provide a rationale for why the results from study CT-P13 1.4 are in alignment with the conclusion that the immunogenicity profiles of CT-P13 and US-licensed Remicade are similar.

Immunogenicity Reviewer Amended Conclusion

The error in data transfer resulting in incorrect analysis in the original review memo dated 5/8/2015. The corrected p value (significance of the difference in ADA titer means) is no longer significant, reducing the primary immunogenicity reviewer's concerns over neutralizing titers. This updated observation helps explain how such differences in neutralizing titers were not correlating with any significant clinical observations.

The change in the analysis of the NAb titers does not remove the primary immunogenicity reviewer's overall concerns over the immunogenicity of the proposed biosimilar. There is still lingering concern over the significant difference in ADA incidence and the combined trend of increased titers against CT-P13 in both the screening and neutralizing assays. The additional comment that is proposed is still applicable when corrected and should be provided to the sponsor.



Center for Drug Evaluation and Research - Food and Drug Administration
DBRRII, Office of Biotechnology Products, Office of Pharmaceutical Science
Bldg. 71, 10903 New Hampshire Ave., Silver Spring, MD 20993

BLA: 125544
 START DATE: 2/13/2015
 FINISH DATE: 5/08/2015
 FROM: William Hallett, Ph.D.
 THROUGH: Harold Dickensheets, Ph.D.
 PRODUCT: CT-P13, a proposed biosimilar for US-licensed Remicade -S
 INDICATION: Crohn's Disease, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis¹, Rheumatoid Arthritis (RA) in combination with methotrexate, Ankylosing Spondylitis (AS), Psoriatic Arthritis, Plaque Psoriasis

ROUTE OF ADMIN. i.v.
 DOSE REGIMEN: RA: 3mg/kg at 0, 2, and 6 weeks, then every 8 weeks increasing up to 10 mg/kg or treating every 4 weeks.
 AS: 5mg/kg at 0, 2, and 6 weeks, then every 6 weeks
 All other indications: 5mg/kg at 0, 2, and 6 weeks, then every 8 weeks with provision in CD adult patients that dose may be increased up to 10mg/kg if they initial respond but later lose response.

SPONSOR: Celltrion
 CLINICAL DIVISION: Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)

William H. Hallett -S
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 0.9.2342.19200300.100.1.1=2007154757, email=William.H.Hallett@FDA.gov
 Date: 2015.05.08 17:01:01 -0400

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 email=Harold.L.Dickensheets@FDA.gov
 Date: 2015.05.08 16:36:29 -0400

DATES FOR REVIEW PROCESS:

COMMENTS FOR SPONSOR

1. You provided data from a limited number of lots showing lower levels of subvisible particulates in the range of 1 to 5 microns in US-licensed Remicade compared to both CT-P13 and EU-approved infliximab. These apparent differences may be due to the limited number of lots of CT-P13, US-licensed Remicade and EU-approved infliximab used to perform the analysis. However, these results do not preclude that analytical differences may exist between US-licensed Remicade and EU-approved infliximab, which, if confirmed, could impact the assessment of the adequacy of the analytical bridge among the three products. To address this concern, provide the results of subvisible particulate analysis from additional CT-P13, US-licensed Remicade and EU-approved infliximab lots.

¹ This reflects information for Inflectra that Celltrion submitted on August 8, 2014. We note that the indication for pediatric ulcerative colitis is protected by orphan drug exclusivity expiring on September 23, 2018. See the Orphan Drug Designations and Approvals database at <http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm>.

2. You conducted comparative clinical study CT-P13 1.4 to assess the immunogenicity of CT-P13 and US-licensed Remicade, and differences were observed in immunogenicity incidence rates between these products. This single dose, healthy volunteer study suggests a potential trend towards increased neutralizing immunogenic responses in CT-P13-treated subjects compared to the pooled group of subjects receiving either U.S.-licensed Remicade or EU-approved infliximab [27%² vs. 19%, respectively (90% confidence Interval: -2.5%, +20%)]. Differences are also observed in binding antibody titers (mean transformed titers 4.74 vs 3.63 in CT-P13 and US-Remicade samples, respectively) and neutralizing antibody titers (mean transformed titers 4.63 vs 2.63, respectively). To resolve this deficiency, provide a rationale for the observed differences in immunogenicity incidence rates, binding antibody titers and neutralizing antibody titers between CT-P13 and US-licensed Remicade, and justify how the immunogenicity profiles of CT-P13 and US-licensed Remicade support a demonstration of no clinically meaningful differences.

EXECUTIVE SUMMARY:

The sponsor needs to submit additional data to demonstrate that their product, CT-P13, and the reference product, US-licensed Remicade, are similar from an immunogenicity perspective to support a demonstration of no clinically meaningful differences. There are two major concerns leading to the above recommendation. The first is that there is a difference in the subvisible particulate levels between US-licensed Remicade and EU-approved infliximab, which could impact the adequacy of the analytical bridge needed to justify the relevance of clinical immunogenicity data derived from studies using EU-approved infliximab. Second, there is a difference in the immunogenicity incidence rates between subjects administered CT-P13 and subjects administered US-licensed Remicade (Study CT-P13 1.4, single dose in healthy subjects). There were also differences observed in binding and neutralizing antibody titers between groups. Even if Celltrion establishes an adequate analytical bridge with additional subvisible particulate data to justify the relevance of immunogenicity data obtained using EU-approved infliximab, concerns still remain on a trend toward higher neutralizing immunogenic responses in subjects receiving CT-P13 compared to the pool of subjects receiving either US-licensed Remicade or EU-approved infliximab. These results contrast those from larger immunogenicity studies involving arthritis patients receiving repeated doses of study drugs (CT-P13 1.1 and 3.1), in which the rates of immunogenicity between CT-P13 and EU-approved infliximab were similar.

To overcome these deficiencies, Celltrion needs to provide subvisible particulate data from additional lots. Inability to demonstrate that this observed difference is minimized with additional data could impact the establishment of an adequate analytical bridge to justify the

² Including subjects 1004 and 1049, both of whom developed neutralizing antibodies during the trials indicating a maturation of the anti-drug antibody response.

relevance of data obtained using EU-approved infliximab, including immunogenicity data. Moreover, they need to address concerns regarding a trend toward increased immunogenic responses in subjects receiving CT-P13 in study 1.4, and also provide a comprehensive argument that their immunogenicity data support a demonstration of no clinically meaningful differences between CT-P13 and US-licensed Remicade.

REVIEW:

This review for the immunogenicity portion of BLA 125445 primarily deals with study CT-P13 1.4. Study CT-P13 1.4 is a healthy subject 3-arm study with subjects receiving a single injection of either CT-P13, US-licensed Remicade, or EU-approved infliximab. Immunogenicity was measured by using a screening assay including titer, a confirmatory assay, and a neutralization assay including titer. The CT-P13 1.4 study is the only study that included US-licensed Remicade; all other studies were patient studies comparing CT-P13 to EU-approved infliximab.

The immunogenicity data generated from study CT-P13 1.4 were originally obtained using the Electro-Chemi-Luminescent Assay (ELCA) that was used for the clinical studies performed with EU-approved infliximab. However, the sponsor's review of those data "suggested that higher than anticipated drug serum levels across all treatment groups could be interfering with the initial ADA assay³."

The assay report for the ECLA is below:

Assay #180524 **Analytical Report Number: 2290/0041 (180525)**
Immunoassay Validation Report for the Detection of Anti-CT-P13, Anti-Remicade (EU), and Anti-Remicade (US) Antibodies in Human Serum by an Electrochemiluminescent Assay (ECLA).

Reviewer Comment: This is the original ECLA assay used for all studies except study CT-P13 1.4.

Data describing the ECLA's tolerance to circulating drug is shown in the Table inserted below from the submission.

Table 2: Study CT-P13 1.4 Drug Tolerance Level for ECLA Assay

	LPC (150 ng/mL)	MPC (575 ng/mL)	HPC (1000 ng/mL)
CT-P13	2 µg/mL	5 µg/mL	5 µg/mL
EU-approved Remicade [®]	2 µg/mL	5 µg/mL	5 µg/mL
US-licensed Remicade [®]	5 µg/mL	5 µg/mL	5 µg/mL

Source: Table 11 in the Report on Immunogenicity Results from CT-P13 1.4 Study

LPC: Low Positive Control, MPC: Medium Positive Control, HPC: High Positive Control

Reviewer Comments:

1. For the EU studies, which used only CT-P13 and EU-approved infliximab, the drug tolerance level for each of those treatments is 2µg/mL.
2. The CT-P13 ECLA data from study 1.4 show that only 2 patients were ADA negative with PK values under 2 µg/mL on day 57. The other subjects either had antibodies or were potential false negatives. Interpretation of these results is problematic because most of the subjects have circulating drug levels over the assay's tolerance level.

³ 3/18/2015 IR response, Question 2, Section 2. Assay-Specific Factors, page 3

3. I reviewed the validation report for the ECLA method located in “CSR CT-P13 1.1 – Appendix 16-1-14”. The assay was later revalidated, and the newest validation is found in “Immunoassay Validation Report for the Detection of Anti-CT-P13, Anti-Remicade (EU) and Anti-Remicade (US) Antibodies in Human Serum by an Electrochemiluminescent Assay (ECLA)”. The assay validation describes that free drug interference was determined by measuring the impact of particular concentrations of CT-P13/Remicade on detection of anti-CT-P13/Remicade high and low positive controls. This original validation describes the assays tolerance as “1ug/mL of Remicade and 5.0 ug/mL of CT-P13”. The updated validation provides drug tolerance levels as described in the table above, 2 µg/mL for CT-P13 and EU-approved infliximab, 5 µg/mL for US-licensed Remicade. The validation is acceptable, provided the serum levels stay below the indicated drug tolerance levels.

Therefore, the sponsor developed a new ELISA assay with better tolerance to circulating drug levels (see table below). The new ELISA assay increased the number of ADA positive subjects from 17 (8.1%) to 43 (20.4%).

The assay report for the ELISA assay is below:

Assay #181548) Analytical Report Number: 2290/0041 (181549)
Immunoassay Validation Report for the Detection of Anti-CT-P13, Anti-Remicade (EU), and Anti-Remicade (US) Antibodies in Human Serum by ELISA

Reviewer Comment: This is the updated ELISA used for ADA in study CT-P13 1.4.

Table 3: Study CT-P13 1.4 Drug Tolerance Level for New ELISA Assay

	Drug Tolerance Level			PK concentration at Day 57 (PK population)	
	LPC (60 ng/mL)	MPC (500 ng/mL)	HPC (1000 ng/mL)	Mean (µg/mL)	Range (µg/mL)
CT-P13	10 µg/mL	20 µg/mL	50 µg/mL	4.243 µg/mL	0 ¹ -19.021 µg/mL
EU-approved Remicade [§]	5 µg/mL	20 µg/mL	50 µg/mL	4.092 µg/mL	0 ¹ -12.458 µg/mL
US-licensed Remicade [§]	10 µg/mL	20 µg/mL	50 µg/mL	4.484 µg/mL	0 ¹ -12.859 µg/mL

Source: Table 12 in the Report on Immunogenicity Results from CT-P13 1.4 Study for ‘Drug Tolerance Level’

¹ <0.200 µg/mL is regarded as BLOQ and calculated as 0.

Applying the replacement assay resulted in the total number of subjects detected as being antibody positive increasing from 17 (8.1 %) to 43 (20.4 %) subjects, distributed between the groups as follows:

17 subjects (24.3 %) in the CT-P13 group, 18 subjects (25.4 %) in the EU-approved Remicade[§] group and 8 subjects (11.4 %) in the US-licensed Remicade[§] group.

Reviewer Comments:

1. *The original ELCA assay had relatively low tolerance for circulating drug. The sponsor states that 71/211 (33.6%) of subjects had circulating drug levels that exceeded the ECLA assay's tolerance to detect low positive controls (LPC). Even with the new ELISA method, 30/211 (14.2%) of subjects had circulating drug levels that exceeded the ELISA assay's tolerance to detect the LPC. These subjects are potential false negatives. The new ELISA method is an improvement, but this level of potential false negatives increases the uncertainty of interpreting the results from the ELISA method.*
2. *I reviewed the validation report for the ELISA method (2290/0041 [181548], "Immunoassay Validation Report for the Detection of Anti-CT-P13, Anti-Remicade (EU), and Anti-Remicade (US) Antibodies in Human Serum by ELISA." There were no objectionable observations with the validation report. The assay is has an improved drug tolerance, though it is still only accurate up to 5 ug/mL of EU-Remicade and 10 µg/mL of CT-P13 or US-Remicade.*
 - a. *In study CT-P13 1.4, 4 subjects were over the drug tolerance limit of the ELISA for CT-P13 (10 µg/mL), 23 subjects were over the drug tolerance limit for EU-approved infliximab (5µg/mL), and 3 subjects were over the drug tolerance limit for US-licensed Remicade (10µg/mL). Some of those patients may represent false negatives.*
 - b. *The PK assay did not use acidified samples as the screening assay did. Drug-antibody conjugates may not be accurately detected in the PK assay for the same reason they are not detected in the ADA screening assay. If the samples used in the PK assay would have been acidified, I would expect the PK values, and the number of subjects that would exceed the drug tolerance limit of the assay, to increase.*
 - c. *Even though the ELISA method is an improvement in drug tolerance to the ECLA method, there is still some question as to the interpretation of the results generated by this assay.*

Study CT-P13 1.4 Immunogenicity Incidence

Overall, the combined results for the screening assay for study CT-P13 1.4 (using the ELISA method) demonstrate that 45/211 (21.3%) of all subjects were confirmed positive for ADA. The numbers of subjects tested positive for ADA at the only sampling timepoint other than baseline, Day 57, were; 19/70 (27%) in the CT-P13 group, 18/71 (25.4%) in the EU-approved Remicade group, and 8/70 (11.4%) in the US-licensed Remicade group. All 45 (100%) subjects who tested positive for ADA also tested positive for NAb.

Sponsor's Immunogenicity Summary

CT-P13: 17/70 (24%)
US-Remicade 8/70 (11%)
EU-Remicade 18/70 (26%)

Combined Remicade 26/140 (19%)

The sponsor excluded the following two subjects from the analysis of CT-P13.

Patient 1004

Day 1, ADA Titer 1473 (7), NAb Titer 0
Day 57, ADA Titer, 92 (3), NAb Titer 20 (3)

Patient 1049

Day 1, ADA Titer 23 (1), NAb titer 0
Day 57, ADA Titer 23 (1), NAb titer 5 (1)

The sponsor excluded the two subjects above due to the lower ADA titers at the end of the study compared to the ADA titers from the beginning of the study.

Reviewer Comments:

- 1. The sponsor reported the immunogenicity incidence rate for CT-P13 as 17/70 (24%). The sponsor excluded two subjects, 1004 and 1049, from their analysis. The exclusion was based on the screening assay titer decreasing from the pre-treatment sample to the day 57 sample. However, the same two patients also developed neutralizing antibodies during the study (see below), demonstrating that the subjects were responding to the study drug. From the Immunogenicity Reviewer's perspective, these two patients should be included.*
- 2. There were no subjects in either the US-licensed Remicade or EU-infliximab with the same pattern.*
- 3. Including these two subjects brought the CT-P13 ADA incidence number up to 19/70 (27%). This is the number that is used for all future reviewer analyses regarding ADA incidence.*

OBP Immunogenicity Incidence Summary:

CT-P13: 19/70 (27%)
US-Remicade 8/70 (11%)
EU-Remicade 18/70 (26%)
Combined Remicade 26/140 (19%)

Reviewer Comments:

- 1. We consulted with the clinical statistics reviewer, Dr. Greg Levin, regarding the incidence data for the comparative 3-way study. He provided the following analyses by email on 4/4/2015:*

“The estimated difference between CT-P13 and US-Remicade is +15% (95% confidence interval: +1%, +30%). The confidence interval indicates that the data

are consistent with true differences between about 1% and 30% higher on CT-P13.

If you combine the EU- and US-Remicade arms, the difference between CT-P13 and the combined Remicade reference group is +11% (95% CI: -2%, +24%). The confidence interval indicates that the data are consistent with true differences ranging from 2% lower on CT-P13 to 24% higher on CT-P13.”

- 2. Dr. Levin indicated that he would lean more on combining the US and EU-Remicade analysis if the sponsor successfully completes the three-way analytical bridge. At this time, it is unclear if the sponsor has successfully completed the bridge; there are outstanding issues with ADCC and subvisible particles, among others.*
- 3. Dr. Levin’s analysis indicates that there is a statistically meaningful difference if the comparison is between CT-P13 and US-Remicade. There is a trend towards difference if the data are combined but we cannot rule out the trend was due to chance.*

The sponsor produced a report located in CTD 5.3.5.4 “Report on Immunogenicity Results from CT-P13 1.4 Study.” The report included an analysis that utilized several statistical methods to analyze the data including: the Bonferroni-Holm Method, Hommel’s method, Fisher’s combination, Permutation resampling min-p method, and False Discovery Rate method. The sponsor concluded “there are no meaningful findings from the adjusted approach considering the multiplicity.” Furthermore, the sponsor’s study found that no product-related or subject-related factors contributed to the numerical imbalance between CT-P13 and US-Remicade. The sponsor’s overall conclusion is “the trend towards lower ADA [in the US-Remicade arm]...are likely due to random distribution factors and are not driven by assay related, product related, or subject related factors.”

Reviewer Comment: *The sponsor’s position regarding the numerical imbalance was unclear to the immunogenicity review team, so an IR was sent 2/25/2015 with the following comment:*

2. The results of study CT-13 1.4 indicate that the percent of samples that screened positive in subjects treated with US-licensed Remicade is lower than the percent of samples that tested positive in subjects treated with EU-approved infliximab and “CT-P13”. Provide a rationale for this difference in the percentage of positive samples observed in the study.

Reviewer Comments (IR response):

- 1. The sponsor’s response (provided 3/18/2015) included a report with much of the same data from the BLA, along with some new data, such as the sub-visible particle data. The sponsor’s conclusion regarding the numerical imbalance was essentially the same, that the results “are likely due to a chance finding and random distribution factors and are not driven by assay related, product related or subject related factors as investigated via multi-disciplinary studies and investigations.”*

2. *The sponsor's investigation into the immunogenicity differences observed in study CT-P13 1.4 was thorough but was unable to identify a cause. While we cannot rule out that the differences are due to 'chance finding and random distribution factors,' we also cannot provide an explanation for the differences in incidence and titers. From an immunogenicity perspective a final conclusion cannot be made on the similarity of CT-P13 and US-licensed Remicade based on the clinical trial data and the uncertainty around the data generated with the ECLA assay.*

ELISA Screening Assay Titers

Samples that tested positive in the screening assay were diluted down to get a titer. The titer was determined by diluting the sample down 23-fold (for the initial dilution), then 2-fold dilutions were tested until the reading was below the cut point. The titer values were then transformed by the Sponsor using the following formula.

ADA: $[\log_2(x/23)] + 1$

The result of this transformation makes samples with the initial dilution only (a dilution of 23) result in a value of '1', while a sample that was positive after a two-fold dilution (a dilution of 46) would be '2'.

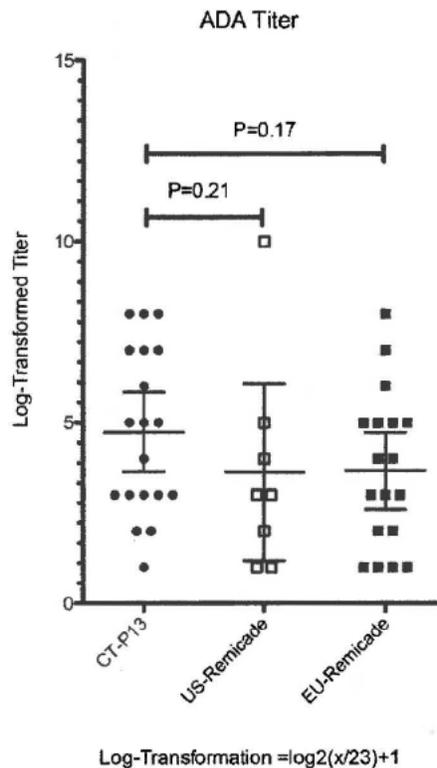
***Reviewer Comment:** The sponsor chose to transform the data using the above-mentioned log transformation. The transformation makes the large range of values easier to handle. If performing rank tests for statistics, the transformation does not change the results. Statistics tests that use means would be altered. Because the statistics we performed were rank tests, this approach is acceptable.*

ADA titer data showed a mean transformed result of:

4.74 for CT-P13

3.67 for EU-approved infliximab

3.63 for US-licensed Remicade.



Reviewer Comment: The data above were created and analyzed by the primary immunogenicity reviewer WH. The data show the screening assay titers from the CT-P13 1.4 study. The CT-P13 group included the two subjects that were not included in the Sponsor's analysis. The data are log transformed, and the means and 95% Confidence Intervals are shown. The statistics shown are Mann Whitney tests showing P values comparing CT-P13 to either US-Remicade or EU-approved infliximab. The statistics do not reach significance ($P < 0.05$) but do indicate a trend towards higher titers in the CT-P13 group. This analysis does not indicate that the screening assay titers are different between the CT-P13 and US-licensed Remicade. The screening assay titers are acceptable.

NAb Assay Titers

The NAb assay used for CT-P13 uses a Gyrolab system, a flow-through immunoassay platform. In the Gyrolab system, biotinylated anti-TNF \pm capture antibody is immobilized on beads. During incubation, neutralizing anti-CT-P13 antibodies bind to Alexa-labeled US-licensed Remicade and prevent it from binding to TNF \pm on the microstructures. Any labeled US-licensed Remicade that is not bound to TNF \pm due to presence of an anti-TNF α antibody will be washed away resulting in signal reduction.

All subjects who tested positive in the screening assay also tested positive in the NAb assay.

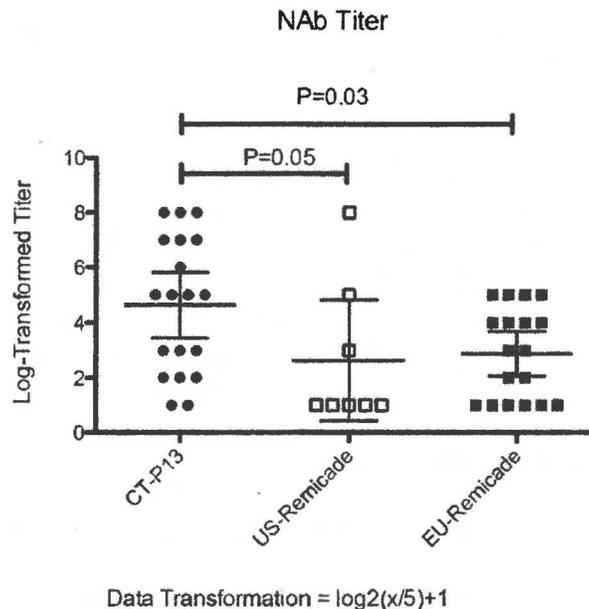
NAb titer were similarly determined and calculated. However, the dilution of the Nabs samples were different, a base of 5-fold dilution. Therefore, the following transformation was used by the Sponsor:

NAb: $[\log_2(x/5)] + 1$

NAb titer data from Study CT-P13 1.4 showed an average of 4.63 for CT-P13, 2.89 for EU-approved infliximab, and 2.63 for US-licensed Remicade.

Reviewer Comment: *The NAb titers were also log transformed using a different formula due to the sample dilution method being different for the NABs then for ADAs. For the same reasons provided above to the screening assay, this approach is acceptable.*

Below are the results for the screening assay, using Mann-Whitney rank test statistics comparing the biosimilar to US or EU infliximab.



Reviewer Comments:

1. The above figure was generated by primary immunogenicity reviewer, WH. It shows the log-transformed NAb titers of the subjects from CT-P13 1.4 who screened positive. The data show means and 95% CI. The statistics are Mann-Whitney rank test results. These data show a significant difference between the NAb titers when comparing the biosimilar to either US-licensed Remicade or EU-approved infliximab.
2. Clin stats (Greg Levin) provided the following statistical analysis of the NAb titers:

CT-P13 versus US-Remicade:

Means: 4.63, 2.63

Mean difference: 2.01 (90% CI: 0.08, 3.93); $p=0.09$

CT-P13 versus combined US- and EU-infliximab:

Means: 4.63, 2.81

Mean difference: 1.82 (90% CI: 0.67, 2.97); $p=0.01$

- a. “So, yes – these analyses do provide more evidence of differences between the groups, although I think they still should be interpreted in the context of the totality of results from all important immunogenicity analyses and studies (because, among many comparisons, we’d expect some to show differences just by chance)”.
3. *I concur with Greg Levin that the data analysis should be interpreted as part of the totality of evidence and that a single assay does not necessarily indicate a lack of biosimilarity.*

Drug Interference

There is a series of issues with drug interference associated with this application. These issues are discussed individually below:

- Sample Acidification (to dissociate drug:ADA complexes if present) was not included in the process validation for the ELISA method but mentioned in the SOP.
- The drug interference from the biosimilar CT-P13 (10µg/mL), US-licensed Remicade (10 µg/mL) and EU- approved infliximab (5µg/mL) were different despite the fact they are supposed to be biosimilar. This difference raises concerns about the validity of the assay.
- The drug tolerance levels in the ECLA assay for CT-P13 (2µg/mL), US-Remicade (5µg/mL), and EU-Remicade (2µg/mL) are very low. However, the actual drug tolerance levels may actually be closer to 0.3 µg/mL, as discussed below.

Sample Acidification and Drug Interference

Comment 3 from the IR sent 2/27/2015 to the Sponsor regarding Sample Acidification is below:

FDA Comment 3. You submitted SOP (b) (4) Job Number 181548 for the ELISA method used to analyze samples collected in Study CT-P13 1.4. The SOP states that ADA samples are acidified to dissociate excess study drug from the ADA in serum samples. However, the validation report you provided does not include validation of the acidification step. Clarify whether the acidification step was performed for the samples collected in Study CT-P13 1.4 and provide your rationale for the inclusion or exclusion of this step in the sample assessment. If acidification was performed in the assay, provide validation data demonstrating that the acidification procedure effectively increases the sensitivity of the screening assay.

The sponsor’s response clarified that acidification was performed on the samples from study CT-P13 1.4. The sponsor also indicated that sample acidification was not part of the validation of the assay, but rather the sponsor was depending on the Contract Testing Organization (CTO)’s experience with sample acidification.

As a result of our inquiry, the sponsor directed the CTO to perform an additional test to confirm that the acidification method was working. They sponsor provided the data below;

Table 1. Drug interference test with sample acidification
 Poitive ADA signals are highlighted in grey

Interference with Acid/Tritims

Plate	Interference Drug		Anti-Remicade (US)	Nominal Concentration: (ng/mL)						
	Drug Name	Concentration		1500	750	375	187.5	93.75	46.875	0.00
				RLU Values						
1	Remicade (US)	200 µg/mL	Mean	0.0281	0.0240	0.0235	0.0220	0.0290	0.0230	0.0200
			SD	0.0000	0.00283	0.000707	0.00	0.00849	0.00141	0.00
			%CV	0.00	11.8	3.01	0.00	29.3	6.13	0.00
1	Remicade (US)	100 µg/mL	Mean	0.0270	0.0310	0.0280	0.0223	0.0250	0.0230	0.0210
			SD	0.00	0.00	0.00	0.000707	0.00141	0.00	0.00141
			%CV	0.00	0.00	0.00	3.14	5.62	0.00	6.71
1	Remicade (US)	50.0 µg/mL	Mean	0.0285	0.0408	0.0365	0.0310	0.0260	0.0240	0.0210
			SD	0.000707	0.00	0.000707	0.00283	0.00	0.00	0.000707
			%CV	0.00	0.00	1.94	9.13	0.00	0.00	3.25
1	Remicade (US)	20.0 µg/mL	Mean	0.0290	0.110	0.0700	0.0400	0.0350	0.0300	0.0200
			SD	0.000707	0.000707	0.00141	0.00566	0.00	0.0012	0.000707
			%CV	2.54	0.594	1.83	12.0	0.00	6.90	3.45
1	Remicade (US)	0.00 µg/mL	Mean	0.0290	0.020	0.021	0.020	0.020	0.015	0.020
			SD	0.000707	0.000707	0.00141	0.00120	0.00566	0.000707	0.000707
			%CV	2.31	2.64	2.83	4.74	2.80	0.867	3.45

*ADA screened positive results are shown in grey.
 Cutpoint^(a) for Plate 1 = 0.0273
 N = 1.71
 Mean FNC_{plate} = 0.0216
 (a) Cutpoint = N * Mean FNC_{plate}

Reviewer Comments:

1. The sample acidification process appears to be effective down to 187.5 ng/mL of anti-Remicade in the presence of 20 µg/mL of Remicade. No subjects from the CT-P13 1.4 study had circulating drug levels greater than 20 µg/mL. The 187.5 ng/mL sensitivity is better than the recommended sensitivity. The sample acidification step appears acceptable.
2. In study CT-P13 1.4, no subjects were observed with CT-P13 PK values higher than 6.1 µg/mL at the time of ADA sampling. Therefore, it is unclear if the sample acidification is effective for samples with PK values over 6.1 µg/mL.

Difference in assay tolerance between EU-infliximab and US-Remicade/CT-P13

The ELISA assay drug tolerance level for EU-infliximab was 5 µg/mL, but it was 10 µg/mL for US-Remicade and CT-P13. As part of IR #1 sent 2/27/2015 FDA stated:

Continued FDA Comment 2: Additionally, clarify why the drug tolerance level for EU-approved infliximab is different than those for US-licensed Remicade and CT-P13.

The sponsor response was that the difference was due to the cut-point on the particular plate used in validation. The table below shows the plate cut points and signals at indicated dose levels.

Table 1. Comparison of Plate Cut Point and Signal of 60.0ng/mL Positive Control by Free Drug Level

Interference drug	Cut point for plate	Signal at Free Drug Level		
		5.0 µg/mL	10.0 µg/mL	20.0 µg/mL
CT-P13	0.0364	0.0555	0.0380	0.0295
US-licensed Remicade	0.0359	0.0545	0.0385	0.0290
EU-approved infliximab	0.0393	0.0520	0.0360	0.0280

*Signals at each drug tolerance level are bolded

Reviewer Comment: The sponsor's interpretation of the data is acceptable. The EU-approved infliximab did not have an acceptable absorbance at 10µg/mL. However, there is no explanation why the US-licensed Remicade and EU-approved infliximab products are different from each other.

Drug Interference Levels from the ECLA Method

As discussed above, the ELCA assay was validated for the following drug tolerance levels:

Table 2: Study CT-P13 1.4 Drug Tolerance Level for ECLA Assay

	LPC (150 ng/mL)	MPC (575 ng/mL)	HPC (1000 ng/mL)
CT-P13	2 µg/mL	5 µg/mL	5 µg/mL
EU-approved Remicade [®]	2 µg/mL	5 µg/mL	5 µg/mL
US-licensed Remicade [®]	5 µg/mL	5 µg/mL	5 µg/mL

Source: Table 11 in the Report on Immunogenicity Results from CT-P13 1.4 Study

LPC: Low Positive Control, MPC: Medium Positive Control, HPC: High Positive Control

The sponsor performed the ADA analysis of study CT-P13 1.4 with the ECLA assay prior to developing the ELISA assay. In response to an IR sent April 7, the sponsor compared the results of the two assays side-by-side from the same patients, including the following data:

Rand#	Treatment	Visit (day)	PK at day 57	ELISA			Gyros		ECLA	
				ADA Screening	ADA Confirmatory	ADA Titer	NAb Results	NAb Titer	ADA Screening	ADA Confirmatory
1031	CT-P13	57	0.288	Positive	Positive	184	Positive	10	Negative	Negative
1126	CT-P13	57	0.465	Positive	Positive	92	Positive	10	Negative	Negative
1069	CT-P13	57	0.495	Positive	Positive	92	Positive	20	Negative	Negative
1066	CT-P13	57	0.496	Positive	Positive	92	Positive	10	Negative	Negative
1027	CT-P13	57	0.542	Positive	Positive	46	Positive	20	Negative	Negative
1004	CT-P13	57	0.721	Positive	Positive	92	Positive	20	Negative	Negative
1041	CT-P13	57	0.828	Positive	Positive	92	Positive	80	Negative	Negative
1151	CT-P13	57	1.026	Negative	-	-	-	-	Negative	Negative
1093	CT-P13	57	1.309	Positive	Positive	46	Positive	5	Negative	Negative

Reviewer Comments:

1. *These data provide an example of the two assays, ECLA and ELISA, on the same subject samples from the CT-P13 arm. The data show all subjects (n=8) with PK values under 1.309 µg/mL, that tested positive for ADA in the ELISA, did not test positive with the ECLA. This indicates the actual tolerance of the ECLA for study drug CT-P13 was less than 0.288 µg/mL, the lowest measureable PK detected for which ADA were detected in the ELISA but not detected by the ELCA. The limit of detection (LOD) of the PK assay is 0.200 µg/mL. The ECLA assay was able to accurately detect ADA in samples from 10 subjects who had PK values below the limit of quantitation. These data further support that the ECLA assay is functional, but values as low as 0.288µg/mL could interfere with the assays ability to detect ADA.*
2. *For the EU-approved infliximab, a similar situation occurred; 9 subjects with PK values between 0.286 – 1.529 µg/mL had detectable anti TNF antibodies by ELISA and not by ECLA. Two subjects who were below the LLOQ had also no anti-Remicade antibody detected by the ECLA assay and detected by ELISA.*
3. *For US-Remicade, all subjects (n=3) with PK values between 0.263 – 1.406 had detectable anti-TNF± antibodies by ELISA but not by ECLA.*
4. *This represents a concern because only subjects who test positive by the screening assay are then tested by the neutralizing assay. Because the ECLA assay was the only assay used in the efficacy trials in the EU, and because there is little confidence the assay is working acceptably above study drug concentrations of > 0.3 µg/mL, there is little confidence in interpretation of immunogenicity data from subjects in the EU studies with PK values > 0.3 µg/mL.*
5. *This concern could be mitigated by clinical studies performed in RA and AS patients to support the approval of CT-P13 as a biosimilar to EU-approved infliximab (assuming an analytical bridge is established between CT-P13, US-licensed Remicade, and EU-approved infliximab). In this regard, these studies showed that efficacy rates were similar between CT-P13 and EU-approved infliximab (Study 1.1, AS; Study 3.1, RA); immunogenicity results correlated inversely with efficacy in RA patients receiving either CT-P13 or EU-approved infliximab (Study 3.1); and immunogenicity-related adverse events were similar in CT-P13-treated vs. EU-approved infliximab-treated patients (Study 1.1, AS; Study 3.1, RA)..*

Subvisible Particulates

As part of their 18-Mar-2015 response to Immunogenicity Comment 2, the Sponsor provided data from studies performed to assess a variety of analytical parameters. Included within these data were orthogonal methods measuring the levels of particulates of various sizes in a small number of lots of the proposed biosimilar CT-P13, US-Remicade and EU-infliximab. These data were presented as part of a multi-page CMC analytical data summary table, Table 17, pages 25-27 of the submission. The table has been copied below, in abbreviated form pertinent to

discussion of the SVP data, and has been annotated by the reviewer to highlight differences among the three-way drug comparison data.

Table 17: Test Results of EU-approved Remicade[®], US-licensed Remicade[®] and CT-P13 Drug Product

Test	US- licensed Remicade [®]			EU-approved Remicade [®]		CT-P13	CT-P13 (retained batches)		
	DCD26 014P1	DED38 015P1	DDM32 016P1	3RMA6 5101	3RMK A82501	12B1C0 04	12B1C0 04-1	12B1C0 04-2	
% ADA positivity in Study CT-P13 1.4	12.8	8.7	-	30.8	22.2	24.3	-	-	
Sub-Visible Particle / Aggregate									
MFI (number/mL)	1.00 ≤ <100.00(um)	9,183	7,891	10,976	36,326	33,226	17,770	16,492	17,136
	2.00 ≤ <100.00(um)	2,257	1,669	2,569	10,588	10,588	4,790	4,565	4,937
	5.00 ≤ <100.00(um)	506	391	692	2,230	1,483	1,068	1,034	1,232
	10.00 ≤ <100.00(um)	48	98	75	233	71	96	143	195
	15.00 ≤ <100.00(um)	13	23	15	44	27	13	25	29
	25.00 ≤ <100.00(um)	0	4	2	6	6	6	4	0
	40.00 ≤ <100.00(um)	0	0	2	0	0	2	0	0
	50.00 ≤ <100.00(um)	0	0	2	0	0	2	0	0
	70.00 ≤ <100.00(um)	0	0	0	0	0	2	0	0
DLS	Z average	24.84	24.71	24.55	24.86	24.71	25.34	25.3	25.43
	PdI (polydispersity index)	0.116	0.147	0.116	0.157	0.141	0.121	0.15	0.128
HIAC (number/mL)	≥2 um	782	602	835	2,301	2,437	940	1,263	1,157
	≥10 um	7	1	5	24	12	7	10	7
	≥25 um	0	0	0	1	0	1	0	0
SEC-HPLC %	100	100	100	100	100	99			

The Sponsor's analysis did not determine a direct relationship between the levels of larger-sized particulates (5 to 100 μm) and ADA titer. In general, the Sponsor acknowledges some differences in the proportions of smaller particulates present in the three drugs, particularly in the size range from 1-5 μm as determined by MFI and HIAC methods. Using the ADA incidence rates from study CT-P13 1.4, the Sponsor attempts to directly correlate the differences in size classes or ranges with ADA incidence. No direct relationship between differences in particulate sizes for the lots analyzed from the three study drugs (including those lots used in study CT-P13 1.4) and differences in ADA levels was noted in their analyses. However, it should be noted that

the Agency has recognized that particulates in this size range have a strong potential to be immunogenic⁴, which could be a factor in cases where particulates escape filtration or re-form post infusion. A particulate study of the CT-P13 drug product lot used in the CT-P13 1.4 trial, post-dilution into saline for infusion, was found in the submission. Briefly, the study demonstrated effective removal of larger particulates (10-100 μ m), and approximately 90% reduction in small particulates (1-10 μ m) size. However, no studies for either of the licensed infliximab drugs were presented for comparison.

Immunogenicity Reviewer Comments:

- 1. It may be that the limited number of drug product lots analyzed has affected the attempted analysis of a direct correlation between SVP counts and ADA incidence in this study. Conversely, the effect of SVP could be a threshold effect rather than a linear relationship between SVP and ADA incidence. However, this may not be observable unless a clinical study is performed with multiple lots of all three drugs for which the SVP content is known or can be determined.*
- 2. Regardless of the potential relationship between SVP and ADA incidence, to support analytical biosimilarity, the sponsor should provide data on additional lots of all three drugs in order to ascertain whether the observed differences in SVP found between the three drug products in the small scale study are maintained, or if the analytical bridge to biosimilarity between CT-P13, US-Remicade and EU-infliximab is supported with additional data.*

⁴ Refer to “Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products”.

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

CLINICAL INSPECTION SUMMARY

DATE: May 7, 2015

TO: Nina Ton, Pharm.D., Regulatory Project Manager
Juwaria Waheed, M.D., Medical Officer
Nikolay Nikolov, M.D., Cross Discipline Team Leader
Division of Pulmonary, Allergy and Rheumatology Products (DPAAP)

FROM: Anthony Orenca, M.D., F.A.C.P.
Medical Officer, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

THROUGH: Janice Pohlman, M.D., M.P.H.
Team Leader, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

Kassa Ayalew, M.D., M.P.H.
Branch Chief, GCP Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

SUBJECT: Evaluation of Clinical Inspections

BLA: 125544

APPLICANT: Celltrion, Inc.

DRUG: CT-P13 infliximab biosimilar

NME: No (505-b1), Biosimilar: Yes (351-k)

THERAPEUTIC CLASSIFICATION/REVIEW: Standard Review

INDICATIONS: Treatment of patients with Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), Plaque Psoriasis (Ps), Crohn's Disease (CD), Pediatric Crohn's Disease, Ulcerative Colitis (UC), Pediatric Ulcerative Colitis

CONSULTATION REQUEST DATE:	October 16, 2014
INSPECTION SUMMARY GOAL DATE (original):	April 15, 2015
INSPECTION SUMMARY GOAL DATE (revised):	May 7, 2015
DIVISION ACTION GOAL DATE	June 1, 2015
PDUFA DATE:	June 8, 2015

I. BACKGROUND:

Infliximab is a chimeric human murine monoclonal antibody that binds with high affinity, avidity and specificity to soluble and transmembrane forms of TNF α (tmTNF α). CT-P13 (infliximab) is a monoclonal antibody developed by Celltrion Inc. intended to be formulated as a biosimilar to Remicade. Infliximab has been used to treat patients with ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and patients with Crohn's Disease.

Two adequate and well-controlled clinical trials (CT-P13 1.1 and CT-P13 3.1) were submitted in support of the applicant's BLA.

Study CT-P13 1.1

CT-P13 1.1 was a randomized, double-blind, multicenter, parallel-group study of multiple, single-dose intravenous (IV) infusions, to assess the pharmacokinetic equivalence and safety of CT-P13 compared to Remicade reference product. The primary study objective was to demonstrate comparable pharmacokinetics at steady state in terms of the area under the concentration-time curve over a dosing interval (AUC τ) and observed maximum serum concentration at steady state (C $_{max,ss}$) between CT-P13 and Remicade reference product in patients with active ankylosing spondylitis (AS) up to Week 30. The investigational product was CT-P13 (5 mg/kg) administered as a two-hour infusion per dose. The reference product was Remicade (5 mg/kg) administered as a two-hour infusion per dose.

The primary pharmacokinetic endpoints were comparisons of pharmacokinetic parameters (a) AUC τ area under the concentration-time curve over the dosing interval, at steady state between Week 22 and Week 30 and (b) C $_{max,ss}$ - observed maximum serum concentration at steady state between Week 22 and Week 30. The secondary efficacy study endpoints of interest to CDER DPARP include (a) proportion of patients achieving clinical response according to the Assessment of SpondyloArthritis International Society (ASAS) 20% improvement scale (ASAS20) and (b) proportion of patients achieving clinical response according to the ASAS40 improvement scale.

Study CT-P13 3.1

Study CT-P13 3.1 was a randomized, double-blind, multicenter, parallel-group, multiple single-dose intravenous (IV) infusion study to assess efficacy equivalence, and to evaluate long-term efficacy, pharmacokinetic, pharmacodynamics, and safety of CT-P13 compared to Remicade reference product. The primary objective was to demonstrate that CT-P13 is equivalent to Remicade up to Week 30, in terms of efficacy as determined by clinical response according to the American College of Rheumatology (ACR) definition of a 20% improvement (ACR20).

CT-P13 (3 mg/kg) was the investigational drug product, administered as a two-hour infusion per dose co-administered with methotrexate between 12.5 to 25 mg/week, oral or parenteral dose (dose and route must be maintained from beginning to end of study) and folic acid (≥ 5 mg/week, oral dose). Remicade was the reference product (3 mg/kg), administered as a two-hour infusion per dose co-administered with methotrexate between 12.5 to 25 mg/week, oral or parenteral dose (dose and route must be maintained from beginning to end of study) and folic acid (≥ 5 mg/week, oral dose). The primary efficacy endpoint was the proportion of patients achieving clinical response (according to the ACR20 criteria) at Week 30.

Four foreign clinical sites were selected for audit, since domestic data were insufficient. The Polish and Chilean sites enrolled a large number of subjects.

II. RESULTS:

Name of CI Location	Study Site/Protocol/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Pedro Miranda, M.D. Centro de Estudios Reumatologicos Avenida Salvador 960 Chile 7501126	Site #2007 Protocol CT-P13 3.1 Subjects=18 Protocol CT-P13 1.1 Subjects=10	January 12-16, 2015	Preliminary: VAI
Pawel Hrycaj, M.D. Prywatna Praktyka Lekarska Os. Rzeczypospolitej 6 Poznan, Poland 61-397	Site #1215 Protocol CT-P13 3.1 Subjects=29 Protocol CT-P13 1.1 Subjects=18	February 2-6, 2015	NAI

Name of CI Location	Study Site/Protocol/Number of Subjects Enrolled (n)	Inspection Date	Classification*
Slawomir Jeka, M.D., Ph.D. “NASZ LEKARZ” Praktyka Grupowa Lekarzy Rodzinnych z Prychodnia Specjalistyczna Szczytna 20 Toru, Poland 87-100	Site #1213 Protocol CT-P13 3.1 Subjects=14 CT-P13 1.1 Subjects=12	January 26-29, 2015	Preliminary: NAI
Janusz Jaworski, M.D. Linea Corporis-Chirurgia Plastyczna Nowiniarska 1 Warszawa, Poland 00-235	Site #1214 Protocol CT-P13 3.1 Subjects=16 CT-P13 1.1 Subjects=14	February 9-13, 2015	NAI
Celltrion, Inc. 23 Academy-ro, Yeon-gu (406-840) Incheon, South Korea	Protocol CT-P13 3.1 and CT-P13 1.1	April 6-10, 2015	Preliminary: NAI

*Key to Classifications

NAI = No deviation from regulations. Data acceptable.

VAI-No Response Requested = Deviations(s) from regulations. Data acceptable.

OAI = Significant deviations from regulations. Data unreliable/critical findings may affect data integrity.

Preliminary=The Establishment Inspection Report (EIR) has not been received, findings are based on preliminary communication with the field at the Office of Regulatory Affairs (ORA), or final review of the EIR is pending. Once a final letter is issued by CDER to the inspected entity and the case file is closed, the preliminary designation is converted to a final regulatory classification.

CLINICAL STUDY SITE INVESTIGATOR

1. Pedro Miranda, M.D., M.D, Site #2007

Chile

a. What was inspected:

The inspection was conducted from January 12 to 16, 2015.

For Study CT-P13 1.1, a total of 12 subjects were screened, and 10 subjects were enrolled and randomized. Ten subjects completed the study. An audit of 10 enrolled subjects’ records was conducted. For Study CT-P13 3.1, a total of 25 subjects were screened and 18 subjects were enrolled and randomized. Twelve subjects completed the study. An audit of six enrolled subjects’ records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

A Form FDA 483 (Inspectional Observations) was issued at the end of the inspection for not conducting the clinical investigation according to the investigational plan and investigational study drug disposition records inadequate with respect to dates, quantity and subject use. Selected regulatory violations and examples of deficiencies are listed below.

1. The study was not conducted according to the investigational plan.

A. Each protocol's specified infusion rate was 125 mL/hr. The study drug administration instruction sheet for the CT-P13 studies, carried by the subjects to the off-site infusion center and utilized from July 2011 to July 2012 state that the rate of infusion was 132 mL/hr (for a period of two hours).

OSI Comment: Despite minor differences in infusion rates, DPARP commented that this difference in rate of infusion did not have any significant impact on the safety of patients and rate of infusion reactions were not significantly different than expected.

Dr. Miranda's February 5, 2015 written response to the Form FDA 483, states that the protocol-specified dose of investigational product (IP) was administered over the specified two hour infusion interval with minimal increase in volume to allow for clearance of product from the intravenous tubing.

B. Temperature excursions during study drug shipments were not always investigated or reported to the sponsor for appropriate resolution.

For example:

- (a) Twenty six kits of study drug for Study CT-P13 1.1 were shipped from the storage facility to the infusion site on April 13, 2011, Order #10648. The temperature of the shipment is documented at 26.1 degrees Celsius (18.1 degrees higher than the protocol-specified storage temperature range) for a period of two days. This shipment was documented as "in good condition" by the infusion site and the study drug was used for subject infusions. No investigation of the temperature excursion was performed.
- (b) Twelve kits of study drug for Study CT-P13 3.1 were shipped from the storage facility to the infusion site on February 2, 2011, Order #10177. The temperature of the shipment is documented at 27.2 degrees Celsius (19.2 degrees higher than

the protocol-specified storage temperature range) for a period of two hours. A determination of the shipment's condition was not made by the infusion site and the shipment was used for subject infusions.

OSI Comment: DPARP reported that the product quality team reviewed additional accelerated stability studies for the IP at 25 ± 2 degrees Celsius for six months, with the test articles remaining within stability specifications. Therefore, the temperature excursions outside the protocol-specified range were not thought to significantly impact efficacy or safety of the IP.

C. The correct informed consent documents were not signed in a timely manner. For instance, the Informed Consent Form Version 5 (Approval date of April 26, 2011) and Version 6 (Approval date of January 3, 2012), for Studies 1.1 and 3.1, respectively were not always obtained from subjects at their next study visit. For Study 1.1, Subject 1001 signed Version 5 on September 8, 2011, and Version 6 on April 25, 2012.

OSI Comment: While these were considered regulatory deficiencies, the observations have no impact on data integrity.

D. Pre-infusion pharmacokinetic samples were not always collected "immediately prior to the beginning of the study treatment infusion" 15 minutes or less prior to the infusion start time, as required by the protocol.

For example:

- (a) For Study CT-P13 1.1, Subject 1001's infusion time for Dose 1 was documented as 11:30 AM, but the collection time was documented as 10:30 AM. Dose 2 infusion time was 11:05 AM but the sample time was documented as 9:15 AM.
- (b) For Study CT-P13 3.1, Subject 3001's infusion time for Dose 1 was documented as 11:45 AM, but the collection time was documented as 9:30 AM. Dose 2 infusion time was 11:30 AM, but the sample time was documented as 11:00 AM. Dose 3 infusion time was 12:20 PM, but the sample time was documented as 9:50 AM.

OSI Comment: Prior to Dose 1, subjects were not receiving IP/active comparator and therefore pre-Dose 1 PK sample times would not be critical. Additionally, following a loading dose period, the IP/active comparator are dosed approximately every eight weeks and therefore a slight variance in time of obtaining "trough" concentrations would not be expected to be critical.

DPARP stated that Studies 1.1 and 3.1 were not dedicated pharmacokinetic studies and that the rigid time points for pre-infusion sampling were not critical.

E. For Study CT-P13 1.1, the following additional regulatory deficiencies were observed.

For example:

- (a) No documentation of personnel training for the study conducted from January 2011 to June 2012, for the study protocol training of at least two sub-investigators and twenty-one individuals who participated in this clinical trial investigation.
- (b) Adverse events were not reported to the sponsor and (if applicable) to the Ethics Committee:
 - (i) Subject 2007-1002 reported Herpes zoster on March 20, 2012 and treated with acyclovir,
 - (ii) Subject 2007-1003 reported abdominal pain on May 20, 2011 and had an ultrasound, and
 - (iii) Subject 2007-1004 reported flu symptoms, had an emergency room visit on April 16, 2012 and received penicillin.

OSI Comment: There were a few instances where non-serious adverse events were not reported. However, these isolated events are unlikely to have a major impact on the safety evaluation of this BLA.

F. For Study CT-P13 3.1, the following additional regulatory deficiencies were observed.

For example:

- (a) Documentation of training of research staff at the principal investigator's site is dated June 29, 2011 after study subjects were known to have been screened and enrolled in the study (January 26, to March 29, 2011).
- (b) Stop date (April 11, 2011) and restart date (May 18, 2011) was not documented on the case report forms of the co-administered methotrexate for Subject 3001.

OSI Comment: DPARP did not consider these inspectional observations as significant.

- 2. Investigational drug disposition records were not adequate with respect to dates, quantity and use by subjects. Specifically,
 - A. No drug accountability records from the off-site infusion center were available at the clinical study site documenting identification of kit number of investigational product (IP) administered to each subject from January 11 to mid-July 2011. During this time period, 10 of 10 subjects enrolled in Study CT-P13 1.1 received at least 34 infusions of the IP/active comparator and 18 of 18 subjects enrolled in CT-P13 3.1 received at least 45 infusions.
 - B. No study drug preparation records from the off-site infusion center were available for review at the clinical study site for IP/active comparator administered to subjects from January 2011 to mid-July 2011. During this time period, 10 of 10 subjects enrolled in Study CT-P13 1.1 received at least 34 infusions of the study medication and 18 of 18 subjects enrolled in Study CT-P13 3.1 received at least 45 infusions.

- C. Documentation of the study drug receipt and drug condition was not performed by the site research staff members who received the shipment, or not conducted at the time the shipments were received.

These study drugs were received by personnel at the infusion site. However, the receipt of the investigational drugs was documented in the IVRS by the principal investigator's staff at a separate site.

For example:

(a) for Study CT-P13 1.1, Order #10196 received by the infusion center on February 1, 2011 was documented as being received in IVRS by the Study Coordinator at the principal investigator's office on February 8, 2011.

(b) for Study CT-P13 3.1, Order #10177 received by the infusion center on February 1, 2011 was documented as being received in IVRS by the Study Coordinator at the principal investigator's office on February 8, 2011.

OSI Comment: At this clinical investigator site, infusion of investigational product (IP)/comparator was performed at a separate off-site infusion center. Two off-site infusion centers were utilized during the course of the studies; Oncomed (January 2011 – July 2011) and INTOP (July 2011 – study completion). Problems were detected (i.e. drug preparation and drug accountability worksheets identifying kit numbers of IP/active comparator prepared/administered to study subjects for Protocols CT-P13 1.1 and 3.1 were reportedly not completed) by the study monitor (b) (4) and clinical investigator in obtaining documentation from Oncomed during the course of the study (January 2011 – July 2011) and a second (new) infusion site (INTOP) was utilized. The infusion centers were not inspected during the course of this inspection. Documentation of Hypersensitivity Monitoring (an infusion-related document recording vital signs during study drug infusion) was present at the CI site, but there was no indication on this worksheet about the identification of kit numbers of IP/active comparator infused (Jan – July 2011). This time period generally corresponded to the dose-loading and early maintenance phase treatment for affected enrolled subjects.

DPARP reviewed copies of the Hypersensitivity Monitoring sheets obtained at the CI site during inspection. These sheets contained vital signs that were to be reported during the course of IP/active comparator administration while monitoring for hypersensitivity reactions. OSI had observed and DPARP agreed, that some blood pressure (BP) measurements reported from the time period January to July 2011 by Oncomed (the first off-site infusion center with identified documentation problems by monitor/CI) for some subjects were identical, raising the question of the reliability of the data. However, DPARP indicated that if a manual BP is taken, it is usually not as precise as a machine BP and rounding to the nearest 10 is not unusual. On the other hand, the heart rate reporting seems variable which may reflect the way heart rate is usually measured and recorded. The Hypersensitivity Monitoring sheet itself did not contain a space to record specific adverse events. The review division noted however, that these enrolled subjects in CT-P13 1.1 and 3.1 continued to receive IP/active comparator infusions was reassuring from a safety perspective.

Following discussion with OSI, the review team performed sensitivity analyses due to drug accountability concerns. As reported to OSI, the sensitivity assessments did not change the overall BLA study results and conclusions.

Dr. Miranda responded adequately to the Form FDA 483 in a letter dated February 5, 2015.

c. Assessment of data integrity:

OSI is unable to verify the identity of IP/active comparator infused to specific subjects enrolled in Protocol CT-P13 1.1 and 3.1 from January to July 2011 due to inadequate documentation of investigational product administered to enrolled subjects at this site as described above. The review team was advised to conduct sensitivity analyses excluding data for the enrolled subjects at this site. By report, there was no apparent impact on efficacy outcomes for the studies, particularly important for Protocol CT-P13 3.1 which was a Phase 3 noninferiority design study used to support clinical efficacy of this biosimilar product (relatively insensitive study design for this purpose per DPARP). Inadequate drug accountability at this site may be related to use of an off-site infusion center for administration of investigational product leading to limitations in CI oversight of conduct, as well as requiring transport of paper source documentation between the CI site and infusion center. There may be similar implications for other sites using off-site infusion centers for these studies.

3. Pawel Hrycaj, M.D., Site #1215
Poznan, Poland

a. What was inspected:

The inspection was conducted in accordance from February 2 to 6, 2015. For Study CT-P13 1.1, a total of 23 subjects were screened, and 18 subjects were enrolled and randomized. Eighteen subjects completed the study. An audit of nine enrolled subjects' records was conducted. For Study CT-P13 3.1, a total of 41 subjects were screened and 29 subjects were enrolled and randomized. Twenty nine subjects completed the study. An audit of seven enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for those enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

3. Slawomir Jeka, M.D., Ph.D., M.D., Site #1213

Toru, Poland

a. What was inspected:

The inspection was conducted in accordance with Compliance Program 7348.811, from January 26 to 29, 2015. For Study CT-P13 1.1, a total of 17 subjects were screened, 12 subjects were enrolled and randomized. Eleven subjects completed the study. An audit of 11 enrolled subjects' records was conducted. For Study CT-P13 3.1, a total of 18 subjects were screened, 14 subjects were enrolled and randomized. Twelve subjects completed the study. An audit of 12 enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for those enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

4. Janusz Jaworski, M.D., Protocols CT-P13 3.1 and CT-P13 1.1/ Site #1214

Warsaw, Poland

a. What was inspected:

The inspection was conducted from February 9 to 13, 2015. For Study CT-P13 1.1, a total of 15 subjects were screened, and 14 subjects were enrolled and randomized. Fourteen subjects completed the study. An audit of seven enrolled subjects' records was

conducted. For Study CT-P13 3.1, a total of 22 subjects were screened and 16 subjects were enrolled and randomized. Fourteen subjects completed the study. An audit of eight enrolled subjects' records was conducted.

The inspection evaluated the following documents: source records, screening and enrollment logs, case report forms, study drug accountability logs, study monitoring visits, and correspondence. Informed consent documents and sponsor-generated correspondence were also inspected.

b. General observations/commentary:

Source documents for those enrolled subjects whose records were reviewed were verified against the case report forms and NDA subject line listings. Source documents for the raw data used to assess the primary study endpoint were verifiable at the study site. No under-reporting of adverse events or serious adverse events was noted. There were no limitations during conduct of the clinical site inspection.

In general, this clinical site appeared to be in compliance with Good Clinical Practices. A Form FDA 483 (List of Inspectional Observations) was not issued at the end of the inspection.

c. Assessment of data integrity:

Data submitted by this clinical site appear acceptable in support of this specific indication.

SPONSOR

5. Celltrion, Inc.

Incheon, South Korea

a. What was inspected:

The inspection was conducted from April 6-10, 2015. The inspection evaluated the following: documents related to study monitoring visits and correspondence, Institutional Review Board (IRB) approvals, completed Form FDA 1572s, monitoring reports, drug accountability, and training of staff and site monitors.

b. General observations/commentary:

The sponsor generally maintained adequate oversight of the clinical trial. For the most part, monitoring of the investigator sites was adequate. There was no evidence of under-reporting of adverse events. A single noncompliant site was found, Site 2101 (Jaller-Raad Juan, M.D.), but the sponsor properly reported this previously to the Agency.

A Form FDA 483 was not issued at the end of the sponsor inspection.

c. Assessment of data integrity:

The sponsor monitoring of sites appeared to be reliable. Data submitted by this sponsor appear acceptable in support of the requested indication.

III. OVERALL ASSESSMENT OF FINDINGS AND GENERAL RECOMMENDATIONS

Two adequate and well-controlled clinical trials (CT-P13 1.1 and CT-P13 3.1) were submitted in support of the applicant's NDA. Four foreign clinical study sites (Dr. Miranda, Dr. Hrycaj, Dr. Jeka and Dr. Jaworski) were selected for audit. The Sponsor (Celltrion, Inc.) was also inspected for this biosimilar [351(k)] application.

The classification for Drs. Hrycaj and Jaworski is No Action Indicated (NAI). The preliminary classification for Dr. Jeka and the sponsor, Celltrion, is also No Action Indicated (NAI). The preliminary classification of Dr. Miranda is Voluntary Action Indicated (VAI). It is recommended that the review team considers doing sensitivity analyses with a set of plausible possibilities for the data from Dr. Miranda's site because of inadequate investigational drug accountability and preparation records (study drug disposition records with respect to dates, quantity and subject use) in several subjects.

Note: The inspectional observations for Dr. Jeka and the sponsor, Celltrion, are based on preliminary communications with the field investigator. A clinical inspection summary addendum will be generated if conclusions on the current inspection report change significantly, upon receipt and review of the Establishment Inspection Report (EIR). The CDER OSI classification of inspection is finalized when written correspondence is issued to the inspected entity.

{See appended electronic signature page}

Anthony Orenca, M.D.
Medical Officer
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ANTHONY J ORENCIA
05/07/2015

JANICE K POHLMAN
05/07/2015

KASSA AYALEW
05/07/2015

LABEL AND LABELING REVIEW

Division of Medication Error Prevention and Analysis (DMEPA)
Office of Medication Error Prevention and Risk Management (OMEPRM)
Office of Surveillance and Epidemiology (OSE)
Center for Drug Evaluation and Research (CDER)

***** This document contains proprietary information that cannot be released to the public*****

Date of This Review:	May 4, 2015
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 125544
Product Name and Strength:	Inflectra (“CT-P13” *) For Injection 100 mg per vial
Product Type:	Single Ingredient Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Celltrion
Submission Date:	August 8, 2014
OSE RCM #:	2014-1728
DMEPA Primary Reviewer:	Teresa McMillan, PharmD
DMEPA Associate Director:	Lubna Merchant, MS, PharmD

* Inflectra has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Since the core name for Inflectra has not yet been determined, “CT-P13” is used throughout this review as the nonproprietary name for this product.

1 REASON FOR REVIEW

This review responds to a request from the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) to evaluate the proposed Prescribing Information (PI), carton labeling, and container labels for Inflectra (“CT-P13” *) BLA 125544, for areas of vulnerability that could lead to medication errors.

2 MATERIALS REVIEWED

We considered the materials listed in Table 1 for this review. The Appendices provide the methods and results for each material reviewed.

Material Reviewed	Appendix Section (for Methods and Results)
Product Information/Prescribing Information	A
Previous DMEPA Reviews	B
Human Factors Study	C-N/A
ISMP Newsletters	D-N/A
FDA Adverse Event Reporting System (FAERS)*	E
Other	F-N/A
Labels and Labeling	G

N/A=not applicable for this review

*We do not typically search FAERS for label and labeling reviews unless we are aware of medication errors through our routine postmarket safety surveillance

3 OVERALL ASSESSMENT OF THE MATERIALS REVIEWED

Our FAERS search did not identify any medication error cases that were relevant to this review and could be addressed by label and labeling revisions. However, a review of the proposed labels and labeling did identify potential areas of confusion.

4 CONCLUSION & RECOMMENDATIONS

We note that the proposed label and labeling reference the proprietary name (b) (4) the Applicant informed us on February 10, 2015 that they intend to market this product with the proprietary name Inflectra.

In addition, we concur with the label and labeling comments from the Office of Biotechnology Products (OBP). We recommend the following be implemented prior to approval of this BLA:

* Inflectra has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Since the core name for Inflectra has not yet been determined, “CT-P13” is used throughout this review as the nonproprietary name for this product.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

Remove all instances of the proprietary name “^{(b) (4)}” and replace with the proprietary name “Inflectra”.

4.2 RECOMMENDATIONS FOR CELLTRION

A. All labels and labeling

Remove all instances of the proprietary name “^{(b) (4)}” and replace with the proprietary name “Inflectra”.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Inflectra that Celltrion submitted on August 8, 2014.

Table 2. Relevant Product Information for Inflectra	
Initial Approval Date	N/A
Active Ingredient	("CT-P13" *)
Indication	Treatment of Crohn's Disease, Rheumatoid Arthritis, Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Ankylosing Spondylitis, Psoriatic Arthritis, and Plaque Psoriasis
Route of Administration	Intravenous
Dosage Form	Injection
Strength	100 mg after reconstitution 10 mg/mL
Dose and Frequency	<p>Crohn's Disease</p> <ul style="list-style-type: none"> ○ 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some adult patients who initially respond to treatment may benefit from increasing the dose to 10 mg/kg if they later lose their response. <p>Pediatric Crohn's Disease, Ulcerative Colitis, Pediatric Ulcerative Colitis, Ankylosing Spondylitis, Psoriatic Arthritis and Plaque Psoriasis</p> <ul style="list-style-type: none"> ○ 5 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. <p>Rheumatoid Arthritis</p> <ul style="list-style-type: none"> ○ In conjunction with methotrexate, 3 mg/kg at 0, 2 and 6 weeks, then every 8 weeks. Some patients may benefit from increasing the dose up to 10 mg/kg or treating as often as every 4 weeks.

* Inflectra has been developed as a proposed biosimilar to US-licensed Remicade (infliximab). Since the core name for Inflectra has not yet been determined, "CT-P13" is used throughout this review as the nonproprietary name for this product.

How Supplied	Each 20 mL vial is individually packaged in a carton. An accumulator carton contains 10 vials.
Storage	Refrigerated at 2°C to 8°C

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On March 31, 2015, we searched the L:drive and AIMS using the terms, Remicade and Infliximab to identify reviews previously performed by DMEPA.

B.2 Results

Our search identified 3 previous reviews¹. The recommendations noted in these review were for Remicade and have been implemented. In addition, we note that the proposed Inflectra labels and labeling are similar to the Remicade labels and labeling.

¹ McMillan,T Label and Labeling Review for Remicade . Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2012 April 17. 8 p. OSE RCM No.: 2012-599.

Tu, A. Label and Labeling Review for Remicade . Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2011 June 1. 32 p. OSE RCM No.: 2011-1269.

Wisniewski,L. Label and Labeling Review for Remicade . Silver Spring (MD): Food and Drug Administration, Center for Drug Evaluation and Research, Office of Surveillance and Epidemiology, Division of Medication Error Prevention and Analysis (US); 2006 August 31. 4 p. OSE RCM No.: 06-0219.

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

E.1 Methods

We searched the FDA Adverse Event Reporting System (FAERS) on March 31, 2015 using the criteria in Table 3, and then individually reviewed each case. We limited our analysis to cases that described errors possibly associated with the label and labeling. We used the NCC MERP Taxonomy of Medication Errors to code the type and factors contributing to the errors when sufficient information was provided by the reporter²

Date Range	May 3, 2011-March 31, 2015 Dated from the last Remicade FAERS search in OSE Review #2011-1269
Product	Infliximab [active ingredient] Remicade [product name]
Event (MedDRA Terms)	DMEPA Official FBIS Search Terms Event List: Medication Errors [HLGT] Product Packaging Issues [HLT] Product Label Issues [HLT] Product Adhesion Issue [PT] Product Compounding Quality Issue [PT] Product Difficult to Remove [PT] Product Formulation Issue [PT] Product Substitution Issue [PT] Inadequate (b) (4) Technique in Use of Product [PT]

E.2 Results

Our search retrieved 206 cases, but after further evaluation, we didn't identify any medication error cases that were relevant for this review and could be addressed by labels and labeling revisions.

² The National Coordinating Council for Medication Error Reporting and Prevention (NCC MERP) Taxonomy of Medication Errors. Website <http://www.nccmerp.org/pdf/taxo2001-07-31.pdf>.

E.3 List of FAERS Case Numbers

Below is a list of the FAERS case number and manufacturer control numbers for the cases relevant for this review.

N/A

E.4 Description of FAERS

The FDA Adverse Event Reporting System (FAERS) is a database that contains information on adverse event and medication error reports submitted to FDA. The database is designed to support the FDA's postmarket safety surveillance program for drug and therapeutic biologic products. The informatic structure of the FAERS database adheres to the international safety reporting guidance issued by the International Conference on Harmonisation. FDA's Office of Surveillance and Epidemiology codes adverse events and medication errors to terms in the Medical Dictionary for Regulatory Activities (MedDRA) terminology. Product names are coded using the FAERS Product Dictionary. More information about FAERS can be found at:

<http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm>.

APPENDIX G. LABELS AND LABELING

G.1 List of Labels and Labeling Reviewed

Using the principles of human factors and Failure Mode and Effects Analysis,³ along with postmarket medication error data, we reviewed the following Inflectra labels and labeling submitted by Celltrion on August 8, 2014.

- Container label
- Carton labeling

G.2 Label and Labeling Images

Carton Labeling (1-count vial)

3 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

³ Institute for Healthcare Improvement (IHI). Failure Modes and Effects Analysis. Boston. IHI:2004.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

TERESA S MCMILLAN
05/04/2015

LUBNA A MERCHANT
05/04/2015

M E M O R A N D U M

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: February 18, 2015

TO: Badrul Chowdhury, M.D., Ph.D.
Director, Division of Pulmonary, Allergy, and
Rheumatology Products
Office of Drug Evaluation II

FROM: Seongeun (Julia) Cho, Ph.D.
Division of New Drug Bioequivalence Evaluation (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Kara Scheibner, Ph.D.
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

THROUGH: Chuck Bonapace, Pharm.D.
Acting Director
Division of New Drug Bioequivalence (DNDBE)
Office of Study Integrity and Surveillance (OSIS)

Sam H. Haidar, Ph.D., R.Ph.
Acting Director
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance (OSIS)

SUBJECT: Review of bioanalytical establishment inspection report
(EIR) covering BLA 125544, CT-P13, from Celltrion Inc.

The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested the Office of Study Integrity and Surveillance (OSIS) to conduct inspections of the clinical and analytical portions of the following study:

Study CT-P13 1.4: A Randomized, Double-blind, Three-arm, Parallel Group, Single dose Study to Compare the Pharmacokinetics, Safety, Tolerability, and Immunogenicity of Three Formulations of Infliximab (CT-P13, EU Sourced Remicade and US Sourced Remicade) in Healthy Subjects

Clinical Site: PAREXEL Early Phase Clinical Unit
Berlin, Germany

Analytical Site: [REDACTED] (b) (4)

This memo provides a review of the bioanalytical inspection only. Inspection of the clinical site is pending at the time of this review, and a separate memo will be provided when the clinical inspection report becomes available.

Inspection of the bioanalytical portions of the study was conducted by [REDACTED] (b) (4)

[REDACTED] The audit covered a thorough review of study records and the method validation for measurements of infliximab, anti-drug antibody (ADA), and neutralizing anti-drug antibody (NAB). All records associated with the study were reviewed, including paper documentation and electronic archives.

At the time of application submission, stability of the frozen plasma sample was available only up to 26 days of storage at -70°C. To provide stability covering the maximum storage duration of 126 days between the sample collection and the final sample analysis, [REDACTED] (b) (4) conducted additional long term plasma stability testing. During the inspection, [REDACTED] (b) (4) provided a copy of validation addenda including the updated stability results. In addition, [REDACTED] (b) (4) indicated that the addenda would be sent to the sponsor Celltrion for formal submission to the Agency.

At the conclusion of the inspection, no Form FDA-483 was issued.

Conclusion:

Based on the inspectional outcome, we conclude that the bioanalytical portions of Study CT-P13 1.4 are acceptable for Agency review. The OCP reviewers should consider results of the long term frozen plasma stability study in their review.

[REDACTED] (b) (4)

Final Classification:

NAI: [REDACTED] (b) (4)

CC: [REDACTED] (b) (4)

Draft: SC 2/18/2015, KS 2/18/2015

Edit: MFS 2/18/2015; SHH 2/21/2015

OSI: BE 6766

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical
Sites [REDACTED] (b) (4)

FACTS: [REDACTED] (b) (4)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

KARA A SCHEIBNER
02/23/2015

SEONGEUN CHO
02/23/2015

CHARLES R BONAPACE
02/23/2015

SAM H HAIDAR
02/23/2015

RPM FILING REVIEW

(Including Memo of Filing Meeting)

To be completed for all new NDAs, BLAs, and Efficacy Supplements [except SE8 (labeling change with clinical data) and SE9 (manufacturing change with clinical data)]

Application Information		
NDA # BLA# 125544	NDA Supplement #:S- BLA Supplement #	Efficacy Supplement Type SE-
Proprietary Name: (b) (4) (pending DMEPA's review) Established/Proper Name: Infliximab Dosage Form: IV Strengths: 100 mg of lyophilized infliximab in a 20 mL vial		
Applicant: Celltrion, Inc. Agent for Applicant: Parexel International		
Date of Application: August 8, 2014 Date of Receipt: August 8, 2014 Date clock started after UN: N/A		
PDUFA Goal Date: June 8, 2015		Action Goal Date (if different): June 1, 2015
Filing Date: October 7, 2014		Date of Filing Meeting: September 29, 2014
Chemical Classification: (1,2,3 etc.) (original NDAs only) N/A		
Proposed indications: Crohn's Disease (CD), Pediatric Crohn's Disease, Ulcerative Colitis (UC), Pediatric Ulcerative Colitis, Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), and Plaque Psoriasis (Ps)		
Type of Original NDA: AND (if applicable)	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of NDA Supplement: <i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at: http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499.</i>	<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)	
Type of BLA	<input type="checkbox"/> 351(a) <input checked="" type="checkbox"/> 351(k)	
<i>If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team</i>		
Review Classification: <i>If the application includes a complete response to pediatric WR, review classification is Priority.</i> <i>If a tropical disease priority review voucher or pediatric rare disease priority review voucher was submitted, review classification is Priority.</i>	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority <input type="checkbox"/> Tropical Disease Priority Review Voucher submitted <input type="checkbox"/> Pediatric Rare Disease Priority Review Voucher submitted	
Resubmission after withdrawal? <input type="checkbox"/> N/A	Resubmission after refuse to file? <input type="checkbox"/> N/A	
Part 3 Combination Product? <input type="checkbox"/> <i>If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults</i>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Pre-filled biologic delivery device/system (syringe, patch, etc.) <input type="checkbox"/> Device coated/impregnated/combined with drug <input type="checkbox"/> Device coated/impregnated/combined with biologic <input type="checkbox"/> Separate products requiring cross-labeling <input type="checkbox"/> Drug/Biologic <input type="checkbox"/> Possible combination based on cross-labeling of separate products <input type="checkbox"/> Other (drug/device/biological product)	

<input type="checkbox"/> Fast Track Designation <input type="checkbox"/> Breakthrough Therapy Designation <i>(set the submission property in DARRTS and notify the CDER Breakthrough Therapy Program Manager)</i> <input type="checkbox"/> Rolling Review <input type="checkbox"/> Orphan Designation <input type="checkbox"/> Rx-to-OTC switch, Full <input type="checkbox"/> Rx-to-OTC switch, Partial <input type="checkbox"/> Direct-to-OTC Other:	<input type="checkbox"/> PMC response <input type="checkbox"/> PMR response: <input type="checkbox"/> FDAAA [505(o)] <input type="checkbox"/> PREA deferred pediatric studies [21 CFR 314.55(b)/21 CFR 601.27(b)] <input type="checkbox"/> Accelerated approval confirmatory studies (21 CFR 314.510/21 CFR 601.41) <input type="checkbox"/> Animal rule postmarketing studies to verify clinical benefit and safety (21 CFR 314.610/21 CFR 601.42)			
Collaborative Review Division (if OTC product): DGIEP and DDDP				
List referenced IND Number(s): 118135				
Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA and Action Goal dates correct in tracking system? <i>If no, ask the document room staff to correct them immediately. These are the dates used for calculating inspection dates.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are the proprietary, established/proper, and applicant names correct in tracking system? <i>If no, ask the document room staff to make the corrections. Also, ask the document room staff to add the established/proper name to the supporting IND(s) if not already entered into tracking system.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug)? <i>For NDAs/NDA supplements, check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at: http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm</i> <i>If no, ask the document room staff to make the appropriate entries.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Application Integrity Policy	YES	NO	NA	Comment
Is the application affected by the Application Integrity Policy (AIP)? <i>Check the AIP list at: http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes, explain in comment column.				
If affected by AIP, has OC/OMPQ been notified of the submission? If yes, date notified:	<input type="checkbox"/>	<input type="checkbox"/>		
User Fees	YES	NO	NA	Comment
Is Form 3397 (User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<p><u>User Fee Status</u></p> <p><i>If a user fee is required and it has not been paid (and it is not exempted or waived), the application is unacceptable for filing following a 5-day grace period. Review stops. Send Unacceptable for Filing (UN) letter and contact user fee staff.</i></p>	<p>Payment for this application:</p> <p><input checked="" type="checkbox"/> Paid <input type="checkbox"/> Exempt (orphan, government) <input type="checkbox"/> Waived (e.g., small business, public health) <input type="checkbox"/> Not required</p>																			
<p><i>If the firm is in arrears for other fees (regardless of whether a user fee has been paid for this application), the application is unacceptable for filing (5-day grace period does not apply). Review stops. Send UN letter and contact the user fee staff.</i></p>	<p>Payment of other user fees:</p> <p><input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears</p>																			
<p>505(b)(2) (NDAs/NDA Efficacy Supplements only)</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action is less than that of the reference listed drug (RLD)? [see 21 CFR 314.54(b)(1)].</p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is the application for a duplicate of a listed drug whose only difference is that the rate at which the proposed product's active ingredient(s) is absorbed or made available to the site of action is unintentionally less than that of the listed drug [see 21 CFR 314.54(b)(2)]?</p> <p><i>If you answered yes to any of the above questions, the application may be refused for filing under 21 CFR 314.101(d)(9). Contact the 505(b)(2) review staff in the Immediate Office of New Drugs</i></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>																	
<p>Is there unexpired exclusivity on any drug product containing the active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?</p> <p><i>Check the Electronic Orange Book at:</i> http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</p> <p>If yes, please list below:</p> <table border="1" data-bbox="203 1482 1349 1619"> <thead> <tr> <th>Application No.</th> <th>Drug Name</th> <th>Exclusivity Code</th> <th>Exclusivity Expiration</th> </tr> </thead> <tbody> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> <tr> <td> </td> <td> </td> <td> </td> <td> </td> </tr> </tbody> </table>	Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration													<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	<p><input type="checkbox"/></p>	
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration																	
<p><i>If there is unexpired, 5-year exclusivity remaining on the active moiety for the proposed drug product, a 505(b)(2) application cannot be submitted until the period of exclusivity expires (unless the applicant provides paragraph IV patent certification; then an application can be submitted four years after the date of approval.) Pediatric exclusivity will extend both of the timeframes in this provision by 6 months. 21 CFR 314.108(b)(2). Unexpired, 3-year exclusivity may block the approval but not the submission of a 505(b)(2) application.</i></p>																				
<p>Exclusivity</p>	<p>YES</p>	<p>NO</p>	<p>NA</p>	<p>Comment</p>																
<p>Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug</i></p>	<p><input checked="" type="checkbox"/></p>	<p><input type="checkbox"/></p>		<p>The Reference Product Remicade (Infliximab) has ODE</p>																

Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/oopd/index.cfm				for the pediatric ulcerative colitis indication
If another product has orphan exclusivity , is the product considered to be the same product according to the orphan drug definition of sameness [see 21 CFR 316.3(b)(13)]? <i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	Under section 351(h) of the PHS Act, if this product is found to be biosimilar to Remicade under section 351(k) of the PHS Act, it may not be licensed for any ODE-protected indication until the expiry of the ODE period for that indication
Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity? (<i>NDAs/NDA efficacy supplements only</i>) If yes, # years requested: <i>Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use (<i>NDAs only</i>)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes , did the applicant: (a) elect to have the single enantiomer (contained as an active ingredient) not be considered the same active ingredient as that contained in an already approved racemic drug, and/or (b): request exclusivity pursuant to section 505(u) of the Act (per FDAAA Section 1113)? <i>If yes, contact the Orange Book Staff (CDER-Orange Book Staff).</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For BLAs: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, OBP Biosimilars RPM</i> <i>Note: Exclusivity requests may be made for an original BLA submitted under Section 351(a) of the PHS Act (i.e., a biological reference product). A request may be located in Module 1.3.5.3 and/or other sections of the BLA and may be included in a supplement (or other correspondence) if exclusivity has not been previously requested in the original 351(a) BLA. An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

Format and Content	
<i>Do not check mixed submission if the only electronic component</i>	<input type="checkbox"/> All paper (except for COL) <input checked="" type="checkbox"/> All electronic

<i>is the content of labeling (COL).</i>	<input type="checkbox"/> Mixed (paper/electronic) <input checked="" type="checkbox"/> CTD <input type="checkbox"/> Non-CTD <input type="checkbox"/> Mixed (CTD/non-CTD)			
If mixed (paper/electronic) submission , which parts of the application are submitted in electronic format?				
Overall Format/Content	YES	NO	NA	Comment
If electronic submission , does it follow the eCTD guidance? ¹ If not , explain (e.g., waiver granted).	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Index : Does the submission contain an accurate comprehensive index?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the submission complete as required under 21 CFR 314.50 (NDAs/NDA efficacy supplements) or under 21 CFR 601.2 (BLAs/BLA efficacy supplements) including: <input checked="" type="checkbox"/> legible <input checked="" type="checkbox"/> English (or translated into English) <input checked="" type="checkbox"/> pagination <input checked="" type="checkbox"/> navigable hyperlinks (electronic submissions only) If no , explain.	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
BLAs only : Companion application received if a shared or divided manufacturing arrangement? If yes , BLA #	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Forms and Certifications				
<i>Electronic forms and certifications with electronic signatures (scanned, digital, or electronic – similar to DARRTS, e.g., /s/) are acceptable. Otherwise, paper forms and certifications with hand-written signatures must be included. Forms include: user fee cover sheet (3397), application form (356h), patent information (3542a), financial disclosure (3454/3455), and clinical trials (3674); Certifications include: debarment certification, patent certification(s), field copy certification, and pediatric certification.</i>				
Application Form	YES	NO	NA	Comment
Is form FDA 356h included with authorized signature per 21 CFR 314.50(a)? If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Are all establishments and their registration numbers listed on the form/attached to the form?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	

1

<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm072349.pdf>

Patent Information (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
Is patent information submitted on form FDA 3542a per 21 CFR 314.53(c)?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Financial Disclosure	YES	NO	NA	Comment
Are financial disclosure forms FDA 3454 and/or 3455 included with authorized signature per 21 CFR 54.4(a)(1) and (3)? <i>Forms must be signed by the APPLICANT, not an Agent [see 21 CFR 54.2(g)].</i> <i>Note: Financial disclosure is required for bioequivalence studies that are the basis for approval.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature? <i>If yes, ensure that the application is also coded with the supporting document category, "Form 3674."</i> <i>If no, ensure that language requesting submission of the form is included in the acknowledgement letter sent to the applicant</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Debarment Certification	YES	NO	NA	Comment
Is a correctly worded Debarment Certification included with authorized signature? <i>Certification is not required for supplements if submitted in the original application; If foreign applicant, <u>both</u> the applicant and the U.S. Agent must sign the certification [per Guidance for Industry: Submitting Debarment Certifications].</i> <i>Note: Debarment Certification should use wording in FD&C Act Section 306(k)(1) i.e., "[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as, "To the best of my knowledge..."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Field Copy Certification (NDAs/NDA efficacy supplements only)	YES	NO	NA	Comment
For paper submissions only: Is a Field Copy Certification (that it is a true copy of the CMC technical section) included? <i>Field Copy Certification is not needed if there is no CMC technical section or if this is an electronic submission (the Field Office has access to the EDR)</i> <i>If maroon field copy jackets from foreign applicants are received, return them to CDR for delivery to the appropriate field office.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Controlled Substance/Product with Abuse Potential	YES	NO	NA	Comment

<u>For NMEs:</u> Is an Abuse Liability Assessment, including a proposal for scheduling, submitted per 21 CFR 314.50(d)(5)(vii)? <i>If yes, date consult sent to the Controlled Substance Staff:</i> <u>For non-NMEs:</u> Date of consult sent to Controlled Substance Staff:	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
Pediatrics	YES	NO	NA	Comment
<u>PREA</u> Does the application trigger PREA? <i>If yes, notify PeRC RPM (PeRC meeting is required)²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration trigger PREA. All waiver & deferral requests, pediatric plans, and pediatric assessment studies must be reviewed by PeRC prior to approval of the application/supplement.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If the application triggers PREA , are the required pediatric assessment studies or a full waiver of pediatric studies included?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
If studies or full waiver not included , is a request for full waiver of pediatric studies OR a request for partial waiver and/or deferral with a pediatric plan included? <i>If no, request in 74-day letter</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If a request for full waiver/partial waiver/deferral is included , does the application contain the certification(s) required by FDCA Section 505B(a)(3) and (4)? <i>If no, request in 74-day letter</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<u>BPCA (NDAs/NDA efficacy supplements only):</u> Is this submission a complete response to a pediatric Written Request? <i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>	<input type="checkbox"/>	<input type="checkbox"/>		
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted? <i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	

² <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027829.htm>

³ <http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/PediatricandMaternalHealthStaff/ucm027837.htm>

<i>If yes, send consult to OSE/DRISK and notify OC/OSI/DSC/PMSB via the CDER OSI RMP mailbox</i>				
Prescription Labeling	<input type="checkbox"/> Not applicable			
Check all types of labeling submitted.	<input checked="" type="checkbox"/> Package Insert (PI) <input type="checkbox"/> Patient Package Insert (PPI) <input type="checkbox"/> Instructions for Use (IFU) <input checked="" type="checkbox"/> Medication Guide (MedGuide) <input checked="" type="checkbox"/> Carton labels <input checked="" type="checkbox"/> Immediate container labels <input type="checkbox"/> Diluent <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is Electronic Content of Labeling (COL) submitted in SPL format? <i>If no, request applicant to submit SPL before the filing date.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
Is the PI submitted in PLR format? ⁴	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
If PI not submitted in PLR format , was a waiver or deferral requested before the application was received or in the submission? If requested before application was submitted , what is the status of the request? <i>If no waiver or deferral, request applicant to submit labeling in PLR format before the filing date.</i>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling (PI, PPI, MedGuide, IFU, carton and immediate container labels) consulted to OPDP?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
MedGuide, PPI, IFU (plus PI) consulted to OSE/DRISK? (send WORD version if available)	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Carton and immediate container labels, PI, PPI sent to OSE/DMEPA and appropriate CMC review office (OBP or ONDQA)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
OTC Labeling	<input checked="" type="checkbox"/> Not Applicable			
Check all types of labeling submitted.	<input type="checkbox"/> Outer carton label <input type="checkbox"/> Immediate container label <input type="checkbox"/> Blister card <input type="checkbox"/> Blister backing label <input type="checkbox"/> Consumer Information Leaflet (CIL) <input type="checkbox"/> Physician sample <input type="checkbox"/> Consumer sample <input type="checkbox"/> Other (specify)			
	YES	NO	NA	Comment
Is electronic content of labeling (COL) submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

4

<http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/StudyEndpointsandLabelingDevelopmentTeam/ucm025576.htm>

<i>If no, request in 74-day letter.</i>				
Are annotated specifications submitted for all stock keeping units (SKUs)?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
If representative labeling is submitted, are all represented SKUs defined?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, request in 74-day letter.</i>				
All labeling/packaging, and current approved Rx PI (if switch) sent to OSE/DMEPA?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Other Consults	YES	NO	NA	Comment
Are additional consults needed? (e.g., IFU to CDRH; QT study report to QT Interdisciplinary Review Team)	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, specify consult(s) and date(s) sent:</i>				
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? BPD Type 3 meeting Date(s): July 10, 2013	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): April 28, 2014	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If yes, distribute minutes before filing meeting</i>				
Any Special Protocol Assessments (SPAs)? Date(s):	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, distribute letter and/or relevant minutes before filing meeting</i>				

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 29, 2014

BLA: 125544

PROPRIETARY NAME: (b) (4)

ESTABLISHED/PROPER NAME: Infliximab

DOSAGE FORM/STRENGTH: 100 mg of lyophilized infliximab in a 20 mL vial

APPLICANT: Celltrion, Inc.

PROPOSED INDICATIONS: Crohn’s Disease (CD), Pediatric Crohn’s Disease, Ulcerative Colitis (UC), Pediatric Ulcerative Colitis, Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), and Plaque Psoriasis (Ps)

BACKGROUND: Celltrion submitted a new biologic application for a proposed biosimilar to Remicade (infliximab) dated August 8, 2014. This application proposes all the indications approved for Remicade.

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Nina Ton	Y
	CPMS/TL:	Ladan Jafari	Y
Cross-Discipline Team Leader (CDTL)	Nikolay Nikolov		Y
Clinical	Reviewer:	Juwaria Waheed	Y
	TL:	Nikolay Nikolov	Y
Social Scientist Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
OTC Labeling Review (<i>for OTC products</i>)	Reviewer:		
	TL:		
Clinical Microbiology (<i>for antimicrobial products</i>)	Reviewer:		

Clinical Pharmacology	Reviewer:	Lei He	Y
	TL:	Satjit Brar	Y
Biostatistics	Reviewer:	Greg Levin	Y
	TL:	Ruthie Davi	Y
Nonclinical (Pharmacology/Toxicology)	Reviewer:	Matt Whittaker	Y
	TL:	Tim Robison	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Immunogenicity (assay/assay validation) (<i>for BLAs/BLA efficacy supplements</i>)	Reviewer:	Erik Read, Kurt Brorson	
	TL:		
Product Quality (CMC)	Reviewers:	Erik Read, Kurt Brorson	Y
	TL:	David Frucht	N
Quality Microbiology (<i>for sterile products</i>)	Reviewers:	Maria Candauchaon, Bo Chi	Y
	TL:	Patricia Hughes	Y
CMC Labeling Review	Reviewer:	Jibril Abdus-Samad	Y
	TL:		
Facility Review/Inspection	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name)	Reviewer:	Teresa Mcmillan	Y
	TL:	Lubna Merchant	N
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Anthony Orenca	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers	DGIEP – Rob Fiorentino		Y
	DDDP – David Kettl		Y
	CMC Stats – Meiyu Shen		Y
	PLT – Sharon Williams, Melissa Hulett		Y
	OPDP – Adewale Adeleye		Y
Other attendees	TBBT – Sue Lim, Carla Lankford, Neel Patel		Y
	Badrul Chowdhury		Y
	Sarah Yim		Y
	Mike Skelly		Y
	Janice Weiner		Y
	Marcie Wood		Y
	Ping Ji		Y
	Sara Stradley		Y
	Sarah Harris		Y
	Tamra Meyer		Y
	Maria Walsh		Y

FILING MEETING DISCUSSION:

<p>GENERAL</p> <ul style="list-style-type: none"> • 505(b)(2) filing issues: <ul style="list-style-type: none"> ○ Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? ○ Did the applicant provide a scientific “bridge” demonstrating the relationship between the proposed product and the referenced product(s)/published literature? <p>Describe the scientific bridge (e.g., BA/BE studies):</p> 	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> • Per reviewers, are all parts in English or English translation? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO

<ul style="list-style-type: none"> Electronic Submission comments <p>List comments:</p>	<input type="checkbox"/> Not Applicable
<p>CLINICAL</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical study site(s) inspections(s) needed? <p>If no, explain:</p>	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Advisory Committee Meeting needed? <p>Comments:</p> <p><i>If no, for an NME NDA or original BLA , include the reason. For example:</i></p> <ul style="list-style-type: none"> <i>this drug/biologic is not the first in its class</i> <i>the clinical study design was acceptable</i> <i>the application did not raise significant safety or efficacy issues</i> <i>the application did not raise significant public health questions on the role of the drug/biologic in the diagnosis, cure, mitigation, treatment or prevention of a disease</i> 	<input checked="" type="checkbox"/> YES Date if known: March 26 & 27, 2015 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<ul style="list-style-type: none"> Abuse Liability/Potential <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance? <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> YES <input type="checkbox"/> NO
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input checked="" type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

CLINICAL PHARMACOLOGY Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<ul style="list-style-type: none"> Clinical pharmacology study site(s) inspections(s) needed? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
BIOSTATISTICS Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
NONCLINICAL (PHARMACOLOGY/TOXICOLOGY) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
IMMUNOGENICITY (BLAs/BLA efficacy supplements only) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
PRODUCT QUALITY (CMC) Comments:	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<u>Environmental Assessment</u> <ul style="list-style-type: none"> Categorical exclusion for environmental assessment (EA) requested? If no, was a complete EA submitted? If EA submitted, consulted to EA officer (OPS)? Comments:	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<u>Quality Microbiology (for sterile products)</u>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> YES

<ul style="list-style-type: none"> Was the Microbiology Team consulted for validation of sterilization? (NDAs/NDA supplements only) <p>Comments:</p>	<input type="checkbox"/> NO
<p><u>Facility Inspection</u></p> <ul style="list-style-type: none"> Establishment(s) ready for inspection? Establishment Evaluation Request (EER/TBP-EER) submitted to OMPQ? <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO <input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<p><u>Facility/Microbiology Review (BLAs only)</u></p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter
<p><u>CMC Labeling Review</u></p> <p>Comments:</p>	<input type="checkbox"/> Review issues for 74-day letter
<p>APPLICATIONS IN THE PROGRAM (PDUFA V) (NME NDAs/Original BLAs)</p> <ul style="list-style-type: none"> Were there agreements made at the application's pre-submission meeting (and documented in the minutes) regarding certain late submission components that could be submitted within 30 days after receipt of the original application? If so, were the late submission components all submitted within 30 days? 	<input checked="" type="checkbox"/> N/A <input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> What late submission components, if any, arrived after 30 days? 	

<ul style="list-style-type: none"> Was the application otherwise complete upon submission, including those applications where there were no agreements regarding late submission components? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all clinical sites included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
<ul style="list-style-type: none"> Is a comprehensive and readily located list of all manufacturing facilities included or referenced in the application? 	<input checked="" type="checkbox"/> YES <input type="checkbox"/> NO
REGULATORY PROJECT MANAGEMENT	
<p>Signatory Authority: Badrul Chowdhury</p> <p>Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V): N/A</p> <p>21st Century Review Milestones (see attached) (listing review milestones in this document is optional):</p> <p>Comments:</p>	
REGULATORY CONCLUSIONS/DEFICIENCIES	
<input type="checkbox"/>	The application is unsuitable for filing. Explain why:
<input checked="" type="checkbox"/>	The application, on its face, appears to be suitable for filing. <u>Review Issues:</u> <input checked="" type="checkbox"/> No review issues have been identified for the 74-day letter. <input type="checkbox"/> Review issues have been identified for the 74-day letter. List (optional): <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTIONS ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into tracking system (e.g., chemical classification, combination product classification, 505(b)(2), orphan drug).
<input type="checkbox"/>	If RTF, notify everybody who already received a consult request, OSE PM, and Product

	Quality PM (to cancel EER/TBP-EER).
<input type="checkbox"/>	If filed, and the application is under AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
<input type="checkbox"/>	BLA/BLA supplements: If filed, send 60-day filing letter
<input type="checkbox"/>	If priority review: <ul style="list-style-type: none"> • notify sponsor in writing by day 60 (For BLAs/BLA supplements: include in 60-day filing letter; For NDAs/NDA supplements: see CST for choices) • notify OMPQ (so facility inspections can be scheduled earlier)
<input checked="" type="checkbox"/>	Send review issues/no review issues by day 74
<input type="checkbox"/>	Conduct a PLR format labeling review and include labeling issues in the 74-day letter
<input type="checkbox"/>	Update the PDUFA V DARRTS page (for NME NDAs in the Program)
<input type="checkbox"/>	BLA/BLA supplements: Send the Product Information Sheet to the product reviewer and the Facility Information Sheet to the facility reviewer for completion. Ensure that the completed forms are forwarded to the CDER RMS-BLA Superuser for data entry into RMS-BLA one month prior to taking an action [These sheets may be found in the CST eRoom at: http://eroom.fda.gov/eRoom/CDER2/CDERStandardLettersCommittee/0_1685f]
<input type="checkbox"/>	Other

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHUONG N TON
10/21/2014

LADAN JAFARI
10/21/2014

REGULATORY PROJECT MANAGER PHYSICIAN'S LABELING RULE (PLR) FORMAT REVIEW OF THE PRESCRIBING INFORMATION

Complete for all new NDAs, BLAs, Efficacy Supplements, and PLR Conversion Labeling Supplements

Application: 125544

Application Type: New BLA

Name of Drug/Dosage Form: Infliximab Lyophilized Concentrate for Injection, for Intravenous Use

Applicant: Celltrion, Inc.

Receipt Date: August 8, 2014

Goal Date: June 8, 2014

1. Regulatory History and Applicant's Main Proposals

Celltrion submitted a new biologic application for a proposed biosimilar to Remicade (infliximab) dated August 8, 2014. This application proposes all the indications approved for Remicade: Crohn's Disease (CD), Pediatric Crohn's Disease, Ulcerative Colitis (UC), Pediatric Ulcerative Colitis, Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA), and Plaque Psoriasis (Ps). In this new application, the Sponsor submitted the prescribing information, medication guide, and carton and container labels.

2. Review of the Prescribing Information

This review is based on the applicant's submitted Word format of the prescribing information (PI). The applicant's proposed PI was reviewed in accordance with the labeling format requirements listed in the "Selected Requirements for Prescribing Information (SRPI)" checklist (see the Appendix).

3. Conclusions/Recommendations

SRPI format deficiencies were identified in the review of this PI. For a list of these deficiencies see the Appendix.

All SRPI format deficiencies of the PI will be conveyed to the applicant in the 74-day letter. The applicant will be asked to correct these deficiencies and resubmit the PI in Word format by November 12, 2014. The resubmitted PI will be used for further labeling review.

Appendix

The Selected Requirement of Prescribing Information (SRPI) is a 42-item, drop-down checklist of important format elements of the prescribing information (PI) based on labeling regulations (21 CFR 201.56 and 201.57) and guidances.

Selected Requirements of Prescribing Information

Highlights

See Appendix A for a sample tool illustrating the format for the Highlights.

HIGHLIGHTS GENERAL FORMAT

- YES** 1. Highlights (HL) must be in a minimum of 8-point font and should be in two-column format, with ½ inch margins on all sides and between columns.

Comment:

- NO** 2. The length of HL must be one-half page or less unless a waiver has been granted in a previous submission. The HL Boxed Warning does not count against the one-half page requirement. Instructions to complete this item: If the length of the HL is one-half page or less, select “YES” in the drop-down menu because this item meets the requirement. However, if HL is longer than one-half page, select “NO” unless a waiver has been granted.

Comment: Sponsor submitted a half page waiver request

- NO** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.

Comment:

- NO** 4. All headings in HL must be **bolded** and presented in the center of a horizontal line (each horizontal line should extend over the entire width of the column as shown in Appendix A). The headings should be in UPPER CASE letters.

Comment: One horizontal line does not extend over the entire width of the column.

- NO** 5. White space should be present before each major heading in HL. There must be no white space between the HL Heading and HL Limitation Statement. There must be no white space between the product title and Initial U.S. Approval. See Appendix A for a sample tool illustrating white space in HL.

Comment: Add white space before each major heading in HL and delete the white space after each major heading in HL.

- YES** 6. Each summarized statement or topic in HL must reference the section(s) or subsection(s) of the Full Prescribing Information (FPI) that contain more detailed information. The preferred format is the numerical identifier in parenthesis [e.g., (1.1)] at the end of each summarized statement or topic.

Comment:

- YES** 7. Section headings must be presented in the following order in HL:

Section	Required/Optional
• Highlights Heading	Required
• Highlights Limitation Statement	Required
• Product Title	Required
• Initial U.S. Approval	Required
• Boxed Warning	Required if a BOXED WARNING is in the FPI
• Recent Major Changes	Required for only certain changes to PI*
• Indications and Usage	Required
• Dosage and Administration	Required
• Dosage Forms and Strengths	Required
• Contraindications	Required (if no contraindications must state “None.”)

Selected Requirements of Prescribing Information

• Warnings and Precautions	Not required by regulation, but should be present
• Adverse Reactions	Required
• Drug Interactions	Optional
• Use in Specific Populations	Optional
• Patient Counseling Information Statement	Required
• Revision Date	Required

* RMC only applies to the BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS sections.

Comment:

HIGHLIGHTS DETAILS

Highlights Heading

- YES** 8. At the beginning of HL, the following heading must be **bolded** and should appear in all UPPER CASE letters: **“HIGHLIGHTS OF PRESCRIBING INFORMATION”**.

Comment:

Highlights Limitation Statement

- YES** 9. The **bolded** HL Limitation Statement must include the following verbatim statement: **“These highlights do not include all the information needed to use (insert name of drug product) safely and effectively. See full prescribing information for (insert name of drug product).”** The name of drug product should appear in UPPER CASE letters.

Comment:

Product Title in Highlights

- YES** 10. Product title must be **bolded**.

Comment:

Initial U.S. Approval in Highlights

- YES** 11. Initial U.S. Approval in HL must be **bolded**, and include the verbatim statement **“Initial U.S. Approval:”** followed by the **4-digit year**.

Comment:

Boxed Warning (BW) in Highlights

- YES** 12. All text in the BW must be **bolded**.

Comment:

- YES** 13. The BW must have a heading in UPPER CASE, containing the word **“WARNING”** (even if more than one warning, the term, **“WARNING”** and not **“WARNINGS”** should be used) and other words to identify the subject of the warning (e.g., **“WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE”**). The BW heading should be centered.

Comment:

- YES** 14. The BW must always have the verbatim statement **“See full prescribing information for complete boxed warning.”** This statement should be centered immediately beneath the heading and appear in *italics*.

Comment:

Selected Requirements of Prescribing Information

- YES** 15. The BW must be limited in length to 20 lines (this includes white space but does not include the BW heading and the statement “*See full prescribing information for complete boxed warning.*”).

Comment:

Recent Major Changes (RMC) in Highlights

- N/A** 16. RMC pertains to only the following five sections of the FPI: BOXED WARNING, INDICATIONS AND USAGE, DOSAGE AND ADMINISTRATION, CONTRAINDICATIONS, and WARNINGS AND PRECAUTIONS. RMC must be listed in the same order in HL as the modified text appears in FPI.

Comment:

- N/A** 17. The RMC must include the section heading(s) and, if appropriate, subsection heading(s) affected by the recent major change, together with each section’s identifying number and date (month/year format) on which the change was incorporated in the PI (supplement approval date). For example, “Warnings and Precautions, Acute Liver Failure (5.1) --- 9/2013”.

Comment:

- N/A** 18. The RMC must list changes for at least one year after the supplement is approved and must be removed at the first printing subsequent to one year (e.g., no listing should be one year older than revision date).

Comment:

Indications and Usage in Highlights

- YES** 19. If a product belongs to an established pharmacologic class, the following statement is required under the Indications and Usage heading in HL: “(Product) is a (name of established pharmacologic class) indicated for (indication)”.

Comment:

Dosage Forms and Strengths in Highlights

- N/A** 20. For a product that has several dosage forms (e.g., capsules, tablets, and injection), bulleted subheadings or tabular presentations of information should be used under the Dosage Forms and Strengths heading.

Comment:

Contraindications in Highlights

- YES** 21. All contraindications listed in the FPI must also be listed in HL or must include the statement “None” if no contraindications are known. Each contraindication should be bulleted when there is more than one contraindication.

Comment:

Adverse Reactions in Highlights

Selected Requirements of Prescribing Information

- YES** 22. For drug products other than vaccines, the verbatim **bolded** statement must be present: “**To report SUSPECTED ADVERSE REACTIONS, contact (insert name of manufacturer) at (insert manufacturer’s U.S. phone number) or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch**”.

Comment:

Patient Counseling Information Statement in Highlights

- YES** 23. The Patient Counseling Information statement must include one of the following three **bolded** verbatim statements that is most applicable:

If a product **does not** have FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION**”

If a product **has** FDA-approved patient labeling:

- “**See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling**”
- “**See 17 for PATIENT COUNSELING INFORMATION and Medication Guide**”

Comment:

Revision Date in Highlights

- NO** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment: *The revision date is not right justified. Move the second page of HL to the right column of the page.*

Selected Requirements of Prescribing Information

Contents: Table of Contents (TOC)

See Appendix A for a sample tool illustrating the format for the Table of Contents.

- YES** 25. The TOC should be in a two-column format.
Comment:
- YES** 26. The following heading must appear at the beginning of the TOC: “**FULL PRESCRIBING INFORMATION: CONTENTS**”. This heading should be in all UPPER CASE letters and **bolded**.
Comment:
- YES** 27. The same heading for the BW that appears in HL and the FPI must also appear at the beginning of the TOC in UPPER CASE letters and **bolded**.
Comment:
- YES** 28. In the TOC, all section headings must be **bolded** and should be in UPPER CASE.
Comment:
- YES** 29. In the TOC, all subsection headings must be indented and not bolded. The headings should be in title case [first letter of all words are capitalized except first letter of prepositions (through), articles (a, an, and the), or conjunctions (for, and)].
Comment:
- YES** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment:
- YES** 31. In the TOC, when a section or subsection is omitted, the numbering must not change. If a section or subsection from 201.56(d)(1) is omitted from the FPI and TOC, the heading “FULL PRESCRIBING INFORMATION: CONTENTS” must be followed by an asterisk and the following statement must appear at the end of TOC: “*Sections or subsections omitted from the full prescribing information are not listed.”
Comment:

Selected Requirements of Prescribing Information

Full Prescribing Information (FPI)

FULL PRESCRIBING INFORMATION: GENERAL FORMAT

- YES** 32. The **bolded** section and subsection headings in the FPI must be named and numbered in accordance with 21 CFR 201.56(d)(1) as noted below (section and subsection headings should be in UPPER CASE and title case, respectively). If a section/subsection required by regulation is omitted, the numbering must not change. Additional subsection headings (i.e., those not named by regulation) must also be **bolded** and numbered.

BOXED WARNING
1 INDICATIONS AND USAGE
2 DOSAGE AND ADMINISTRATION
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
6 ADVERSE REACTIONS
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
8.2 Labor and Delivery
8.3 Nursing Mothers
8.4 Pediatric Use
8.5 Geriatric Use
9 DRUG ABUSE AND DEPENDENCE
9.1 Controlled Substance
9.2 Abuse
9.3 Dependence
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
12.2 Pharmacodynamics
12.3 Pharmacokinetics
12.4 Microbiology (by guidance)
12.5 Pharmacogenomics (by guidance)
13 NONCLINICAL TOXICOLOGY
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
13.2 Animal Toxicology and/or Pharmacology
14 CLINICAL STUDIES
15 REFERENCES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION

Comment:

- YES** 33. The preferred presentation for cross-references in the FPI is the section (not subsection) heading followed by the numerical identifier. The entire cross-reference should be in *italics* and enclosed within brackets. For example, “[*see Warnings and Precautions (5.2)*]” or “[*see Warnings and Precautions (5.2)*]”.

Comment:

Selected Requirements of Prescribing Information

- N/A** 34. If RMCs are listed in HL, the corresponding new or modified text in the FPI sections or subsections must be marked with a vertical line on the left edge.

Comment:

FULL PRESCRIBING INFORMATION DETAILS

FPI Heading

- YES** 35. The following heading must be **bolded** and appear at the beginning of the FPI: “**FULL PRESCRIBING INFORMATION**”. This heading should be in UPPER CASE.

Comment:

BOXED WARNING Section in the FPI

- YES** 36. In the BW, all text should be **bolded**.

Comment:

- YES** 37. The BW must have a heading in UPPER CASE, containing the word “**WARNING**” (even if more than one Warning, the term, “**WARNING**” and not “**WARNINGS**” should be used) and other words to identify the subject of the Warning (e.g., “**WARNING: SERIOUS INFECTIONS and ACUTE HEPATIC FAILURE**”).

Comment:

CONTRAINDICATIONS Section in the FPI

- N/A** 38. If no Contraindications are known, this section must state “None.”

Comment:

ADVERSE REACTIONS Section in the FPI

- YES** 39. When clinical trials adverse reactions data are included (typically in the “Clinical Trials Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.”

Comment:

- YES** 40. When postmarketing adverse reaction data are included (typically in the “Postmarketing Experience” subsection of ADVERSE REACTIONS), the following verbatim statement or appropriate modification should precede the presentation of adverse reactions:

“The following adverse reactions have been identified during post-approval use of (insert drug name). Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.”

Comment:

PATIENT COUNSELING INFORMATION Section in the FPI

- YES** 41. Must reference any FDA-approved patient labeling in Section 17 (PATIENT COUNSELING INFORMATION section). The reference should appear at the beginning of Section 17 and

Selected Requirements of Prescribing Information

include the type(s) of FDA-approved patient labeling (e.g., Patient Information, Medication Guide, Instructions for Use).

Comment:

- YES** 42. FDA-approved patient labeling (e.g., Medication Guide, Patient Information, or Instructions for Use) must not be included as a subsection under section 17 (PATIENT COUNSELING INFORMATION). All FDA-approved patient labeling must appear at the end of the PI upon approval.

Comment:

Selected Requirements of Prescribing Information

Appendix A: Format of the Highlights and Table of Contents

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use [DRUG NAME] safely and effectively. See full prescribing information for [DRUG NAME].

[DRUG NAME (nonproprietary name) dosage form, route of administration, controlled substance symbol]
Initial U.S. Approval: [year]

WARNING: [SUBJECT OF WARNING]

See full prescribing information for complete boxed warning.

- [text]
- [text]

RECENT MAJOR CHANGES

[section (X.X)] [m/year]
[section (X.X)] [m/year]

INDICATIONS AND USAGE

[DRUG NAME] is a [name of pharmacologic class] indicated for [text]

DOSAGE AND ADMINISTRATION

- [text]
- [text]

DOSAGE FORMS AND STRENGTHS

[text]

CONTRAINDICATIONS

- [text]
- [text]

WARNINGS AND PRECAUTIONS

- [text]
- [text]

ADVERSE REACTIONS

Most common adverse reactions (incidence > x%) are [text].

To report SUSPECTED ADVERSE REACTIONS, contact [name of manufacturer] at [phone #] or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

DRUG INTERACTIONS

- [text]
- [text]

USE IN SPECIFIC POPULATIONS

- [text]
- [text]

See 17 for PATIENT COUNSELING INFORMATION [and FDA-approved patient labeling OR and Medication Guide].

Revised: [m/year]

FULL PRESCRIBING INFORMATION: CONTENTS*

WARNING: [SUBJECT OF WARNING]

1 INDICATIONS AND USAGE

2 DOSAGE AND ADMINISTRATION

2.1 [text]

2.2 [text]

3 DOSAGE FORMS AND STRENGTHS

4 CONTRAINDICATIONS

5 WARNINGS AND PRECAUTIONS

5.1 [text]

5.2 [text]

6 ADVERSE REACTIONS

6.1 [text]

6.2 [text]

7 DRUG INTERACTIONS

7.1 [text]

7.2 [text]

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

8.2 Labor and Delivery

8.3 Nursing Mothers

8.4 Pediatric Use

8.5 Geriatric Use

9 DRUG ABUSE AND DEPENDENCE

9.1 Controlled Substance

9.2 Abuse

9.3 Dependence

10 OVERDOSAGE

11 DESCRIPTION

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

12.2 Pharmacodynamics

12.3 Pharmacokinetics

12.4 Microbiology

12.5 Pharmacogenomics

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

13.2 Animal Toxicology and/or Pharmacology

14 CLINICAL STUDIES

14.1 [text]

14.2 [text]

15 REFERENCES

16 HOW SUPPLIED/STORAGE AND HANDLING

17 PATIENT COUNSELING INFORMATION

*Sections or subsections omitted from the full prescribing information are not listed.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

PHUONG N TON
09/19/2014

LADAN JAFARI
09/19/2014