

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

761042Orig1s000

OTHER REVIEW(S)



FINAL LABEL AND LABELING REVIEW

Date:	August 29, 2016
Reviewer:	Jibril Abdus-Samad, PharmD, Labeling Reviewer Office of Biotechnology Products
Through:	Peter Adams, PhD, Quality Reviewer Division of Biotechnology Review and Research I
Application:	BLA 761042
Product:	Erelzi (etanercept-szzs*)
Applicant:	Sandoz Inc.
Submission Dates:	July 30 2015; August 23, 26 2016

Executive Summary:

The prescribing information (PI), Medication Guide (MG), Instructions for Use (IFU), container labels, and carton labeling for Erelzi (etanercept-szzs*) 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 and United States Pharmacopeia (USP), [USP 39/NF 34 August 1, 2016 to November 30, 2016]. Labeling deficiencies were identified and resolved. The PI, MG, IFU, container labels, and carton labeling submitted on August 26, 2016 are acceptable.

Background and Summary Description:

The Applicant, Sandoz, Inc. submitted a 351(k) BLA 761042/0 (etanercept-szzs*) on July 30, 2015 as a proposed biosimilar to US-licensed Enbrel (etanercept). Table 1 lists the proposed characteristics of Erelzi (etanercept-szzs*). This review evaluates the proposed labels and labeling submitted on July 30, 2015 ([Application 761042 - Sequence 0000 - 0000 \(1\) 07/30/2015 ORIG-1 /Multiple Categories/Subcategories](#)).

* Erelzi has been developed as a proposed biosimilar to US-licensed Enbrel (etanercept). Subsequent to submission of the 351(k) BLA, the nonproprietary name for Erelzi was determined to be etanercept-szzs.

Table 1: Proposed Product Characteristics of Erelzi (etanercept-szszs*).

Proprietary Name:	Erelzi
Proper Name:	etanercept-szszs*
Indication:	<ul style="list-style-type: none"> • Rheumatoid Arthritis (RA) • Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Plaque Psoriasis (PsO)
Dose:	<ul style="list-style-type: none"> • Adult RA and PsA: 50 mg once weekly with or without methotrexate • AS: 50 mg once weekly • Adult PsO: 50 mg twice weekly for 3 months, followed by 50 mg once weekly • JIA: 0.8 mg/kg weekly, with a maximum of 50 mg per wee
Route of Administration:	Subcutaneous Injection
Dosage Form:	Injection
Strength and Container-Closure:	25 mg/0.5 mL and 50 mg/mL prefilled syringe 50 mg/mL prefilled Sensoready Pen
Storage and Handling:	<ul style="list-style-type: none"> • Refrigerated at 36°F to 46°F (2°C to 8°C). DO NOT SHAKE. Store ERELZI in the original carton to protect from light or physical damage. • For convenience, storage of individual syringes or Sensoready Pens at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum single period of 28 days is permissible, with protection from light and sources of heat. Once a syringe or Sensoready Pen has been stored at room temperature, it should not be placed back into the refrigerator. If not used within 28 days at room temperature, the syringe or Sensoready Pens should be discarded. Do not store ERELZI in extreme heat or cold. DO NOT FREEZE. Keep out of the reach of children.

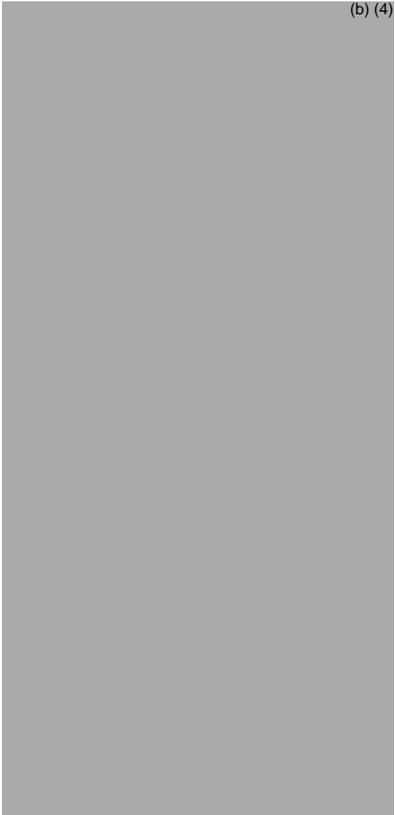
Materials Reviewed:

- PFS container label
- PFS blister foil labeling
- Sensoready Pen container label
- PFS Carton Labeling
- Sensoready Pen Carton Labeling

Start of Sponsor Material

PFS container label

(b) (4)



(b) (4)



End of Sponsor 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:

(1) The proper name of the product [see 21 CFR 600.3 (k) and section 351 of the PHS Act]; *does not conform.*

DMEPA communicated the nonproprietary name containing the distinguishing suffix, etanercept-szszs, will be the proper name designated in the license for this if this 351(k) BLA be approved and to revise the proposed labels and labeling accordingly.
Applicant revised as requested.

(2) The name, address, and license number of manufacturer; *conforms. However, we recommend the license number to appear with the name and address.*

Pen Label and Pen Blister Labeling

OBP Request: Relocate the license number from under the country of origin statement to appear directly under the licensed manufacturer information.

Manufactured by Sandoz Inc.
Princeton, NJ 08540
U.S. License No. 2003
At Novartis Pharma AG, Stein, Switzerland

Product of Austria

Applicant revised as requested.

(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; *conforms.*

(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.

PFS label does not conform.

OBP Requests:

DMEPA communicated the nonproprietary name containing the distinguishing suffix, etanercept-szszs, will be the proper name designated in the license for this if this 351(k) BLA be approved and to revise the proposed labels and labeling accordingly.

Applicant revised as requested.

On the lower peel off portion, the dosage form is inappropriately placed adjacent to the proper name. The dosage form for specified biological products should appear under the proper name. Therefore, switch the positions of the dosage form "Injection" and strength (e.g. 25 mg/0.5 mL). Alternatively, you can delete the dosage form "Injection" from the lower peel off portion of the label.

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; *conforms*.

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*.

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

E. 21CFR 201.10 Drugs; statement of ingredients; placement and prominence; *conforms*.

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

OBP Requests:

PFS Container Label

Revise [REDACTED]^{(b) (4)} to read "For Subcutaneous Use Only" on the PFS label.

Applicant revised as requested.

Pen Label and Pen Blister Labeling

Increase the prominence (e.g. bolding) of the route of administration statement "For Subcutaneous Use Only".

Applicant revised as requested.

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

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

OBP Request:

Pen Blister Labeling

Relocate the two-dimensional barcode away from the required linear barcode.

Applicant revised as requested.

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

J. 21 CFR 201.51 Declaration of net quantity of contents; *does not conform*.

OBP Requests: Revise [REDACTED]^{(b) (4)} to read "50 mg/mL" to comply with USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products.

Applicant revised as requested.

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

L. 21 CFR 201.100 Prescription drugs for human use; *conforms*. *The inactive ingredients appear on the carton labeling.*

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

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]; *does not conform.*

OBP Requests:

DMEPA communicated the nonproprietary name containing the distinguishing suffix, etanercept-szszs, will be the proper name designated in the license for this if this 351(k) BLA be approved and to revise the proposed labels and labeling accordingly.

Applicant revised as requested.

Revise the position of the dosage form "Injection" from adjacent to the proper name to appear under the proper name. The dosage form for specified biological products should appear under the proper name.

Applicant revised as requested.

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

OBP Requests: Revise [REDACTED]^{(b) (4)} to read "50 mg/mL" to comply with USP General Chapters: <1> Injections,

Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products.
Applicant revised as requested.

h) The recommended storage temperature; does not conform. The carton labeling lacks the room temperature storage instructions that appear in the prescribing information.

OBP Request: Revise the storage instructions to read:

Store refrigerated at 2°C to 8°C (36°F to 46°F) in the original carton to protect from light or physical damage. DO NOT FREEZE. DO NOT SHAKE.

For convenience, patients/caregivers may store individual syringes or Sensoready® Pens at room temperature between 68°F to 77°F (20°C to 25°C) for a maximum single period of 28 days in the original carton. Once stored at room temperature, do not place back in the refrigerator. Use within 28 days or discard. Do not store ERELZI above 77°F (25°C). DO NOT FREEZE.

Write the date removed from the refrigerator ___/___/___.
Applicant revised as requested.

- 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.*
- 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; *conforms. The labeling contains a natural rubber latex warning.*
- 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; *conforms*.
- 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*.

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)]. *Etanercept is a therapeutic recombinant DNA-derived product therefore exempt.*

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

D. 21 CFR 610.64 Name and address of distributor: *not applicable*.

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*.
- H. 21 CFR 201.6 Drugs; misleading statements; *conforms*.
- I. 21 CFR 201.10 Drugs; statement of ingredients [Placement and Prominence]; *conforms*.
- J. 21 CFR 201.15 Drugs; prominence of required label statements; *does not conform*.

OBP Requests:

We concur with DMEPA's recommendation to revise the colors to improve strength differentiation.

Applicant revised as requested.

Increase the prominence (e.g. bolding) of the route of administration statement "For Subcutaneous Use Only."

Applicant revised as requested.

Consider revising the schematic image of the PFS and Pen by utilizing a more realistic image or photo.

Applicant revised as requested.

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

OBP Requests: Revise "(b) (4)" to read "50 mg/mL" to comply with USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products.

Applicant revised as requested.

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

P. 21 CFR 201.100 Prescription drugs for human use; *conforms*.
However, we recommend the list of ingredients complies with USP <1091> Labeling of Inactive Ingredients.

OBP Requests:

Revise the list of ingredients by listing the inactive ingredients in alphabetical order to comply with USP <1091> Labeling of Inactive Ingredients. For example:

Each single-use prefilled syringe contains 25 mg etanercept, citric acid (0.393 mg), L-lysine HCl (2.3 mg), sodium chloride (0.75 mg), sodium citrate dihydrate (6.76 mg), sucrose (5 mg), hydrochloric acid and sodium hydroxide to adjust pH, Water for Injection, USP.

Applicant revised as requested.

Delete all trailing zeros (e.g. 1.50 mg to 1.5 mg) within the list of ingredients.

Applicant revised as requested.

Ensure the listing of ingredients on the carton labeling is consistent with the *Description and Composition of the Drug Product* submitted in the BLA.

Applicant revised as requested.

Prescribing Information

We provided the following revisions to the PI. The Applicant agreed to all the revisions.

A. Product Title:

1. We updated the product title with the dosage form per 21 CFR 201.57(a)(2). The dosage form for this product is "Injection" per USP General Chapters: <1> Injections, Nomenclature and Definitions. to comply with our best labeling practices to appear as **TRADE NAME (proper name) dosage form, route of administration,**

ERELZI (etanercept-szszs) injection, for subcutaneous use

B. Dosage Forms and Strengths (Highlights and section 3)

1. We revised this section to include the dosage form and identifying characteristics per 21 CFR 201.57(a)(8) and 21 CFR 201.57(c)(4). The dosage form for this product is "Injection" per USP General Chapters: <1> Injections, Nomenclature and Definitions.

Additionally, we ensured the strength presentation complies with USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products.

---DOSAGE FORMS AND STRENGTHS-----

- **Injection: 25 mg/0.5 mL and 50 mg/mL** solution in a single-dose prefilled syringe with BD UltraSafe Passive® Needle Guard (3)
- **Injection: 50 mg/mL** solution in single-dose prefilled Sensoready® Pen (3)

3 DOSAGE FORMS AND STRENGTHS

ERELZI is a clear and colorless to slightly yellow solution available as:

Injection: 25 mg/0.5 mL and 50 mg/mL solution in a single-dose prefilled syringe with BD UltraSafe Passive™ Needle Guard

Injection: 50 mg/mL solution in a single-dose prefilled Sensoready® Pen

C. Section 11 – Description

1. We revised this section to added the dosage form “Injection” and route of administration per 21 CFR 201.57(c)(12).

The solution of ERELZI (etanercept-szszs) **Injection** in the single-^{(b) (4)} prefilled syringe with BD UltraSafe Passive™ Needle Guard and the single-^{(b) (4)} prefilled Sensoready® Pen is clear and colorless to slightly yellowish, sterile, preservative-free, and is formulated at pH 6.3 ± 0.2. **ERELZI is for subcutaneous use.**

2. We revised the active ingredient description for consistency with the strength presentation.



D. Section 16 – How Supplied/Storage and Handling

1. We added the dosage form and identifying characteristics per 21 CFR 201.57(c)(17). Additionally, we updated the strength presentation per USP General Chapters: <1> Injections, Labels and Labeling, Labeling, Strength and Total Volume for Single- and Multiple-Dose Injectable Drug Products.

Each ERELZI (etanercept-szszs) **Injection** single-^{(b) (4)} prefilled syringe with BD UltraSafe Passive™ Needle Guard and ERELZI single-^{(b) (4)} prefilled Sensoready® Pen contains **clear and colorless to slightly yellow solution containing 25 mg/0.5 mL or 50 mg/mL** of etanercept-szszs in a single-dose syringe with a 27-gauge, ½-inch needle.

50 mg/mL single-^{(b) (4)} prefilled syringe

25 mg/0.5 mL single-^{(b) (4)} prefilled syringe

Medication Guide:

We concur with the Applicant adding citric acid to the list of ingredients to ensure consistency throughout labeling.

Instructions for Use:

We updated the strength presentation (25mg/0.5mL to **25 mg/0.5 mL**) with appropriate spacing. The Applicant agreed to this revision.

Conclusions:

The PI, MG, IFU, container labels and carton labeling for Erelzi (etanercept-szszs*) 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 and United States Pharmacopeia (USP), [USP 39/NF 34 August 1, 2016 to November 30, 2016]. Labeling deficiencies were identified and resolved. The PI, MG, IFU, container labels and carton labeling submitted on August 26, 2016 are acceptable (see below).

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



Jibril
Abdus-Samad

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Peter
Adams

Digitally signed by Peter Adams
Date: 8/30/2016 09:16:43AM
GUID: 508da6d8000263a9c010d3b058703747



DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
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Office of Drug Evaluation IV
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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: Tamara Johnson, M.D., M.S., Maternal Health Team
Leader
John Alexander, M.D., M.P.H, Deputy Director
Division of Pediatric and Maternal Health (DPMH),
Office of New Drugs

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

Drug: GP2015/Erelzi (proposed biosimilar to Enbrel
[etanercept])

Application Number: IND 114187/BLA 761042

Re: Review of the initial Pediatric Study Plan (iPSP) and
labeling for pregnancy, lactation and pediatric use

Sponsor: Sandoz, Inc.

Proposed Indications: Treatment of:

- Rheumatoid Arthritis (RA)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in
patients aged 2 years or older
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Plaque Psoriasis (PsO)

Proposed dosage forms

& route of administration: 50 mg single-use prefilled syringe for subcutaneous injection.

Proposed Dosing Regimen:

Adult RA and PsA

- 50 mg once weekly with or without methotrexate (MTX)

Adult AS

- 50 mg once weekly

Adult PsO

- 50 mg twice weekly for 3 months, followed by 50 mg once weekly

JIA in patients 2 years and older

- 0.8 mg/kg weekly, with a maximum of 50 mg per week

Consult Request: DPARP requests assistance in evaluating the sponsor's initial Pediatric Study Plan and preparing for the Pediatric Review Committee (PeRC) meeting. DPARP also requests assistance with labeling for pregnancy, lactation and pediatric use.

Materials Reviewed:

- GP2015 initial Pediatric Study Plan (July 28, 2014; November 26, 2014; April 2, 2015; June 9, 2015; and June 30, 2015)
- Division of Pediatric Maternal Health Staff (DPMH) consult request
- Current Enbrel (etanercept) labeling (March 25, 2016)
- Pediatric Review Committee (PeRC) Meeting Minutes (dated February 23, 2015 and May 14, 2015 in DARRTS)
- Sponsor's proposed labeling for GP2015, BLA 761042 (December 11, 2015)

Consult and Regulatory Background:

Sandoz, Inc. is developing GP2015 as a proposed biosimilar to Enbrel (etanercept) which is currently licensed by Amgen, Inc. and was first approved in 1998. Etanercept is a dimeric fusion protein consisting of a portion of the p75 tumor necrosis factor (TNF) receptor linked to a portion of human IgG1 antibody. Etanercept inhibits binding of TNF α and TNF- β to cell surface TNF receptors, rendering TNF biologically inactive.¹ TNF is a cytokine involved in inflammatory and immune responses, and elevated TNF levels also play a role in pathology of anti-inflammatory diseases.

Enbrel has the following indications for which Sandoz plans to seek approval: Rheumatoid Arthritis (RA), Ankylosing Spondylitis (AS), Psoriatic Arthritis (PsA) and Plaque Psoriasis (PsO). Pediatric study requirements for Enbrel for AS and PsA were fully waived because studies were determined to be impossible or highly impracticable (b) (4). Enbrel was granted orphan designation for juvenile RA (JRA) (currently referred to as juvenile idiopathic arthritis or JIA) on October 27, 1998 and was approved for RA on November 2, 1998. Although Enbrel was exempt from pediatric study requirements for RA as a result of the

¹ Current Enbrel (etanercept) labeling (March 25, 2016)

orphan status for this indication, the sponsor completed studies in patients 2 years and older and was approved for JIA in this population. The exclusivity for this indication has now expired. Finally, Enbrel was approved for plaque psoriasis in April 30, 2004 at which time a required post-marketing commitment (PMC) was issued to conduct studies for psoriasis in patients 4 to 17 years of age. Studies were completed in plaque psoriasis patients 4 to 17 years of age and submitted in an efficacy supplement on September 26, 2007. The completed studies were discussed at the Dermatologic and Ophthalmic Drugs Advisory Committee Meeting in June, 2008. The majority of the committee agreed that data presented demonstrated efficacy of etanercept in the pediatric population. However, there were concerns about longer term efficacy (>2 years) and risk of malignancy. The committee unanimously voted to approve Enbrel for pediatric patients with severe (but not mild or moderate) PsO. There was some concern over low numbers of pediatric patients 4 to 8 years of age. Though, the majority voted to approve in patients 4 to 17 years of age.

Despite a demonstration of efficacy, the Division of Dermatology and Dental Products (DDDP) elected not to label or grant an indication for PsO in pediatric patients for Enbrel [REDACTED] (b) (4). The division has decided that there is a negative risk/benefit profile with TNF inhibitors (Humira, Remicade and Enbrel) and the safety concerns outweigh the benefits in pediatrics; therefore, they have decided to waive pediatric studies for psoriasis due to safety concerns for TNF inhibitors. However, for newer interleukin antagonists, they have deferred studies 4 years and older pending safety information in adults because these agents appear to have more directed targets and a potentially safer profile.

DDDP released the sponsor from the pediatric study requirement due to safety concerns, and the PMC was determined to be fulfilled. Note that DDDP determined that a description of the studies were not required to be placed in labeling because the sponsor submitted the efficacy supplement just before the passage of the Food and Drug Administration Amendments Act (FDAAA) which requires the inclusion of information in labeling describing a concern for safety or ineffectiveness that resulted in a full or partial waiver. The current Enbrel labeling states “The safety and efficacy of Enbrel in pediatric patients with PsO have not been studied”. However, DPMH has recommended that this labeling be changed and a stronger warning against use for pediatric psoriasis be included.

Amgen, the sponsor for Enbrel, has since submitted a BLA on January 5, 2016 seeking approval for pediatric plaque psoriasis, which includes postmarketing data to support safe use of Enbrel for this indication in pediatric patients. The application is currently under review with a pending determination by November 5, 2016 [REDACTED] (b) (4)

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 GP2015, 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 GP2015 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. Sandoz submitted an iPSP on July 28, 2014 and 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 July 28, 2014, and determined that the sponsor did not address PREA for (b) (4). The sponsor proposed to demonstrate biosimilarity to Enbrel and extrapolate pediatric data from Enbrel based on their biosimilar development program for (b) (4).

DPARP advised the sponsor that their submission was materially incomplete and advised them to submit an iPSP which addresses PREA requirements for every indication for which they are seeking licensure. They were advised to consider the indications for which US-licensed Enbrel is licensed and where a justification for extrapolation across biological products (i.e., from the reference product to the proposed biosimilar product) could be provided in the context of their biosimilar development program. Additionally, recommendations to address PREA for each of Enbrel's licensed indications were provided. Accordingly, Sandoz resubmitted their iPSP on November 28, 2014. During the negotiations of the iPSP, Sandoz submitted several versions, and agreement was ultimately reached as discussed below. This agreed iPSP was also submitted with their BLA submission on July 30, 2015 without any changes.

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 Agency has partially waived studies in patients <2 years of age because the condition is rare in this age group and such studies would be highly impracticable. The pediatric assessment is complete for Enbrel for JIA for patients 2 to 17 years of age.

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 Enbrel (etanercept), “are not recommended for use in pediatric psoriasis” because of the risk of malignancy and infection.

The iPSP was reviewed by the PeRC on February 11, 2015 and April 29, 2015, and following with their concurrence, a non-agreed iPSP letter was issued on June 1, 2015,

[REDACTED] (b) (4)

[REDACTED]. The sponsor was advised that a proposed biosimilar product must demonstrate, among other things, that it has the same strength, dosage form, and route of administration as the reference product, and can only be licensed for a condition of use that has been previously approved for the reference product. FDA considers “injection” (e.g., a solution) to be a different dosage form from “for injection” (e.g., a lyophilized powder) in the context of proposed biosimilar products intended to be injected. (b) (4)

[REDACTED] The following plan regarding the iPSP and the approach to address PREA was ultimately agreed upon and conveyed in the agreed iPSP letter issued on July 16, 2016 as summarized in the table below:

Approved Indications	Pediatric Information in Package Insert Labeling for Enbrel	Recommendations for the Pediatric Study Plan	Notes
RA	Enbrel is indicated in pediatric patients for the treatment of JIA	The pediatric assessment is complete for patients 2 years and older. Demonstrate biosimilarity and extrapolate pediatric data from the reference product based on the biosimilar development program to fulfill PREA for patients 4 years and older.	The reference product’s orphan drug exclusivity for pediatric JIA has expired.

Approved Indications	Pediatric Information in Package Insert Labeling for Enbrel	Recommendations for the Pediatric Study Plan	Notes
		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.	
AS/PsA	Enbrel 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.	
PsO	Enbrel 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.	<p>Although labeling incorrectly states that the safety and efficacy of Enbrel in pediatric patients with PsO have not been studied, a pediatric study was conducted for plaque psoriasis in patients 4 -17 years of age. However, the Division elected not to label or award an indication (b) (4)</p> <p>(b) (4) For TNF products there is a negative risk/benefit profile and the safety concerns outweigh the benefits.</p> <p>FDA previously waived submission of pediatric studies by the BLA holder for Enbrel (b) (4)</p> <p>(b) (4) Postmarketing requirements for other TNFα 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.</p>

Sandoz submitted their BLA on July 30, 2015 with no changes to the pediatric plan. (b) (4)

(b) (4)

(b) (4) PeRC again reviewed and concurred with the pediatric plan as outlined above on March 9, 2016. The Agency ultimately agreed upon a product name of Erelzi.

Of note, DDDP's review of Enbrel's application for pediatric plaque PsO is currently ongoing. (b) (4)

(b) (4)
This approach was discussed and agreed upon with PeRC on August 17, 2016.

DPMH Review of labeling:

The DPMH labeling review will focus on edits to sections 1 and 2, and subsections 8.1 (Pregnancy), 8.3 (Nursing Mothers, now 8.2 [Lactation]) and 8.4 Pediatric Use.

Pregnancy and Lactation Labeling

On June 30, 2015, the “*Content and Format of Labeling for Human Prescription Drug and Biological Products; Requirements for Pregnancy and Lactation Labeling*,” also known as the Pregnancy and Lactation Labeling Rule (PLLR), went into effect. The PLLR requirements include a change to the structure and content of labeling for human prescription drug and biologic products with regard to pregnancy and lactation, and create a new subsection for information with regard to females and males of reproductive potential. Specifically, the pregnancy categories (A, B, C, D and X) will be removed from all prescription drug and biological product labeling and a new format is required for all products that are subject to the 2006 Physicians Labeling Rule format to include information about the risks and benefits of using these products during pregnancy and lactation.

Pediatric Use Labeling:

The Pediatric Use subsection must describe what is known and unknown about use of the drug in the pediatric population, including limitations of use, and must highlight any differences in efficacy or safety in the pediatric population versus the adult population. When substantial evidence does not exist to support a pediatric indication, all relevant pediatric information related to the unapproved use should be restricted to the Pediatric Use subsection only, to avoid an inference of an approved pediatric indication as required by 21 CFR 201.57(c)(9)(iv). This regulation describes the appropriate use statements to include in labeling based on findings of safety and effectiveness in the pediatric use population. The guidance also states that any negative or inconclusive pediatric studies

must be described in the Pediatric Use subsection, and the basis for the determination of safety and effectiveness in the pediatric population should also be provided (e.g., providing an explanation for why the available evidence does not support pediatric approval). (Also see draft Guidance for Industry and Review Staff Pediatric Information Incorporated Into Human Prescription Drug and Biological Products Labeling, February, 2013.)

See Appendix 1 for proposed applicant labeling for Erelzi dated December 11, 2015.

Discussion on Pregnancy and Lactation Labeling Recommendations:

PREGNANCY

(b) (4)
Developmental toxicity studies (b) (4) in rats and rabbits (b) (4) at doses ranging from 60- to 100-fold higher than the human dose revealed no evidence of harm to the fetus due to etanercept.

Review of Literature

The applicant provided a review and summary of all available published literature regarding etanercept use in pregnancy and lactation which identified 15 primary studies, 16 case reports, 27 reviews and commentaries and five abstracts. The review focused on primary studies and case reports only. Publications not directly related to etanercept in pregnancy or lactation were excluded, as were studies which looked at pregnancy outcomes with TNF- α inhibitors in general and not specifically with etanercept. The following is a summary of the relevant publications related to pregnancy:

- “In a prospective study that included 56 patients exposed to etanercept, there were three neonatal complications in newborns exposed to etanercept in the first trimester of pregnancy (respiratory distress syndrome, n=2; pneumothorax, n=1).²
- In a cohort study of women who received etanercept during the 3 months prior to conception (n=32) or during the first (n=20) second (n=1) or third trimester (n=1) of pregnancy, none of the children were born with a major malformation.³
- In a review of the FDA database for reporting adverse events, 22 mothers who received etanercept at some point during their pregnancy were identified. Among the children, there were 34 congenital abnormalities.⁴ (See further description below.)
- A total of 12 case studies of etanercept-treated women who became pregnant were identified, which included 29 patients (RA, n=19; AS, n=7; PsA, n=2; JIA, n=1) and 32 pregnancies. Of the 32 documented pregnancies, 25 were successful, one

² Bazzani C, Scrivo R, Andreoli L, et al (2015) Prospectively-followed pregnancies in patients with inflammatory arthritis taking biological drugs: an Italian multicentre study. *Clin Exp Rheumatol.* 33(5):688–693.

³ Viktil KK, Engeland A, Furu K (2012) Outcomes after anti-rheumatic drug use before and during pregnancy: a cohort study among 150,000 pregnant women and expectant fathers. *Scand J Rheumatol.* 41(3):196–201.

⁴ Carter JD, Ladhani A, Ricca LR, et al (2009) A safety assessment of tumor necrosis factor antagonists during pregnancy: a review of the Food and Drug Administration database. *J Rheumatol.* 36(3):635–641.

ended in an elective termination and three ended in miscarriage. One child was born with VATER association, one child was born with coarctation of aorta, and one child was born with megacolon congenitum.⁵

- When cord blood levels of etanercept were determined at delivery in infants born to two mothers administered etanercept (RA, n=1; AS, n=1), the etanercept concentration ratio between maternal serum and umbilical cord serum was 14:1 and 28:1.^{6,7}

DPMH conducted a review of literature regarding pregnancy and lactation for etanercept using TERIS and REPROTOX, which also was consistent with the applicant's review. The literature review was notable for an individual case report⁸ and adverse events reported to the FDA that describe a potential association of TNF alpha antagonists with congenital anomalies consistent with the VACTERL (vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limb abnormalities) spectrum. In the review of >120,000 adverse events reported to the FDA through December 2005 noted above⁴, 41 children with 61 congenital anomalies born to 40 mothers taking a TNF antagonist. Heart defects (n=11) were the most common congenital anomaly reported. Overall, twenty-four (59%) of the live-born infants had one or more congenital anomalies part of vertebral abnormalities, anal atresia, cardiac defect, tracheoesophageal, renal, and limb abnormalities (VACTERL) association. However, only 1 child was diagnosed with VACTERL. In 24 of the 41 cases, no other concomitant medications were being used by the mothers. The authors concluded that number of congenital anomalies part of the VACTERL spectrum occurred at a higher rate than historical controls. However, the potential selection bias associated with the data reported in this database, lack of confirmed diagnoses of VACTERL limits a conclusion of causality. Furthermore, there were numerous reported normal pregnancy outcomes after etanercept exposure in other published observational studies.^{3,9} The reported rates of birth defects among children of women treated with etanercept during pregnancy in other series collected through rheumatologists do not appear to be high, and even reveal rates that appear to be lower than expected in unexposed pregnancies in some of the studies.¹⁰ Therefore, this association is not confirmed.

⁵ See Appendix 2: Case studies of etanercept exposure in pregnancy

⁶ Murashima A, Watanabe N, Ozawa N, et al (2009) Etanercept during pregnancy and lactation in a patient with rheumatoid arthritis: drug levels in maternal serum, cord blood, breast milk and the infant's serum. *Ann Rheum Dis.* 68(11):1793–1794

⁷ Berthelsen BG, Fjeldsøe-Nielsen H, Nielsen CT, et al (2010) Etanercept concentrations in maternal serum, umbilical cord serum, breast milk and child serum during breastfeeding. *Rheumatology (Oxford).* 49(11):2225–2227.

⁸ Carter JD, Valeriano J, Vasey FB (2006) Tumor necrosis factor-alpha inhibition and VATER association: a causal relationship. *J Rheumatol.* 33(5):1014–1017.

⁹ Chambers CD, Johnson DL, Jones KL: Pregnancy outcome in women exposed to anti-TNF-alpha medications: the OTIS Rheumatoid Arthritis in Pregnancy Study. *Arthritis Rheum* 50:S479-S480, 2004.

¹⁰ See Appendix 3: Published literature supporting low rates of birth defects with etanercept exposure during pregnancy.

Summary

The findings of the applicant's literature review are consistent with DPMH's literature review which found that overall, the data is conflicting and no obvious safety signal trends or patterns could be identified. Therefore, the available data on etanercept use in pregnant women do not report a clear association with a potential risk of major birth defects, miscarriage, or adverse maternal or fetal outcomes.

Current Enbrel labeling discusses the developmental toxicity studies conducted in rats and rabbits and provides the dosing relative to the human dose, but does not specifically state whether this is the maximum human recommended dose. Because the current Enbrel label does not contain the nonclinical information needed to calculate the dose ratios, the Pharmacology/Toxicology reviewers proposed to leave the language describing the dosing used in the animal studies as it is represented in the Enbrel label.

Current Enbrel labeling also includes the following sentence: "Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed." We would typically recommend exclusion of such statements that are not consistent with current PLLR recommended language and convey no specific risk. However, for this biosimilar product, we have strived to limit differences between Erelzi and Enbrel labeling that may confer a difference in efficacy or safety; therefore, we have decided to retain this sentence at this time.

The applicant asserts that their literature review is in line with the labeling approved for Enbrel, and proposes no revisions other than restructuring current Enbrel pregnancy and lactation labeling to comply with PLLR requirements. However, we also propose to provide additional information in the Human Data section on the limited conflicting data in published literature regarding major birth defects, miscarriage, or adverse maternal or fetal outcomes with etanercept use. Although, no clear association with these outcomes could be determined, the absence of risk also cannot be established due to methodological limitations with the studies, including small sample size and inconsistent comparator groups. DPMH also provided labeling recommendations that revised the sponsor's proposed labeling with current regulatory language.

Information from the Enbrel pregnancy registry PMR has been submitted and is currently under review. Therefore, the team decided not to request a Pregnancy Surveillance Program for this etanercept biosimilar because any updated labeling for Enbrel following the review of this data can also be incorporated in Erelzi labeling.

LACTATION

Nonclinical Experience

No nonclinical data was available in Enbrel labeling.

Review of Literature

The applicant's literature review identified four cases of etanercept-treated lactating women (RA, n=3; AS, n=1) with concentrations of etanercept in breast milk were low, ranging from <2 ng/mL to 75.4 ng/mL (<2 mcg/L to 75.4 mcg/L).

DPMH conducted a review of literature regarding pregnancy and lactation for etanercept using LactMed which also noted similar levels of etanercept in breast milk and no adverse events in the limited data on breastfed infants.

Summary

Limited data from published literature show that etanercept is present in low levels in human milk. However, no data was found on the effects on the breastfed infant, or the effects on milk production. Therefore, the limited clinical data during lactation precludes a clear determination of the risk of etanercept to an infant during lactation.

(b) (4)

(b) (4)

Discussion on Pediatric Labeling Recommendations:

Sandoz is able to extrapolate the pediatric data included throughout Enbrel's labeling. Thus, Erelzi labeling should incorporate similar labeling language regarding pediatric use in JIA patients 2 years and older. However, Erelzi will not have an adequate presentation to allow dosing for patients >63 kg upon initial approval. Therefore, the following indication language was initially proposed: "JIA in patients aged 2 years or older

(b) (4)

(b) (4)

, the division opted to address the weight restriction and lack of an age-appropriate presentation in the Dosage and Administration section. Accordingly, dosing is only provided for patients >63 kg and the lack of a presentation allowing dosing in patients ≤ 63 kg is included.

A full waiver will be granted for PsO based on safety concerns related to increased risk of malignancy and infection with etanercept use. Therefore, labeling must reflect these concerns. Enbrel labeling currently describes these risks in a boxed warning in addition to the Warnings and Precautions, and Adverse Reactions sections. Similar labeling should be included for Erelzi. While DPMH has recommended inclusion of language in the Pediatric Use section stating that TNF- α blockers, such as Enbrel (etanercept), "are not recommended for use in pediatric psoriasis" because of the risk of malignancy and infection, if possible, these changes should preferably be made to reference product labeling first to harmonize labeling between biosimilar similar products and the reference product as much as possible. Furthermore, the safety concerns will otherwise be noted throughout Erelzi labeling. Nevertheless, the current statement in Enbrel labeling that

(b) (4)

" is inaccurate and should be revised to state that safety and efficacy of etanercept in pediatric patients with PsO have not been established.

Conclusion:

DPMH agrees with the proposed pediatric development plans as outlined above. A PREA PMR will be issued to develop a presentation of Erelzi that can allow accurate administration to pediatric patients who weigh less than 63 kg.

DPMH participated in the internal meetings from September, 2014 to July, 2016, 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 October 27, 2014; February 26, 2015; June 1, 2015; and July 16, 2015.

DPMH reviewed the applicant's draft labeling, and participated in the team and labeling meetings held between April, 2016 and July, 2016. DPMH revised subsections 8.1 and 8.2 in Erelzi labeling for compliance with the PLLR (see below). DPMH also edited subsection 8.4 and recommended labeling for the pediatric population is provided below per 21 CFR 201.57(c)(9)(iv). The following recommendations are based on labeling discussions between DPARP and DPMH. DPMH's input will be reflected in the final labeling and the approval letter. Final labeling will be negotiated with the applicant and may not fully reflect changes suggested here.

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

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

/s/

ERICA D RADDEN
08/27/2016

TAMARA N JOHNSON
08/29/2016

JOHN J ALEXANDER
08/29/2016

The goal is to develop a presentation that can be used to (b) (4) accurately administer etanercept-xxxx to pediatric patients who weigh less than 63 kg.

3. If the study/clinical trial is a **PMR**, check the applicable regulation.

If not a PMR, skip to 4.

– **Which regulation?**

- Accelerated Approval (subpart H/E)
- Animal Efficacy Rule
- Pediatric Research Equity Act
- FDAAA required safety study/clinical trial

– **If the PMR is a FDAAA safety study/clinical trial, does it: (check all that apply)**

- Assess a known serious risk related to the use of the drug?
- Assess signals of serious risk related to the use of the drug?
- Identify an unexpected serious risk when available data indicate the potential for a serious risk?

– **If the PMR is a FDAAA safety study/clinical trial, will it be conducted as:**

- Analysis of spontaneous postmarketing adverse events?

Do not select the above study/clinical trial type if: such an analysis will not be sufficient to assess or identify a serious risk

- Analysis using pharmacovigilance system?

Do not select the above study/clinical trial type if: the new pharmacovigilance system that the FDA is required to establish under section 505(k)(3) has not yet been established and is thus not sufficient to assess this known serious risk, or has been established but is nevertheless not sufficient to assess or identify a serious risk

- Study: all other investigations, such as investigations in humans that are not clinical trials as defined below (e.g., observational epidemiologic studies), animal studies, and laboratory experiments?

Do not select the above study type if: a study will not be sufficient to identify or assess a serious risk

- Clinical trial: any prospective investigation in which the sponsor or investigator determines the method of assigning investigational product or other interventions to one or more human subjects?

4. What type of study or clinical trial is required or agreed upon (describe and check type below)? If the study or trial will be performed in a subpopulation, list here.

The sponsor will need to develop the new presentation and any studies necessary will depend on the presentation.

Required

- Observational pharmacoepidemiologic study
- Registry studies
- Primary safety study or clinical trial
- Pharmacogenetic or pharmacogenomic study or clinical trial if required to further assess safety
- Thorough Q-T clinical trial
- Nonclinical (animal) safety study (e.g., carcinogenicity, reproductive toxicology)
- Nonclinical study (laboratory resistance, receptor affinity, quality study related to safety)
- Pharmacokinetic studies or clinical trials
- Drug interaction or bioavailability studies or clinical trials
- Dosing trials

Continuation of Question 4

- Additional data or analysis required for a previously submitted or expected study/clinical trial (provide explanation)

-
- Meta-analysis or pooled analysis of previous studies/clinical trials
 - Immunogenicity as a marker of safety
 - Other (provide explanation)
Studies to be determined based on the presentation developed; may include stability testing and other CMC-related studies.
-

Agreed upon:

- Quality study without a safety endpoint (e.g., manufacturing, stability)
- Pharmacoepidemiologic study not related to safe drug use (e.g., natural history of disease, background rates of adverse events)
- Clinical trials primarily designed to further define efficacy (e.g., in another condition, different disease severity, or subgroup) that are NOT required under Subpart H/E
- Dose-response study or clinical trial performed for effectiveness
- Nonclinical study, not safety-related (specify)

-
- Other
-

5. Is the PMR/PMC clear, feasible, and appropriate?

- Does the study/clinical trial meet criteria for PMRs or PMCs?
- Are the objectives clear from the description of the PMR/PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMRs/PMCs, ask questions, determine feasibility, and contribute to the development process?

- Check if this form describes a FDAAA PMR that is a randomized controlled clinical trial

If so, does the clinical trial meet the following criteria?

- There is a significant question about the public health risks of an approved drug
- There is not enough existing information to assess these risks
- Information cannot be gained through a different kind of investigation
- The trial will be appropriately designed to answer question about a drug's efficacy and safety, and
- The trial will emphasize risk minimization for participants as the protocol is developed

PMR/PMC Development Coordinator:

This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.

(signature line for BLAs)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

BLA # 761042

Product Name:

PMC #1 Description: Develop and implement an analytical method for release and stability testing of GP2015 drug substance and drug product that can adequately assess levels of hydrophobic variants, including wrongly bridged disulfide bond variants. Submit the final validation report and release and stability acceptance criteria as a Prior Approval Supplement.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>12/31/2017</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA AA OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

FDA requested that a method be added as a release test for GP2015 drug substance and drug product in order to assess and control hydrophobic variants. Sandoz needs time to properly develop the method as a QC test. They are currently evaluating _____ (b) (4),
_____,
this should be submitted as a Prior Approval supplement.

2. Describe the particular review issue and the goal of the study.

This method measures the levels of hydrophobic variants found in the RPC “post-peak”. The hydrophobic variants in this peak contain misfolded etanercept protein that has reduced activity.

(b) (4)

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

Sandoz will implement the

(b) (4)

5. To be completed by OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

PMR/PMC Development Template: Product Quality (CMC)

This template should be completed by the review chemist (ONDQA) or biologist (OBP) and included for *each* type of CMC PMR/PMC in the Action Package. See #4 for a list of CMC PMR/PMC types

NDA/BLA # 761042
Product Name: GP2015

PMC #1 Description: Repeat the microbial retention study using a more suitable surrogate solution. Attributes of the surrogate solution that are known to affect microbial retention (surface tension, viscosity, ionic strength, etc.) should model the drug product as closely as possible while preserving viability of the challenge organism. Alternatively, use of a reduced exposure time or modified process conditions (e.g., temperature) may be appropriate. Provide the summary data, the associated report, and justification for any modifications to the study. Submit the final report as a CBE30 and include any change in filtration parameters based upon the study.

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>09/30/2017</u>
	Other: _____	<u>MM/DD/YYYY</u>

PMC #2 Description: _____

PMC Schedule Milestones:	Final Protocol Submission:	<u>MM/DD/YYYY</u>
	Study/Trial Completion:	<u>MM/DD/YYYY</u>
	Final Report Submission:	<u>MM/DD/YYYY</u>
	Other: _____	<u>MM/DD/YYYY</u>

- **ADD MORE AS NEEDED USING THE SAME TABULAR FORMAT FOR EACH PMC.**
- **INCLUDE DESCRIPTIONS AND MILESTONES IN THE TABLE ABOVE FOR ALL CMC/OBP NON-REPORTABLE PMCS FOR WHICH THE FOLLOWING ANSWERS WILL BE IDENTICAL. USE A SEPARATE TEMPLATE FOR EACH PMR/PMC FOR WHICH THE ANSWERS TO THE FOLLOWING QUESTIONS DIFFER.**
- **DO NOT USE THIS FORM IF ANY STUDIES WILL BE REQUIRED UNDER FDA 201 CMC OR WILL BE PUBLICALLY REPORTABLE**

1. During application review, explain why this issue is appropriate for a PMC instead of a pre-approval requirement. Check reason below and describe.

- Need for drug (unmet need/life-threatening condition)
- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern

- Manufacturing process analysis
- Other

(b) (4)



2. Describe the particular review issue and the goal of the study.

(b) (4)



3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

The sponsor will repeat the bacterial retention study using a surrogate fluid that resembles the drug product more closely. The study will include the following three components:

(b) (4)



5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
 - Are the objectives clear from the description of the PMC?
 - Has the applicant adequately justified the choice of schedule milestone dates?
 - Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?
-

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

- Long-term data needed (e.g., stability data)
- Only feasible to conduct post-approval
- Improvements to methods
- Theoretical concern
- Manufacturing process analysis
- Other

PMC 1 and 2: Verification and Validation for the essential performance requirements were provided. The above post market commitments were to add the essential performance requirements to the lot release criteria.

PMC3: The Sponsor completed mechanical stress testing for the packaging and has committed to completing additional transport validation prior to launch of the product. The risk associated with the results of this testing is not indicative of a pre-approval requirement given the other testing that the Sponsor has completed.

2. Describe the particular review issue and the goal of the study.

PMC 1 and 2: The sponsor did not include the essential performance requirements in the lot release criteria. During interactive review, the sponsor committed to including the essential performance requirements for the lot release criteria.

PMC 3: The sponsor has committed to providing the transportation validation test report. This report should be reviewed when available.

3. [OMIT – for PMRs only]

4. What type of study is agreed upon (describe and check type below)?

Select only one. Fill out a new sheet for each type of PMR/PMC study.

- Dissolution testing
- Assay
- Sterility
- Potency
- Product delivery
- Drug substance characterization
- Intermediates characterization
- Impurity characterization
- Reformulation
- Manufacturing process issues
- Other

Describe the agreed-upon study:

PMC 1 and 2: Performance testing for the lot release criteria.

PMC 3: Transportation validation testing.

5. To be completed by ONDQA/OBP Manager:

- Does the study meet criteria for PMCs?
- Are the objectives clear from the description of the PMC?
- Has the applicant adequately justified the choice of schedule milestone dates?
- Has the applicant had sufficient time to review the PMCs, ask questions, determine feasibility, and contribute to the development process?

PMR/PMC Development Coordinator:

- This PMR/PMC has been reviewed for clarity and consistency, and is necessary to further refine the safety, efficacy, or optimal use of a drug, or to ensure consistency and reliability of drug quality.*

(signature line for BLAs only)

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

/s/

SALLY M SEYMOUR
08/25/2016

MEMORANDUM
REVIEW OF REVISED LABELS AND LABELING AND NONPROPRIETARY NAME SUFFIX

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)

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Date of This Review:	August 24, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761042
Product Name and Strength:	Erelzi (etanercept-szsz) Injection 25 mg/0.5 mL Prefilled Syringe (PFS) 50 mg/mL Prefilled Syringe (PFS) 50 mg/mL Autoinjector (AI)
Product Type:	Single Ingredient Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sandoz
Submission Date:	August 5, 2016 and August 23, 2016
OSE RCM #:	2015-1845-1 and 2016-1834
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
DMEPA Deputy Director:	Lubna Merchant, MS, PharmD

1 PURPOSE OF MEMO

DPARP requested that we review the revised container labels and carton labeling for Erelzi (Appendix A) to determine if they are acceptable from a medication error perspective. The revisions are in response to recommendations that we made during a previous label and labeling review.¹

In addition, this memorandum also summarizes our evaluation of the suffix proposed by Sandoz 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 Sandoz's Erelzi product is necessary to distinguish this proposed product from Enbrel (etanercept). As explained in FDA's draft Guidance for Industry, Nonproprietary Naming of Biological Products ("draft guidance"), FDA expects that a nonproprietary name for Erelzi that includes a distinguishing suffix will facilitate safe use and optimal pharmacovigilance. FDA advised Sandoz to provide proposed suffixes in accordance with the principles that are described in Section V of the draft guidance². FDA has not finalized a policy on the nonproprietary naming of biological products. Accordingly, we reviewed Sandoz's proposed suffixes against the criteria described in the draft guidance.

On August 5, 2016, Sandoz submitted a list of suffixes, in their order of preference, to be used in the nonproprietary name of their product. We evaluated the proposed suffixes in the order of the preference listed by the Applicant. (b) (4)

FDA reviewed the second alternative, -szzs provided by Sandoz. We determined that Sandoz's suffix, -szzs, 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 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 guidance⁴. As a result, the nonproprietary name is

¹ Mena-Grillasca, C. Human Factors, Label, Labeling, and Packaging review for Erelzi (GP2015) BLA 761042. 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 Jul 21. OSE RCM No.: 2015-1845 and 2015-2148.

² 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>

³ Neil M Davis, *Medical Abbreviations: 30,000 Conveniences at the Expense of Communication and Safety*. Pennsylvania, 2009.

⁴ 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,

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 Sandoz to minimize the impact this would have to its manufacture and distribution of this product, should it be licensed.

3 CONCLUSION

The revised container label and carton labeling are unacceptable from a medication error perspective. We have drafted proposed letter-ready comments to convey to the Sponsor (see section 2.1).

We note that the Sponsor did not implement one of our previous recommendations correctly. We requested to increase the prominence of the route of administration statement by bolding; however, the prominence of the dosage form statement was increased instead. In addition, we concur with the label and labeling comments from the Office of Biotechnology Products (OBP).

Finally, we find that Sandoz's proposed suffix "-szzs" is acceptable and recommend the nonproprietary name be revised throughout the draft labels and labeling to etanercept-szzs.

3.1 RECOMMENDATIONS FOR SANDOZ

A. Nonproprietary name

1. We find your proposed nonproprietary name, etanercept-^{(b) (4)}, unacceptable as the proposed

^{(b) (4)}
[Redacted text block]

2. We find the nonproprietary name, etanercept-szzs, conditionally acceptable for your proposed product. This nonproprietary name containing the distinguishing suffix, etanercept-szzs, will be the proper name designated in the license should your 351(k) BLA be approved. You should revise your proposed labels and labeling accordingly.

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.

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 Erelzi, 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.

B. General Comments (All container labels, foil, and carton labeling)

1. Increase the prominence of the route of administration statement (i.e., For Subcutaneous Use Only) by bolding. We requested the revision on our original Advice/Information Request letter, however the prominence appears unchanged.
2. It seems our comment requesting that you increase the prominence of the route of administration statement on the original Advice/Information Request letter was misinterpreted and we note the dosage form statement (i.e., Injection) was bolded instead of the route of administration statement. Please unbold the dosage form statement (i.e., Injection).

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/s/

CARLOS M MENA-GRILLASCA
08/24/2016

LUBNA A MERCHANT on behalf of MISHALE P MISTRY
08/24/2016

LUBNA A MERCHANT
08/24/2016

**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: August 10, 2016

To: Badrul Chowdhury, MD, PhD
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)
Marcia Williams, PhD
Team Leader, Patient Labeling
Division of Medical Policy Programs (DMPP)

From: Nyedra W. Booker, PharmD, MPH
Patient Labeling Reviewer
Division of Medical Policy Programs (DMPP)

Subject: Review of Patient Labeling: Medication Guide (MG) and
Instructions for Use (IFU)

Drug Name (nonproprietary name): ERELZI (etanercept-xxxx¹)

Dosage Form and Route: injection, for Subcutaneous Use

Application Type/Number: BLA 761042

Applicant: Sandoz Inc.

¹ A four letter suffix for the nonproprietary name for Erelzi has not been determined. FDA is using “-xxxx” as a placeholder for the suffix. “-xxxx” is not intended to be included in the final printed labels and labeling.

1 INTRODUCTION

On July 30, 2015, Sandoz Inc. submitted for the Agency's review a 351(k) Biologics License Application (BLA) for ERELZI (etanercept-xxxx) injection, for Subcutaneous Use. Sandoz Inc. seeks approval for ERELZI (etanercept-xxxx) as a biosimilar product to the single reference biologic product Enbrel[®] licensed under BLA 103795 by Amgen Inc. The Applicant has proposed the same indications for ERELZI (etanercept-xxxx) as the approved single reference product Enbrel (etanercept), for the treatment of the following:

- Rheumatoid Arthritis (RA)
- Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years or older (b) (4)
- Psoriatic Arthritis (PsA)
- Ankylosing Spondylitis (AS)
- Plaque Psoriasis (PsO)

On April 29, 2016 the Agency informed the Applicant of a Major Amendment regarding their April 28, 2016 submission and extended the goal date by three months in order to provide time for a full review of the submission.

This review is written by the Division of Medical Policy Programs (DMPP) in response to a request by the Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) on August 19, 2015 for DMPP to review the Applicant's proposed Medication Guide (MG) and Instructions for Use (IFU) for ERELZI (etanercept-xxxx) injection, for Subcutaneous Use.

DMPP conferred with the Division of Medication Error, Prevention, and Analysis (DMEPA) and a separate DMEPA review was completed on July 21, 2016.

2 MATERIAL REVIEWED

- Draft ERELZI (etanercept-xxxx) injection, for Subcutaneous Use MG and IFU received on July 30, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on July 26, 2016.
- Draft ERELZI (etanercept-xxxx) injection, for Subcutaneous Use Prescribing Information (PI) received on July 30, 2015, revised by the Review Division throughout the review cycle, and received by DMPP on July 26, 2016.
- Approved ENBREL (etanercept) Solution for Subcutaneous Use comparator labeling dated March 25, 2015.
- Approved COSENTYX (secukinumab) injection, for subcutaneous use comparator labeling dated January 15, 2016.

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. In our review of the MG and IFU the target reading level is at or below an 8th grade 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 have reformatted the MG and IFU document using the Arial font, size 10 and 11 respectively.

In our review of the MG and IFU we have:

- ensured that the MG and IFU are consistent with the Prescribing Information (PI)
- ensured that the MG meets the Regulations as specified in 21 CFR 208.20
- ensured that the MG and IFU meet 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 and IFU are acceptable with our recommended changes.

5 RECOMMENDATIONS

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

Please let us know if you have any questions.

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/s/

NYEDRA W BOOKER
08/10/2016

LASHAWN M GRIFFITHS
08/10/2016

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

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

Memorandum

Date: August 5, 2016

To: Jessica Lee, 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 # 761042 – ERELZI (etanercept-xxxx) solution injection, for
subcutaneous use

Reference is made to DPARP's consult request dated August 19, 2015, requesting review of the proposed Package Insert (PI), Carton/Container Labeling, Medication Guide (MG), and Instructions for Use (IFU) for ERELZI (etanercept-xxxx) solution injection, for subcutaneous use (Erelzi).

OPDP has reviewed the proposed PI entitled, "BLA 761042_PI_121115.docx" that was sent via e-mail from DPARP to OPDP on July 26, 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 MG and IFU entitled, "BLA 761042_MG_IFU.docx" that was sent via e-mail from DPARP to OPDP on July 26, 2016. OPDP's comments on the proposed MG and IFU are provided on the attached marked-up copy of the labeling (see below).

OPDP has also reviewed the proposed Carton/Container labeling that was submitted by the sponsor on July 30, 2015. OPDP has no comments at this time on the proposed Carton/Container labeling.

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

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08/05/2016



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

Office of Biotechnology Products
Division of Biotechnology Review
and Research I

Memorandum

To: File for STN: 761042 (SDN 1, SDN 9)
Date: July 26, 2016
From: Brian M. Janelsins, Ph.D. -S (Affiliate)
Through: Jee Chung, Ph.D.
Marjorie Shapiro, Ph.D.
Subject: Immunogenicity review for BLA 761042
Sponsor: Sandoz, Inc.
Product: GP2015, proposed biosimilar to Enbrel
Indications: Rheumatoid arthritis (RA), polyarticular juvenile idiopathic arthritis (JIA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), plaque psoriasis (PsO)
Dose Strength: 25 mg (25 mg/0.5 ml; pre-filled syringe) and 50 mg (50 mg/1.0 ml; pre-filled syringe, auto-injector)
Route of admin.: Subcutaneous
Dose Regimen: RA and PsA: 50 mg once weekly with or without methotrexate
AS: 50 mg once weekly
PsO: 50 mg twice weekly for 3 months, followed by 50 mg once weekly
JIA: 0.8 mg/kg weekly with a maximum of 50 mg per week

Proposed Proprietary Name: Erelzi, Erelzi Sensoready Pen (auto-injector)
Proper Name: TBD
PDUFA goal Date: August 30, 2016

RECOMMENDATION

Approval of BLA 761042 is recommended from an immunogenicity perspective. The development and validation of the immunogenicity assays used to assess the immunogenicity of GP2015 and EU-approved Enbrel (i.e., etanercept) are acceptable and the immunogenicity data obtained from the clinical trials suggest that both products are similar from an immunogenicity perspective, i.e., the data are supportive of finding no clinically meaningful differences with respect to the anti-drug antibody (ADA) incidence in patients treated with GP2015 or EU-approved Enbrel.

EXECUTIVE SUMMARY

Sandoz is seeking licensure for GP2015 as a biosimilar to US-licensed Enbrel, manufactured by Amgen Inc., for the same indications for which US-licensed Enbrel is currently approved. In support of their 351(k) BLA application (STN 761042), Sandoz evaluated the immunogenicity of GP2015 and EU-approved Enbrel in the pivotal PK clinical study (GP15-102) and the supportive PK clinical studies (GP15-101, GP15-103, and GP15-104; US-licensed Enbrel was used in comparison with EU-approved Enbrel in GP15-101) in healthy volunteers and the pivotal efficacy

and safety study (GP15-302) in a patient population (i.e., plaque psoriasis, PsO). Immunogenicity assays to screen and confirm the presence of binding ADAs and to determine the neutralizing capability of confirmed positive ADAs were developed, validated, and used to determine the clinical immunogenicity rates between GP2015 and EU-approved Enbrel. Appropriate bridging data between US-licensed and EU-approved Enbrel are provided to support the use of EU-approved Enbrel for licensure of GP2015 as a biosimilar to US-licensed Enbrel in the US. The BLA submission includes method validation data for each immunogenicity assay ([Section 1 of the review](#)) and the immunogenicity data derived from each clinical trial ([Section II of the review](#)). During the course of the review, it was determined that sufficient information was not provided to fully assess the immunogenicity similarity between GP2015, EU-approved Enbrel, and US-licensed Enbrel; therefore, information requests (IR) were sent on December 11, 2015. Responses were received on January 15, 2016 (SDN 9) with adequate information, including bioanalytical statistical evaluation reports, to allow for a complete review, and subsequently, it was determined that there were no significant deficiencies present to prevent the approval of the BLA from an immunogenicity perspective.

REVIEW

Note: Reviewer Comments are indicated by italic font. Tables and Figures are copied directly from the submission unless otherwise stated.

Section 1 – Assay Development and Validation

The sponsor developed and validated an electrochemiluminescence (ECL) assay for screening and confirmatory analyses of binding ADAs ([Section 1a](#)) and an ELISA-based competitive ligand-binding (CLB) assay for neutralizing activity analysis of confirmed positive binding ADAs ([Section 1b](#)) using serum from healthy volunteers and psoriasis patients. HEXAL AG is the contract research organization who validated the immunogenicity assays.

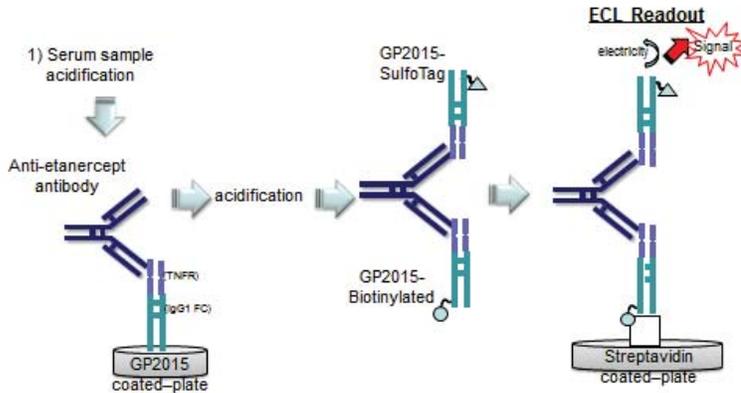
Reviewer Comment: *The ECL and CLB immunogenicity assays were originally validated with sera from healthy volunteers, which were reviewed and determined to be inadequate. Because the assays were later validated with sera from a patient population, and subsequently determined to be acceptable, the review of the assays validated with healthy volunteer sera is not shown.*

Section 1a – Screening and Confirmatory ECL Bridging Assay

BA13019 study was conducted to validate the ECL bridging method for the detection of binding ADAs in serum samples of psoriasis patients receiving GP2015 or EU-approved Enbrel. Results are displayed in the validation report BA13019-R and statistical analyses of the data are included in a bioanalytical statistical evaluation report (BSER_BA13019). The principle of the screening and confirmatory assays within the ECL bridging method is illustrated below in Figure 1.

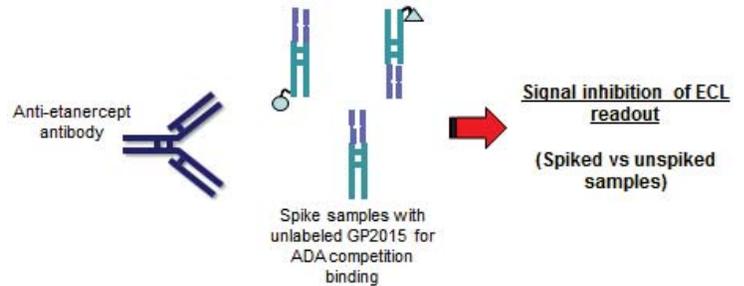
Figure 1 - Screening and Confirmatory Assays

Screening Assay – ECL bridge format



Confirmatory Assay – ECL bridge format

The same 50 individual serum samples that were analyzed for the screening cut-point were spiked with excess of GP2015 (10 µg/ml) and compared with unspiked samples.



*The illustration is made by the primary reviewer.

The validation experiments were performed in 55 independent runs (listed in Table 4-16 of the validation report) from November 04, 2013 to November 11, 2014. Five runs failed and were not considered for the evaluation of the validation parameters.

Reviewer Comment: Failed runs were due to technical error; however, an explanation of what that error was and why it occurred is not provided. This is acceptable because the technical error did not compromise the method validation as failed runs were successfully repeated without incident.

Matrix

Individual psoriasis patient serum samples were provided by (b) (4). Select samples were pooled to create the psoriasis serum pool (internal no. 260213_Ps-hSP-GP2015^{(b) (4)}), while other samples were individually used for cut-point determination. Each serum sample used in the validation is listed in Table 4-9 of the validation report and the serum samples used for cut-point determination and generation of the serum pool are specified in Table 4-10 to Table 4-12 of the validation report.

ECL method validation also included the use of human serum pool (healthy volunteers, HV; (b) (4)), which was used as a negative control for the calibration curve (STD 08), a matrix for calibration curves and quality controls, and a diluent for further dilution of psoriasis patient samples concentrated with the positive control antibody above the upper limit of quantification (refer to [Dilution Testing section](#)).

All individual samples and the serum pool were used prior to their respective expiration dates and properly stored. Due to the matrix-related interferences observed in the validation, each matrix was diluted 1:3 in blocking buffer (5% BSA and 0.05% Tween® 20 in D-PBS) prior to executing the method validation.

Reviewer Comment: The impact of matrix-related interference, including pre-existing antibodies and serum components, on ECL method performance is evaluated in the [Selectivity/Matrix Interference](#) section of the review.

Assay controls

Positive Control Antibody

A rabbit anti-etanercept polyclonal antibody was supplied by (b) (4) and produced by hyper-immunization of rabbits with etanercept. After immunization, the extracted antiserum of these rabbits was affinity purified in order to isolate etanercept-specific polyclonal antibodies. The positive control antibody was properly stored at -70°C and used within a reasonable amount of time from delivery for an antibody that is properly handled and stored. The stability of the positive control antibody was monitored during routine sample analysis via calibration and QC samples and no trends were reported in the method validation and study reports. The positive control antibody was used to prepare the (i) [calibration curve](#), (ii) [quality control samples](#), and (iii) [validation samples](#).

Calibration Curve

As a part of system suitability testing, the assay signal, i.e., ECL counts, from control and test samples were compared to ECL count values of a calibration curve to determine back-calculated concentration values (Table 4-6 of the validation report, see below).

Table 4-6 Preparation of calibration curve samples

Calibration curve sample	Dilution	Total volume [µl]	Dilution matrix [µl]	Anti-etanercept antibodies [µl]	Concentration in 33.3% serum [ng/ml]	Concentration in 100% serum [ng/ml]
STD 1	1:3	180	120 ¹⁾	60 of Vv-STD (see Table 4-5)	8,000	24,000
STD 2	1:2.5	200	120 ²⁾	80 of STD 1	3,200	9,600
STD 3	1:4	200	150 ²⁾	50 of STD 2	800	2,400
STD 4	1:2	200	100 ²⁾	100 of STD 3	400	1,200
STD 5	1:2	200	100 ²⁾	100 of STD 4	200	600
STD 6	1:2	200	100 ²⁾	100 of STD 5	100	300
STD 7	1:2	100	50 ²⁾	50 of STD 6	50	150
STD 8	-----	100	-----	-----	-----	150

¹⁾ Blocking buffer (5% BSA and 0.05% Tween® 20 in D-PBS)

²⁾ 1:3 diluted human serum pool

Appendix 1 (Table 1-1) of the validation report displays the measured counts and back-calculated concentrations values from each of the calibration curve standard samples in replicates of two from the 55 plate runs. Accuracy of back-calculated concentration values from all valid plates ranged from 99.5% to 123% for STD 1 and STD 7 with the exception of STD 7 from run #55 (129%). Accuracy of back-calculated concentration values from the valid plates ranged from 88% to 118% for STD 2 to STD 6 with the exception of STD 6 from run #15 (122%). The coefficient of variation (CV) of mean concentration values for all seven standards from each valid run ranged from 0% to 14%. The count values of the blank (STD 8) ranged from 42 to 66 counts and concentration values could not be determined. The coefficient of correlation for each standard curve ranged from 0.997 and 1.0, which complied with the acceptance criterion of NLT 0.990.

Reviewer Comment: Because every run met the plate acceptance criterion [i.e., each plate has a minimum of six calibration curve standards that are within the acceptance criteria for accuracy (75 – 120% for STD 1,7 and 80 – 120% for STD 2-6) and precision (CV% NMT 25% for STD 1,7 and CV% NMT 20% for STD 2-6)], the accuracy exceptions are considered acceptable. The calibration curve is suitable for its intended purpose of correlating counts to concentration in a linear manner with high precision and accuracy. Although the blank did not have an acceptance criterion, the negative control appears suitable for its intended purpose because the blank values drift in the same direction as individual sample values. Also, all blank values are less than the cut-point value of 67 counts and are NMT 10% for sample variance (CV).

Quality Controls

As a part of system suitability testing, two sets of quality control (QC) samples were prepared by spiking known concentrations of the positive control antibody into diluted (1:3) human serum pool (HV; Table 4-7 of the validation report) to generate QC1 (18,000 ng/ml), QC2 (2,700 ng/ml), and QC3 (900 ng/ml).

Measured counts and back-calculated concentrations values from each of QC samples ran on the 55 plate runs are displayed in Appendix 2 (Table 2-1) of the validation report. The accuracy of the QC samples ranged from 81% to 119% with the exception of a QC3 replicate in run #40 (145%), #41 (123%), #42 (121%), and #50 (126%) and a QC1 replicate in run #49 (76%) and #50 (122%). The acceptance criteria for precision, i.e., CV of mean concentration (NMT 20%), and total error (NMT 30%) were met for all data points with the exception of a QC3 replicate in run #40 (46%) for total error

Reviewer Comment: Because the acceptance criterion for plate acceptability was fulfilled, i.e., at least four of the six quality control samples (two sets of QC1, QC2, and QC3) conform to the acceptance criteria of accuracy, precision and total error, the exceptions described above are acceptable. The QC samples are suitable for their intended purpose to ensure the validity of the assay and production of meaningful data.

Validation Samples

The positive control polyclonal antibody was spiked in diluted (1:3) psoriasis serum pool to create the validation samples (Table 4-2 of the validation report, see below).

Validation sample	Concentration in 33.3% human psoriasis serum pool [ng/ml]	Concentration in 100% human psoriasis serum pool [ng/ml]
ULOQ-VS	8,000	24,000
VS1	6,000	18,000
VS2	900	2,700
VS3	150	450
LLOQ-VS	50	150

Cut-point – Screening Assay

Fifty individual psoriasis patient serum samples were diluted (1:3) and ran three times by two analysts (i.e., (b) (4); n=300). Measured ECL counts were back-calculated into concentration measurements against the calibration curve and negative controls. The results are displayed in

Appendix 15 of the validation report and a statistical evaluation is shown in Appendix 19 of the validation report and in BSER_BA13019.

Cut-point Approach:

Data distribution from the unspiked samples was evaluated for normality, and Shapiro-Wilk analysis of the data verifies the assumption of normally distributed data [$p = 0.0538$, Appendix 19 (page 121) of the validation report]. It was determined that no outliers were present in the data distribution. Therefore, the full data set was used and kept non-transformed for the determination of the validation cut-point value. Because of the normality of data, a parametric approach was used to determine the validation cut-point (mean + 1.645 x SD) as 67.3 counts.

Reviewer Comment: *The sponsor did not provide statistical data to support the conclusion that there are no outliers present in the data distribution. An IR was communicated to the sponsor to provide the statistical approach that was used to identify potential outliers.*

Outliers

The sponsor provided BSER_BA13019 in the IR response, which outlines the statistical approach used during cut-point determination. Statistical outliers were defined using a box-plot method as any points above the 75th percentile (Q3) plus 1.5 times the interquartile range (Q3-Q1) and all points that are below the 25th percentile (Q1) minus 1.5 times the interquartile range. As shown in Figure 5-2 from BSER_BA13019, no outliers were identified during the screening cut-point determination.

Reviewer Comment: *This is an acceptable approach to statistically determine outliers in the data population.*

Type of cut-point

A statistical analysis of assay variance and assay means between analyst and runs is provided in BSER_BA13019. The two analysts ran the assay on separate plates and it was determined that the assay variance was similar between analysts ($p=0.5321$, Levene's Test; page 10 of BSER_BA13019) and between plate runs [$p=0.5484$, Levene's Test; page 12 of BSER_BA13019), while assay means were not proven to be statistically similar between analysts and between plate runs ($p<0.0001$, ANOVA; pages 11 and 12 of BSER_BA13019). Therefore, a floating cut-point is justified to determine the screening cut-point value. However, due to the fact that there is a true difference between analysts or plate runs, an overall and analyst specific floating cut-points were calculated (see page 12 of the BSER_BA13019).

Method 1 (Overall): This method includes a cut-point for both analysts. Normalization factor was determined to be 12.8 (67.3 – 54.5). The value of 54.5 is the mean of blank values as assessed by both analysts. Therefore, the floating cut-point for both analysts is blank value + 12.8.

Method 2 (Analyst-specific): This method includes a cut-point for each analyst. The normalization factor for (b)(4) analyst is 14.2 (67.3-53.1). The 53.1 value is the mean of blank values as assessed by (b)(4) analyst. Thus, the floating cut point for (b)(4) analyst is blank value + 14.2. The normalization factor for (b)(4) analyst is 11.5 (67.3-55.8). The 55.8

value is the mean of blank values as assessed by (b) (4) analyst. Thus, the floating cut point for analyst (b) (4) is blank value + 11.5

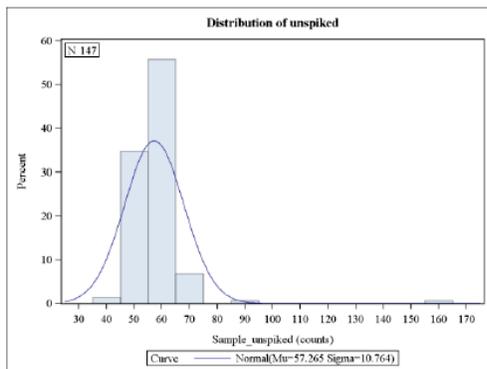
The sponsor described both approaches as acceptable, but used Method 1 cut-point (blank value + 12.8) because this method gives a more conservative cut-point value in comparison to analyst-specific floating cut-points. Therefore, all samples at or above the screening cut-point of “**blank value per plate + 12.8**” will be re-analyzed in the confirmatory assay (see below).

Reviewer Comment: *The analytical study report for the determination of ADAs in serum samples of psoriasis patients from clinical study GP15-302 describes an additional analyst (b) (4) as the analyst who screened the clinical serum samples for ADA determination by the ECL method (BA14001R). Because this analyst was not a part of the method validation, the screening cut-point was calculated for the (b) (4) analyst using the same principles as described above to determine the suitability of the cut-point determined during validation and whether the cut-point calculated for analyst (b) (4) should be used. Data were provided in analytical study report BA14001-R and BSER_BA14001 describing the calculation of the cut-point for analyst (b) (4) (evaluated below).*

Calculation of the Screening Cut-point for Analyst (b) (4)

The same commercial psoriasis serum samples were used to evaluate data distribution of unspiked samples by the (b) (4) analyst. As shown below in Figure 5-1 of BSER_BA14001, unspiked samples show a deviation from normality prior to outlier exclusion. Two outliers were identified by the boxplot method and were removed from further analysis.

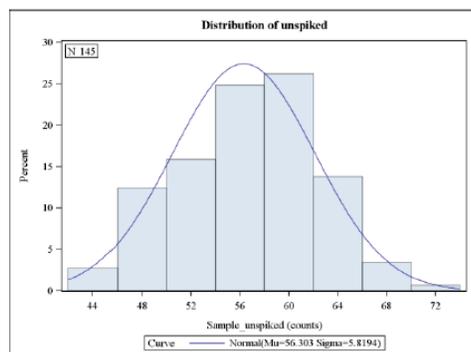
Figure 5-1 Histogram and p-p-plot for



patient	unspiked value	outlier, lower limit	outlier, upper limit
130612-10	160	38.5	74.5
130612-10	94	38.5	74.5

While the data distribution after outlier exclusion appears normal according to the histogram presented in Figure 5-3 of BSER_14001 (see below), the statistical assessment of the data by the Shapiro-Wilk test suggests that there is evidence that the data distribution deviates from normality ($p=0.0466$, see below).

Figure 5-3 Histogram and p-plot for u



Tests for Normality				
Test	Statistic		p Value	
Shapiro-Wilk	W	0.981419	Pr < W	0.0466
Kolmogorov-Smirnov	D	0.089078	Pr > D	<0.0100
Cramer-von Mises	W-Sq	0.115923	Pr > W-Sq	0.0720
Anderson-Darling	A-Sq	0.770333	Pr > A-Sq	0.0454

Data were log-transformed and statistical analysis still demonstrates that the data distribution deviates from normality (not shown in the review). The sponsor used the Central Limit Theorem to assume normality of data.

Reviewer Comment: *The Central Limit Theorem is not a recommended approach to assume normality during cut-point determination because the central limit theorem involves the comparison of means, while cut-point determination compares individual values. An IR was communicated to the sponsor, and in response to that IR, the sponsor provided additional data to support the assumption of data normality, which was determined to be acceptable and is shown below.*

Graphical assessment of the non-transformed data (Figure 5-3, see above) suggests that the data might be symmetric. The skewness of the data was calculated, and because the skewness of the data was calculated below a value of one (-0.09, page 9 of BSER_14001), it is appropriate to use a parametric approach (i.e., mean + 1.645 x SD) to determine the cut-point. Thus, the sponsor calculated the cut-point using a parametric approach, and because of evidence of non-normality, cut-points were also determined by a robust-parametric and a non-robust parametric approach for comparison purposes.

The calculation of the validation cut-point:

- 65.9 counts** using a parametric approach (mean + 1.645 x SD)
- 66.8 counts using a robust parametric [median + 1.645 * (1.483 * MAD)]
- 65.0 using a non-parametric (95th percentile)

Reviewer Comment: *The parametric approach used to determine the validation cut-point for analyst (b) (4) is appropriate. Because the validation cut-points are similar as determined by different statistical approaches, the assumption of data normality did not significantly impact the determination of the cut-point value.*

Data and statistical analysis are provided in BSER_BA14001 in determining whether assay variances and assay means are similar or different between runs. Statistical and graphical data (page 11 of BSER-BA14001) demonstrate a difference of assay means between runs ($p < 0.0001$, ANOVA), while there is no statistical evidence to the 5% level that suggests the assay variances are not equal ($p = 0.5333$, Levene’s Test).

Because the assay means are not statistically similar and the assay variances are not statistically different, a floating cut-point using an additive normalization factor is appropriate. The mean blank value (55.9 counts) was subtracted from the validation cut-point of the parametric method (65.9 counts) to yield a normalization factor of 10. Therefore, the screening cut-point was configured to be **blank value per plate + 10**. The cut-point for analyst (b)(4) did not lead to different screening results when compared to the screening results from the original screening cut-point.

Reviewer Comment: *Because the calculated validation cut-point specific to the analyst (b)(4) (65.9 counts) is comparable to the validation cut-point determined during the original method validation (67.3 counts), both validation cut-points are suitable for their intended purpose. The difference of less than two counts is within assay variability and likely not to impact the immunogenicity evaluation. Because the screening cut-point calculated for analyst (b)(4) after normalization resulted in a more conservative screening cut-point (i.e., blank value per plate + 10) in comparison to any of the cut-points calculated during validation (e.g., blank value per plate + 12.8), the sponsor used the analyst (b)(4) screening cut-point during the assessment of ADAs in clinical samples (Study GP15-302). This is acceptable because (i) the use of analyst (b)(4) cut-point did not lead to different screening results of commercial patient sera when compared to the screening results obtained with the cut-point determined during method validation and (ii) the determined validation cut-point for analyst (b)(4) using commercial patient sera is comparable to when using pre-dosed in-study patient sera (65.5 counts, see below).*

Verification of the cut-point in clinical samples

The suitability of the validation cut-point determined during validation (67.3 counts) and by analyst (b)(4) (65.9 counts) was evaluated by testing pre-dose in-study patients (BSER_BA13019). During the study, serum samples were collected from randomized pre-dosed patients. The distribution of the unspiked data was evaluated for normality and outliers. Using a box-plot method, 11 outliers were identified and removed from further analysis. The data distribution after outlier exclusion resulted in a normal distribution (Shapiro-Wilk, $p=0.1052$, page 18 of BSER_BA13019). Because of the data normality, a validation cut-point of **65.5 counts** was determined by a parametric method (mean + 1.645 x SD, using a 5% false-positive rate).

Reviewer Comment: *The commercial psoriasis patient sera are representative of the clinical psoriasis patient sera; the cut-point (analyst (b)(4)) determined based on the commercial sera is suitable to analyze the clinical serum samples. Additionally, the number of positive pre-dosed in-study patients was in the expected and calculated false positive range of 5% (i.e., 4.8%) and the LPC was consistently detected positive and slightly above the screening cut-point (analyst (b)(4)), further supporting that the commercial patient sera used for cut-point calculation for analyst (b)(4) reflect the GP15-302 study population.*

Cut-point - Confirmatory Assay

A confirmatory assay was established within the assay as described above. For determination of the confirmatory cut-point, the same 50 individual psoriasis patient serum samples that were analyzed for establishing the screening cut-point were spiked with excess of drug (10 µg/ml of GP2015.02REF in neutralization buffer) after the second acid treatment and analyzed together with unspiked samples in one run. This analysis was performed three times by two separate analysts (i.e., (b)(4)). Percent inhibition was defined as $(100 - ((\text{counts spiked} / \text{counts unspiked}) * 100))$.

Cut-point Approach:

A thorough statistical analysis of outlier determination from the % signal inhibition data is provided in the BSER_BA13019 document. The boxplot method identified four outliers in the data distribution [Figure 5-6 of BSER_BA13019 (page 14)], and subsequently, the outliers were excluded from further analysis. After outlier exclusion, the data distribution was determined to be normal [Figure 5-7 of BSER_BA13019 (page 15)], as there is no evidence from a 5% significance level using the Shapiro-Wilk test that the data distribution is not normal ($p=0.4032$). Because of the normally distributed data, a parametric formula (cut-point = mean percent inhibition + 3.09 x SD) was used to calculate the cut-point value of non-transformed data. The value of 3.09 corresponds to the 99.9th percentile of the normal distribution, allowing a false-positive error rate of 0.1%. The mean was calculated as one and the standard deviation was calculated as seven. The confirmatory cut-point was determined to be at **23% assay signal inhibition**.

Sensitivity and LPC

Assay sensitivity

Eight serial dilutions of the positive control antibody spanning the screening cut-point were prepared in diluted (1:3) psoriasis patient serum pool by two analysts on three different days (n=6). Each dilution series was fitted by a linear regression model to interpolate the concentration corresponding to the screening assay cut-point counts (Table 8-1 in Appendix 08 of the validation report). Statistical analysis for the derivation of the assay sensitivity in 100% serum is provided in Appendix 18 of the validation report. The geometric mean was calculated as 73.6 and the assay sensitivity was determined to be **116.5 ng/ml** (mean + $t_{0.05,df}$ x SD; upper confidence limit of 95%).

Calculation of Low positive control

A LPC close to the screening cut-point was objectively determined and validated to ensure consistent assay performance at the cut-point level. This control was included in screening and confirmatory assays for clinical assessment and was set to fail 1% of the time (i.e., 99% of the data from the LPC will be at or above the cut-point). Calculation of the LPC was determined to be **158.3 ng/ml** (mean concentration sensitivity + $t_{0.01,df}$ x SD) after transformation and back-transformation of data.

Verification of low positive control

An experiment was performed to verify that a sample with an ADA concentration at the level of the LPC (158.3 ng/ml) will be detected as positive during the confirmatory assay (the % inhibition is NLT the specificity cut-point). Three sets of LPCs were spiked and unspiked with excess of drug (10 µg/ml of GP2015.02REF in neutralization buffer) and analyzed on three different days by two separate analysts. QC sets were also spiked and unspiked. Data from these experiments are summarized in Table 17-1 through 17-4 (Appendix 17) of the validation report and support the suitability of the LPC; the LPC could be confirmed as positive in the confirmatory assay (i.e., the % inhibition was NLT 23%).

Reviewer Comment: *The assay sensitivity (116.5 ng/ml) and LPC (158.3 ng/ml) values are appropriately determined and allow for consistent detection of low levels of anti-etanercept antibodies at the cut-point level.*

Titer Determination

Titers of confirmed positive ADAs to etanercept are determined after testing positive in the screening and confirmatory assays. The titer assay uses the same platform as the screening assay. The analytical results of the sensitivity experiments were used for titer determination. The last dilution which led to a result above the determined screening cut-point is reported as titer. Results from the sensitivity experiment demonstrate that five of the six dilution series crossed the screening assay cut-point within \pm one dilution step and met the acceptance criteria [Appendix 8 (Table 8-1) of the validation report]. The titer was determined for each sample except one that had the most diluted sample of the series still above the cut-point. It was determined that further dilution of this sample was not necessary.

Reviewer Comment: *The approach used for titer determination is acceptable and the low sensitivity value of the assay ensures that dilutions can be made while still allowing for positive diluted samples to test positive in determining the ADA titer.*

Selectivity/Interference from matrix components

Ten individual psoriasis patient serum samples were diluted 1:3 and spiked three times independently with two different concentrations of the positive control antibody (VS1, 18,000 ng/ml and LLOQ, 150 ng/ml). The spiked samples were analyzed in duplicate against a calibration curve. The mean and analysis of back-calculated concentration values are displayed in Table 4-1 and Table 4-2 (Appendix 4) of the validation report.

LLOQ failed the acceptance criteria for accuracy and precision (%CV) during runs A01 and A03, respectively. Excluding these failed runs, %CV values were NMT 18% and accuracy values ranged from 88% to 114%. Because ninety percent of the individual sera fulfilled the acceptance criteria for both accuracy (80% to 120%) and precision (NMT 20%, CV), it was concluded that there are no matrix interference effects at a 1:3 dilution of matrix (psoriatic serum).

Reviewer Comment: *The back-calculated ADA concentrations from samples spiked with VS1 and LLOQ preparations are considered close to the expected values with high precision and accuracy; therefore, the ECL assay can detect a broad concentration range of anti-etanercept antibodies (150 ng/ml to 18,000 ng/ml) in the presence of matrix components from 1:3-diluted psoriasis patient serum.*

The above selectivity experiment analyzed matrix interference between spiked samples in serum of healthy volunteers and in serum of psoriasis patients (i.e., disease-related factors). No data were provided describing matrix interference from serum samples in comparison to assay buffer. An IR was communicated to the sponsor to provide data supporting the 1:3 MRD used for the psoriasis patient serum and an evaluation of serum components that could potentially interfere with the detection of ADAs.

MRD

In response to the IR, the sponsor summarized the results from pre-validation experiments to support the derivation of the 1:3 MRD using individual psoriasis patient sera and psoriasis serum pool. A positive control antibody at a high concentration (HPC, 15,000 ng/ml) and at a low concentration (LPC, 300 ng/ml) was spiked into individual psoriasis sera and the accuracy of the

back-calculated concentration values was determined from a standard curve. Spiking samples with neat serum, i.e., without serum dilution, and at a 1:2 dilution showed matrix interference, i.e., back-calculated values were determined to be outside the acceptable range of accuracy (data not provided). In contrast, the 1:3 dilution led to back-calculated concentration values within the acceptable range of accuracy (data not provided). The appropriateness of the 1:3 dilution was confirmed by spiking the 1:3 diluted psoriasis serum pool with different concentrations of the positive control antibody (i.e., 150 ng/ml to 24,000 ng/ml). As shown in Table 3-4 of the IR response, the 1:3 dilution results in the detection of a broad concentration range of ADAs without matrix-related interferences.

Matrix Components

Furthermore, the effects of lipids in the serum was assessed during pre-validation experiments by spiking a HPC (6,000 ng/ml) or a LPC (150 ng/ml) into lipaemic psoriasis serum samples. Results are displayed in Table 3-3 of the IR response (see below). Given the similarity between hemolytic and lipaemic states, hemolytic sera were not evaluated for the ECL method, but were evaluated for the CLB assay and shown not to impact method performance.

Table 3-3 Selectivity results of lipaemic serum

lipaemic serum no.	Expected concentration [ng/mL]	Mean calculated concentration [ng/mL]	Accuracy [%]
01	6000	5950	99
	150	237	158 ¹⁾
02	6000	5810	97
	150	148	99
03	6000	5453	92
	150	126	84
04	6000	5765	96
	150	134	89

¹⁾ Acceptance criteria for accuracy not met

Reviewer Comment: *Because the obtained accuracy values, with the exception of one sample spiked with the LPC (#01), met the pre-defined acceptance criteria (80% - 120%, Table 3-3; shown above), it is not expected that serum lipids will impact the ECL method results. Because this sample failed the acceptance criterion with a higher than expected concentration value (i.e., 237 vs. 150 ng/ml), which results in a false positive, it should not interfere with the detection of anti-etanercept antibodies.*

Pre-existing antibodies

In response to one of the questions sent in the IR, the sponsor (i) clarified that individual sera were selected from the vendor excluding psoriasis patients that received etanercept or any other biologic and (ii) provided pre-validation data demonstrating that individual sera samples used to generate the psoriasis patient serum pool were determined to have an acceptable level of accurate back-calculated concentration values when spiked with a LPC and a HPC (Table 3-6 of the IR response). All samples with the exception of sample 9 (124%) and sample 16 (129%), both spiked with the LPC, resulted in accuracy values of back-calculated concentrations of ADAs within the acceptable range (80% - 120%). Samples not spiked with the positive control antibody showed ADA concentrations NMT 7.5 ng/ml, which is below the assay sensitivity level.

Reviewer Comment: The additional information provided supports the 1:3 MRD and demonstrates that the psoriasis patient serum samples are suitable for their intended purpose and will allow for assay calculation of meaningful values without matrix-related interferences.

Precision and Accuracy

Intra-assay precision

Five sets of validation samples were prepared in psoriasis patient serum pool (VS1, VS2, VS3, LLOQ-VS, and ULOQ-VS) and duplicates were measured together with a calibration curve prepared in HV human serum pool. The intra-assay precision of the five sets of validation samples were within the pre-defined acceptance criteria for precision (%CV, NMT 8%) and accuracy (91% for ULOQ-VS, 87% to 101% for VS1 to VS3, and 125% for LLOQ-VS). Total error was not included as an acceptance criterion.

Inter-assay precision and accuracy

One set of validation samples was prepared in psoriasis patient serum pool (VS1-VS3, LLOQ-VS, and ULOQ-VS) and duplicates were measured together with a calibration curve prepared in HV human serum pool in seven different runs on seven different days. Two analysts and two microplate washers were used within the seven runs. The acceptance criteria were fulfilled for all validation parameters. Results are shown below in Table 6-1 (Appendix 6) of the validation report (see below).

Table 6-1 Inter-assay

Test Item	Expected conc. [ng/ml]	Set 1 Conc. [ng/ml]	Set 2 conc. [ng/ml]	Set 3 ²⁾ conc. [ng/ml]	Set 3_2 conc. [ng/ml]	Set 4 conc. [ng/ml]	Set 5 conc. [ng/ml]	Set 6 conc. [ng/ml]	Set 7 ²⁾ conc. [ng/ml]	Mean conc. [ng/ml]	SD [ng/ml]	CV [%]	Accuracy [%]	Total error ¹⁾ [%]
ULOQ-VS	24000	23687	24040	14432	22287	24293	22305	26101	23078	23684	1327	6	99	7
VS1	18000	17402	17251	14794	15657	18174	17118	19752	17000	17479	1251	7	97	10
VS2	2700	2390	2412	2239	2350	2609	2544	2611	2482	2485	106	4	92	12
VS3	450	461	442	441	409	503	481	485	463	463	31	7	103	10
LLOQ-VS	150	151	170	109	163	190	162	153	164	165	13	8	110	18
Internal washer no.		3	3	5	3	3	3	3	5					
Analyst									(b) (4)					

¹⁾ sum of absolute value of the % relative error and % CV

²⁾ different wash device was used

technical error

Reviewer Comment: The assay can be performed with high intra- and inter-assay precision and accuracy for detection of anti-etanercept antibodies in a range of 24,000 ng/ml to 150 ng/ml. ULOQ and LLOQ were verified as 24,000 ng/ml and 150 ng/ml, respectively. The LLOQ is appropriate, as it is slightly above the assay sensitivity (116 ng/ml) and slightly below the positive control (158.3 ng/ml). Because the LLOQ was evaluated for precision, it is acceptable that the LPC was not.

Robustness

Robustness was assessed during the inter-assay precision experiment through the use of two washers (Table 6-1, see above).

Reviewer Comment: Because the back-calculated concentration values between different washers are similar and result in acceptance criteria fulfillment of precision and accuracy, it can be concluded that different washers do not impact the detection of ADAs near the assay cut-point.

Linearity

The mean, standard deviation, and CV were calculated for all concentration data points from the calibration curves obtained in the inter-assay precision experiment performed above (Table 7-1 of the validation report). The expected concentration (i.e., 24,000 ng/ml to 150 ng/ml) was plotted against the average of the back-calculated concentration and a linear regression was performed (Graph in Appendix 7). The acceptance criteria for precision were met for each standard across seven runs (NMT 4%; Table 7-1 of the validation report).

Reviewer Comment: *The assay is linear between an ADA range of 24,000 ng/ml and 150 ng/ml. These data indicate that the assay performs well across a broad range of ADA concentrations.*

Dilution Testing

Pre-validation experiments were performed to determine the appropriate medium to dilute psoriasis patient serum samples containing ADAs outside the upper linear calibration range of the assay (i.e., ULOQ). Psoriasis serum samples (i.e., validation samples) are diluted 1:3 in blocking buffer (5% BSA and 0.05% Tween® 20 in D-PBS) and all further dilutions are performed in 1:3 diluted HV human serum pool.

To evaluate the impact of the 1:3 diluted HV human serum pool, three independent dilution series of the positive control antibody starting at 40,000 ng/ml in non-diluted psoriatic serum pool were prepared. After the initial 1:3 dilution in blocking buffer (40,000 ng/ml), dilutions of 20,000 ng/ml, 10,000 ng/ml, 5,000 ng/ml, 1,000 ng/ml, and 500 ng/ml were prepared in 1:3 diluted human serum from healthy volunteers. The results are multiplied by the dilution factor and displayed in Table 13-2 of Appendix 13 of the validation report.

The averaged back-calculated concentration at each concentration level was between 89% and 101% of the expected concentration. The precision of the final concentration, after multiplying by the dilution factor, was NMT 6%. These results meet the acceptance criteria. To assess linearity, the expected concentration was plotted against the average of the back-calculated concentration and a linear regression was performed (Figure in Appendix 13). The slope of the curve was 0.9222 and the coefficient of correlation was 0.9995, which fulfilled the acceptance criterion for dilution linearity.

The prozone effect, false negative responses resulting from high antibody titer which interferes with assay detection, was evaluated and results are shown in Appendix 13 (Table 13-1) of the validation report. Because samples with an expected concentration above the ULOQ (40,000 ng/ml) measured above ULOQ with an accuracy of 101% (i.e., 39,673 ng/ml to 41,408 ng/ml) and a CV value of 2%, a prozone effect was determined to not apply for the data.

Reviewer Comment: *The diluted (1:3) human serum pool from healthy volunteers can be used as a diluent to further dilute serum samples with ADA concentrations above the ULOQ and yield accurate and precise results.*

Stability

Positive Control antibody

The stability of the positive control antibody prepared in psoriasis serum pool at 18,000 ng/ml (VS1) and 450 ng/ml (VS3) was evaluated under various conditions, including freeze/thaw cycles (0, 1, 3, and 5 cycles), short-term at 2°C – 8°C (0, 1, and 3 days), short-term at RT (0, 8, and 22.5 hours), and long-term at -70°C or -20°C (0, 3, 4, 6, 8, and 12 months). Detailed procedures of each stability assay are described in Section 5.12 to 5.15 of the validation report and results are included in data tables in Appendix 9 through Appendix 12 of the validation report.

<u>Freeze/thaw</u>	Accuracy: 93% - 105%,	CV: NMT 7%
<u>Short-term at 2 – 8°C</u>	Accuracy: 85% - 101%,	CV: NMT 9%
<u>Short-term at RT</u>	Accuracy: 89% - 99%,	CV: NMT 6%
<u>Long-term at -70°C</u>	Accuracy: 87% - 117%,	CV: NMT 11%
<u>Long-term at -20°C</u>	Accuracy: 87% - 123% ,	CV: NMT 9%

Reviewer Comment: *Although the accuracy acceptance criterion was not fulfilled for the VS3 sample at 4 months of testing at -20°C, the positive control antibody at both 18,000 ng/ml and 450 ng/ml concentrations were stable at 6 and 12 months at -20°C. Therefore, the positive control antibody preparations at VS1 and VS3 concentrations are stable in human serum from psoriasis patients for up to 5 freeze/thaw cycles, 3 days at 2-8°C, 22.5 hours at RT, and 12 months at -70°C or -20°C.*

The LPC that detects low levels of ADA near the assay cut-point was not tested under the described stability testing conditions. However, this is acceptable because the positive control antibody at a concentration of 450 ng/ml, which is within the recommended assay sensitivity range (200 – 500 ng/ml), was determined to be stable under all tested stability conditions.

Stability of critical reagents

GP2015-Biotin and GP2015-Sulfotag were also shown to be stable up to 6 months at -70°C (recommend storage temperature), as the mean measured concentration of VS1 (15,000 ng/ml) and VS3 (600 ng/ml) was 116% (17,469 ng/ml) and 120% (819) of the expected value (0h) with acceptable precision [CV% NMT 7% (VS1), NMT 9% (VS3)]. Data are shown in BA12013-RA01 validation report.

Drug Interference

The potential of drug interference of the ECL assay was investigated. The positive control antibody was spiked in 1:3 diluted human psoriatic serum pool at the VS1, VS2, and VS3 concentrations (24,000 ng/ml, 600 ng/ml, and 200 ng/ml, respectively). These samples received serial dilutions of drug (GP2015 or EU-approved Enbrel) before the first acid treatment and then tested in duplicates in one run together with a calibration curve prepared in 1:3 diluted HV human serum pool. Counts for each situation were compared to the assay cut-point and drug interference shows counts that are below the cut-point value. Results are displayed in data tables in Appendix 16 of the validation report and successful detection of ADAs at the highest level of drug is shown below as drug tolerance limits.

- Drug concentration of 100 µg/ml does not interfere with the detection of 24,000 ng/ml of ADAs
- Drug concentration of 50 µg/ml (GP2015) does not interfere with the detection of 600 ng/ml of ADAs, while drug concentrations above 20 µg/ml (EU-approved Enbrel) interfere with detection of 600 ng/ml of ADAs
- Drug concentrations above 1 µg/ml interfere with the detection of 200 ng/ml of ADAs

Reviewer Comment: *The drug tolerance results above demonstrate that mid/low amounts (i.e., 600 ng/ml) and high amounts (i.e., 24,000 ng/ml) of ADAs can still be detected in presence of trough serum levels of GP2015 [4,000 – 10,000 ng/ml (4 – 10 µg/ml)]. Although it is not clear what the lowest concentration of on-board drug is that would modify the sensitivity of the assay to detect 600 ng/ml and 24,000 ng/ml of ADAs, the level of drug would be substantially higher than trough levels and this is considered acceptable.*

Low amounts of ADAs (i.e., 200 ng/ml) that are close to the assay sensitivity and LPC value are able to tolerate up to 1 µg/ml of drug, suggesting that trough levels of drugs are capable of interfering with the detection of low levels of anti-etanercept ADAs that are near the assay cut-point. However, the drug tolerance level determined at an ADA level of 600 ng/ml was at least twice as high as the highest measured PK concentration value at trough, and because 250 – 500 ng/ml is the recommended level of assay sensitivity for a binding ADA assay, the assay is expected to have a reasonable drug tolerance level at a slightly lower ADA level at 500 ng/ml, which can be expected to be detected within a similar drug tolerance background when compared to an ADA level at 600 ng/ml. Therefore, the drug tolerance capacity of the screening assay is acceptable.

Specificity

A confirmatory assay was implemented to show that the ECL assay can specifically detect etanercept-specific ADAs. Immunodepletion analysis was used to demonstrate specificity of analyte binding. Positive control preparations, i.e. VS1 and VS3, were treated with different concentrations of soluble drug (GP2015 and EU-approved Enbrel). The results are displayed in Appendix 14 (Table 14-1 and 14-2) of the validation report. Counts were plotted against the drug concentrations and mean concentrations were back-calculated from individual counts in relation to the calibration curve. The reduction in assay signal was calculated and compared to the confirmatory cut-point. For both drug products (GP2015 and EU-approved Enbrel) at a concentration of 1 µg/ml and up to 20 µg/ml, a reduction of the assay signal higher than the specificity cut-point of 23% inhibition was observed for anti-etanercept ADA concentrations of 18,000 ng/ml (VS1) or 450 ng/ml (VS3). The depletion curves are superimposable when comparing samples spiked with Enbrel and GP2015.

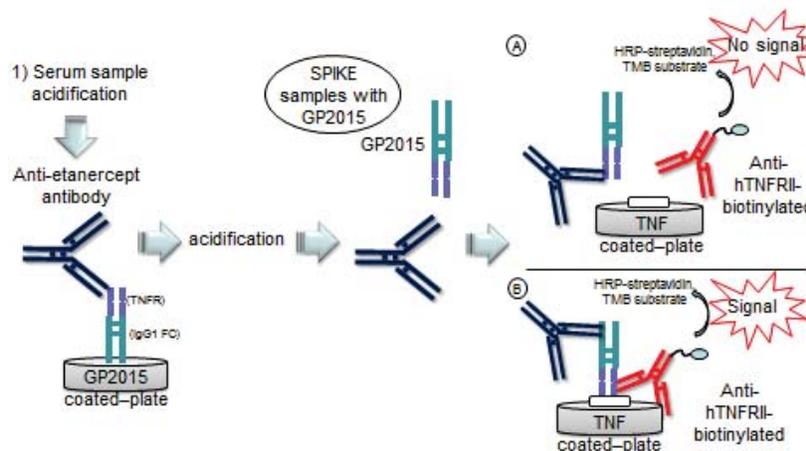
Reviewer Comment: *Because the detection of high and low concentrations of ADAs can be similarly depleted with both EU-approved Enbrel and GP2015 at concentrations of drug below, at, or above trough levels, the assay is suitable to detect both ADAs against EU-approved Enbrel and GP2015. For the analysis of in-study samples, a concentration of 10 µg/ml of drug was used, and as discussed above, the ADA responses were similarly depleted with both GP2015 and EU-approved Enbrel.*

Section 1b – Neutralizing CLB Assay

Serum samples that confirm positive for anti-etanercept binding ADAs in the confirmatory assay are further tested for their neutralizing potential. Study BA14023 was conducted to validate the CLB assay for the detection of neutralizing antibodies against GP2015 and EU-approved Enbrel in psoriasis patient serum. Results are displayed in the validation report (BA14023-R) and statistical analysis is provided in BSER_BA14023. The principle of method is illustrated below in Figure 1.

Figure 1 - Neutralization Assay

Neutralization Assay – CLB format



**The illustration is made by the primary reviewer.*

The ELISA-based method uses OD values as the readout and OD readings from spiked (GP2015) and unspiked individual psoriasis patient samples were compared to OD readings from spiked and unspiked HV human serum pool. The percent of inhibition (formula shown below) is calculated from these OD readings, and if the % inhibition is above the cut-point for a test sample, then that sample contains ADAs with neutralizing activity.

$$\text{Neutralization / \% inhibition} = 100 \left[1 - \left(\frac{(\text{OD}_{\text{individualsample} + \text{GP2015}}) - (\text{OD}_{\text{individualsample}})}{(\text{OD}_{\text{human serum pool} + \text{GP2015}}) - (\text{OD}_{\text{human serum pool}})} \right) \right]$$

Reviewer Comment: *Data supporting the suitability of the GP2015 concentration used in the assay (i.e., 20 ng/ml) were not provided. An IR was communicated to the sponsor to demonstrate that 20 ng/ml is within the linear range of the activity curve for GP2015.*

In response to the IR, the sponsor provided a GP2015 response curve of the CLB assay testing different concentrations of GP2015 (10 ng/ml to 60 ng/ml) in the ability to detect neutralizing antibody-GP2015 complexes. In Figure 5-1 of the IR response (not shown), several calibration curves are graphed, plotting the OD value for each standard of the calibration curve or blank when 10 – 60 ng/ml of GP2015 are used in the assay.

Reviewer Comment: While GP2015 concentration and reported OD value (assay signal) for each standard are not directly proportional, GP2015 at a high concentration (60 ng/ml) leads to weaker binding to neutralizing ADAs and a higher assay signal and GP2015 at a low concentration (10 ng/ml) leads to greater binding to neutralizing ADAs and lower assay signal. The GP2015 response curve data indicate that the percent inhibition of the OD values by the different concentrations of GP2015 (i.e., 10 to 60 ng/ml) is the highest at 20 ng/ml. For example, comparing standard 6 (1000 ng/ml of the positive control) OD values of 1.5, 2.4, 2.6, and 3.0 for 10, 20, 40, and 60 ng/ml of GP2015, respectively, with standard 8 (0 ng/ml of positive control) OD values of 1.6, 2.6, 2.75, and 3.2 for 10, 20, 40, and 60 ng/ml of GP2015, respectively, the % inhibition is calculated as 6.25%, 7.7%, 5.45%, and 6.25% for 10, 20, 40, and 60 ng/ml of GP2015, respectively. Therefore, based on the data provided, the sponsor's selection of 20 ng/ml is justified.

The validation analyses were performed in 40 runs starting from September 22, 2014 and ending on March 25, 2015 (Table 4-15 of the validation report). Eleven runs failed due to technical error or standard/QC failure and were not considered for the evaluation of the validation parameters.

Reviewer Comment: Failed runs were due to technical error; however, an explanation of what that error was and why it occurred is not provided. This is acceptable because the technical error did not compromise the method validation as failed runs were successfully repeated without incident.

Matrix

The psoriasis serum pool was comprised of individual sera from psoriasis patients (n=9) provided by (b) (4) (Table 4-11 of the validation report). Twenty one additional individual samples were also provided by (b) (4) and the total of 30 individual serum samples was used for validation of the cut-point (Table 4-10 of the validation report). The samples were used prior to their expiration date, ranging from March 2015 to July 2017.

The HV human serum pool (Lot# IR11-1626) was provided by (b) (4). The negative control was prepared in HV human serum pool and contains all assay components (e.g., GP2015) except the positive control antibodies (maximum signal). Diluted HV human serum pool was used as a blank.

All individual samples and the serum pool were used prior to their respective expiration dates and properly stored. Due to the matrix-related interferences observed in the validation, the matrix was diluted 1:3 in blocking buffer (5% BSA and 0.05% Tween® 20 in D-PBS) prior to executing the method validation.

Reviewer Comment: The impact of matrix-related interference, including pre-existing antibodies and serum components, on CLB method performance is evaluated in the [Selectivity/Matrix Interference](#) section of the review.

Assay controls

Positive Control(s)

A polyclonal anti-etanercept antibody and a monoclonal anti-etanercept antibody were used in the validation of the assay (Table 4-1 of the validation report).

- The same polyclonal antibody used for the validation of the ECL assay was used for the validation of the CLB neutralizing assay.
- The monoclonal antibody (TNFRSF1B/TNFR2/p75 mouse anti-human monoclonal antibody_LS-C4009-LSbio) is a commercially available neutralizing antibody that was purchased from LifeSpan BioScience, Inc. This antibody functions by binding to human TNFR, preventing TNF- α to TNFR binding. The monoclonal antibody was only used to create validation samples for the drug tolerance and specificity experiments.

The positive control antibodies were properly stored at -70°C and used within a reasonable amount of time from delivery for an antibody that is properly handled and stored. While the monoclonal antibody was used fresh, the stability of the positive control polyclonal antibody was monitored during routine sample analysis via calibration and QC samples and no trends were reported in the method validation and study reports.

Calibration Curve

As a part of system suitability testing, two sets of calibration curve samples were prepared as shown below in Table 4-6 of the validation report (see below). OD readings from control and test samples were compared to OD readings of a calibration curve to determine back-calculated concentration values.

Table 4-6 Preparation of calibration curve samples

Calibration curve sample	Dilution	Total volume [μl]	Matrix [μl]	Rabbit anti-etanercept PAb [μl]	Concentration in 100% serum [ng/ml]
STD1	1:3	600	400 ¹⁾	200 of PD _{STD} (see Table 4-5)	10,000
STD2	1:1.25	500	100 ²⁾	400 of STD1	8,000
STD3	1:1.333	400	100 ²⁾	300 of STD2	6,000
STD4	1:1.5	300	100 ²⁾	200 of STD3	4,000
STD5	1:2	300	150 ²⁾	150 of STD4	2,000
STD6	1:2	300	150 ²⁾	150 of STD5	1,000
STD7	1:2	300	150 ²⁾	150 of STD6	500
STD8	n/a	150	150 ²⁾	n/a	0

¹⁾ Matrix buffer

²⁾ 1:3 diluted human serum pool HV

The mean OD and back-calculated concentration values of the calibration curve samples (two replicates per sample) from each of the 40 validation runs are displayed in Appendix 01 of the validation report. The accuracy of back-calculated concentration values from valid plates ranged from 86% to 118% with the exception of standard 7 in run #31 (129%), #33 (129%), and #37 (131%). The CV of back-calculated concentration values from valid plates ranged from 0% to 18%. The coefficient of correlation of each calibration curve ranged from 0.998 to 1.000. Mean OD values from the blank samples (standard 8) ranged from 0.298 to 1.059 from plate to plate.

Reviewer Comment: *Because every run met the plate acceptance criterion [i.e., each plate has a minimum of six calibration curve standards that are within the acceptance criteria for accuracy (75 – 120% for STD 1,7 and 80 – 120% for STD 2-6) and precision (CV% NMT 25% for STD 1,7 and CV% NMT 20% for STD 2-6)], the accuracy exceptions are considered acceptable. The calibration curve is suitable for its intended purpose of correlating counts to concentration in a linear manner*

with high precision and accuracy. Although the blank did not have an acceptance criterion, the negative control appears suitable for its intended purpose because the blank values drift in the same direction as individual sample values.

Quality Controls

As a part of system suitability testing, two sets of QC samples were prepared by spiking defined concentrations of the polyclonal positive control antibody into diluted (1:3) human serum pool (HV; Table 4-7 of the validation report) to generate QC1 (7,500 ng/ml), QC2 (4,000 ng/ml), and QC3 (1,500 ng/ml).

Mean OD and back-calculated concentration values of the QC samples from each plate are displayed in Appendix 02. The CV values of back-calculated concentrations for QC1, QC2, and QC3 samples from valid plates ranged from 0% to 19%. The accuracy of back-calculated concentrations for QC1, QC2, and QC3 samples from valid plates ranged from 87% to 120% with the exception of run #10 (62%), #11 (132%), #38 (135%), and #39 (122%) for QC1, run #35 (69%) and #37 (122%) for QC2, and run #34 (124%), #37 (159%), #38 (121%), and #39 (123%) for QC3. The total error values of the same samples ranged from 0% to 29% with the exception of run #10 (105%), #11 (34%), #38 (49%), and #39 (40%) for QC1, run #35 (32%) for QC2, and run #10 (32%) and #37 (61%) for QC3.

Reviewer Comment: Because the acceptance criterion for plate acceptability was fulfilled, i.e., at least four of the six quality control samples (two sets of QC1, QC2, and QC3) conform to the acceptance criteria of accuracy, precision, and total error, the exceptions described above are acceptable. The QC samples are suitable for their intended purpose to ensure the validity of the assay and production of meaningful data.

Validation Samples

Validation samples (VS) were prepared by spiking psoriasis serum pool with defined concentrations of the polyclonal or monoclonal positive control antibody. Samples were diluted as shown in Table 4-4 of the validation report (see below) for the polyclonal control antibody.

Validation sample	Dilution	Total volume [μl]	Matrix [μl]	Anti-etanercept PAb [μl]	Concentration in 100% serum [ng/ml]
33% PD _{VS} (PsO)	1:3	390	260 ¹⁾	130 of 100% PD _{VS} (see Table 4-3)	10,000
VS1	1:1.333	320	80 ²⁾	240 of 33% PD _{VS}	7,500
VS2	1:1.875	375	175 ²⁾	200 of VS1	4,000
VS3	1:2.667	267	167 ²⁾	100 of VS2	1,500

¹⁾ Matrix buffer

²⁾ 1:3 diluted human psoriasis serum pool

Cut-point

Thirty individual diluted (1:3) psoriasis patient serum samples were analyzed by two analysts (i.e., CW and FR) in three runs on three different days (n=180). Two samples were prepared from each individual patient serum (i.e., spiked with or without GP2015) and OD readings were compared to the negative control and blank. Additionally, HV human serum pool samples were spiked or unspiked with GP2015. All unspiked samples were run on the same plate to minimize background.

The mean OD value of individual psoriasis serum samples unspiked or spiked, blanks, and negative controls are presented in Appendix 12 of the validation report and the statistical analysis used in determining the cut-point is presented in BSER_BA14023.

Reviewer Comment: *Only data from analyst (b)(4) was used for the statistical evaluation of the cut-point, and because of this, it is unclear if results from the other analyst were similar or not. Because the number of individual samples used for cut-point determination was significantly below the recommended amount of 50, the IR that was communicated to the sponsor included a comment requesting the sponsor to submit the data from both analysts and the statistical evaluation of those data to determine whether a cut-point determined by analyst (b)(4) is comparable to the cut-point determined by analyst (b)(4).*

The sponsor clarified that only analyst (b)(4) was used to determine the cut-point during assay validation because that analyst was involved in the in-study sample analysis. The sponsor believed that only one analyst to run the in-study samples was sufficient because the number of confirmed positive ADAs samples was very low and all confirmed positive ADA samples would be analyzed in one experiment. The sponsor did re-calculate the CLB cut-point using both analysts (Sections 5.1 and 5.2 of BSER_BA14023) and it was determined that the original cut-point determination was more conservative (**20% signal inhibition**, analyst (b)(4)) than the cut-point determined when data from both analysts were used (**24% signal inhibition**, both analysts).

Reviewer Comment: *Although it is recommended that two analysts be used to validate the cut-point, the use of analyst (b)(4) alone to validate the cut-point is acceptable because excluding the other analyst allows for a more conservative cut-point.*

Cut-point Approach:

Outliers were not assessed. Graphical and statistical analyses demonstrate that the % signal inhibition data distribution is not normal (Shapiro-Wilk, $p=0.0003$; pages 7 and 8 of BSER_BA14023). Because the data distribution was not normal, the % signal inhibition data (ratio) were log-transformed. Distribution of the log(ratio)-transformed data is graphed and presented in Figure 5-2 of BSER_BA14023 and graphical and statistical analyses (Shapiro-Wilk, $p=0.0015$; page 6 of Appendix 14 of the validation report) suggest that the data is still not normally distributed.

Although the Shapiro-Wilk analysis of data distribution does not agree with normality, the Central Limit Theorem was used to support normality. Therefore, a parametric approach to determine the cut-point was used (cut-point = mean inhibition + $3.09 \times \text{SD}$). The 3.09 value corresponds to a 0.1% false positive rate. The low false positive rate was justified by the sponsor because there was no confirmatory step included in the CLB assay and the assay itself is used after the sensitive ECL assay. The cut-point was calculated as 0.80 (**NLT 20% signal inhibition**).

Reviewer Comment: *The Central Limit Theorem is not a recommended approach to assume normality during cut-point determination because the central limit theorem involves the comparison of means, while cut-point determination compares individual values. Therefore, the IR that was communicated to the sponsor included a comment to re-determine their cut-point based on a more suitable approach.*

The sponsor re-determined the assay cut-point using a non-parametric approach (Section 5.1.4.1 of BSER_BA14023), which is based on non-normal data distribution, and the robust parametric approach (Section 5.1.4.2 of BSER_BA14023, see above) for comparison purposes. A non-parametric approach at the 99.9th percentile using a 0.1% false positive rate was employed and the cut-point was determined as **NLT 11% signal inhibition**. A robust parametric method was used to calculate a cut-point of **NLT 20% signal inhibition** [cut-point = median + $t_{0.001,df} * (1.483 * MAD)$]. The re-calculated CLB assay cut-point using a non-parametric approach (i.e., NLT 11% signal inhibition) replaces the previously validated NLT 20% signal inhibition cut-point.

Reviewer Comment: *It is acceptable that statistical outliers were not evaluated and identified because of the non-normality distribution of the data and the method chosen. Derivation of the cut-point value by a non-parametric method using a 99.9th percentile is acceptable, although using a 99.0th percentile is more ideal to reduce the chance of missing detection of ADAs at low levels.*

Because the revised cut-point is the most conservative cut-point for the CLB assay and re-analysis of clinical data with the revised cut-point did not change the assessment of neutralizing activity from confirmed positive binding ADA samples (Table 1-2 of the IR response, see below), the revised cut-point is suitable for its intended purpose.

Table 1-2 Final study sample results using CP derived from non-parametric method

Patient no. / Visit	Mean values spiked; OD [450 nm/620nm]	CV spiked [%]	Mean values unspiked; OD [450nm/620nm]	CV unspiked [%]	Signal inhibition [%] ¹⁾	Evaluation
3601002, V4 (Day 29)	2.615	0	0.501	0	1	Negative Neutralizing
3701003, V4 (Day 29)	2.658	2	0.342	1	-9	Negative Neutralizing
3701004, V3 (Day 15)	2.665	2	0.415	1	-5	Negative Neutralizing
3701004, V4 (Day 29)	2.555	1	0.359	1	-3	Negative Neutralizing
3704018, V4 (Day 29)	2.439	1	0.411	1	5	Negative Neutralizing
4218001, V4 (Day 29)	2.594	2	0.504	2	2	Negative Neutralizing

¹⁾ CP: ≥11% inhibition

Sensitivity and LPC

Assay sensitivity

The sensitivity of the assay was determined by performing five serial dilutions of the positive control polyclonal antibody in diluted (1:3) psoriasis patient serum pool. These dilution steps were performed by two analysts (i.e., (b) (4)) on three separate days (n=6). The data shown below are derived from analyst (b) (4) (Appendix 8 of the validation report); the analyst used to determine the assay cut-point.

Table - Assay Sensitivity

Experiment ID	Concentration [ng/ml]											
	Blank	STD8	2000	1000	500	250	125	2000	1000	500	250	125
	Mean value OD [450-620 nm]						CV [%]					
BA14023_140923-4 (b) (4) eda	0.905	3.256	1.525	2.371	2.801	3.047	3.095	1	0	1	0	1
BA14023_140924-3 (b) (4) eda	0.728	3.083	1.620	2.429	2.732	2.894	3.082	2	2	2	2	1
BA14023_140925-3 (b) (4) eda	1.048	2.957	1.480	2.283	2.596	2.777	2.812	3	3	0	0	2

Each dilution series performed by analyst (b)(4) (Table, see above) was fitted by a linear regression model to interpolate the concentration corresponding to the assay cut-point. Regression analysis for each run is displayed in Appendix 13 of the validation report. The assay sensitivity was calculated from the mean of all interpolated concentrations from the three assay runs, and the calculation was based on a 95% consistency/5% rejection rate. The assay sensitivity was calculated to be **935.42 ng/ml** [mean concentration + $t_{0.05,df} \times SD$ (df=2)]. Therefore, 935.42 ng/ml is the lowest concentration at which a polyclonal positive control would consistency produce a positive signal.

Calculation of the low positive control

A LPC close to the cut-point was determined for the polyclonal positive control antibody and was validated to ensure consistent assay performance at the cut-point level. LPC was calculated to be **1,852.7 ng/ml** (mean concentration sensitivity + $t_{0.01,df} \times SD$, 1% rejection rate). The LPC was successfully verified in the selective/interference experiments ([see next section](#)).

Reviewer Comment: *Because the cut-point for the CLB method was re-calculated and was significantly different, the assay sensitivity and the LPC were updated to reflect the new cut-point value (see below).*

Updated Assay Sensitivity and LPC values (IR Response 01/15/2015)

Linear regression curves from all three (b)(4) runs were provided and show very good fit R-square values (Figure 5-4 through 5-6 of BSER_BA14023). Using the cut-point (y-axis), the corresponding concentration (x-axis) was calculated for each run (concentration = cut-point – intercept/slope). Refer to the table below for concentration values. (Table in Section 5.3.1 of BSER_BA14023, see below).

This leads to the following results:

run	Plate ID	CP	Intercept	Slope	concentration(CP)
1	BA14023_140923-4_ (b)(4) eda	11	1.20	0.036	276
2	BA14023_140924-3_ (b)(4) eda	11	-2.10	0.032	417
3	BA14023_140925-3_ (b)(4) eda	11	0.51	0.038	283

The assay sensitivity was then calculated from the mean of all interpolated concentrations from the three runs. At a 95% consistency, assay sensitivity was determined by the following formula: mean concentration sensitivity + $t_{0.05, df} \times SD$. The mean and SD of the concentrations determined in the above table were logged and re-calculated (Table in Section 5.3.2 of BSER_BA14023, see below), resulting in a mean of 5.77 and a SD of 0.232 on the log-scale. The assay sensitivity was then computed as a value of **629 ng/ml**.

run	Plate ID	concentration(CP)	log(concentration(CP))
1	BA14023_140923-4_ (b)(4) eda	276	5.62
2	BA14023_140924-3_ (b)(4) eda	417	6.03
3	BA14023_140925-3_ (b)(4) eda	283	5.65

The LPC was re-calculated based on the new assay sensitivity value and set to fail 1% of the time (99% of the data from the LPC will be at or above the cut-point). Using the formula mean concentration sensitivity + $t_{0.01,df}$ * SD, yields a LPC value of **1,606 ng/ml**.

Reviewer Comment: *The assay sensitivity and LPC were also re-calculated using both analysts (b) (4); however, this led to a higher assay sensitivity value (i.e., 1027 ng/ml, data not shown). Because analyst (b) (4) was the analyst who ran the in-study samples and generated a more conservative cut-point, it is acceptable to determine the assay sensitivity and the LPC level with data generated only from analyst (b) (4). The re-calculated assay sensitivity level is acceptable and supported by statistical data. Although the re-calculated LPC doesn't provide an accurate assessment of assay performance at the cut-point level, assay sensitivity at this level is still within an acceptable range (<1106.1> USP general chapter, Immunogenicity Assays- Design and Validation of Assays to Detect Anti-Drug Neutralizing Antibody).*

Selectivity and Interference

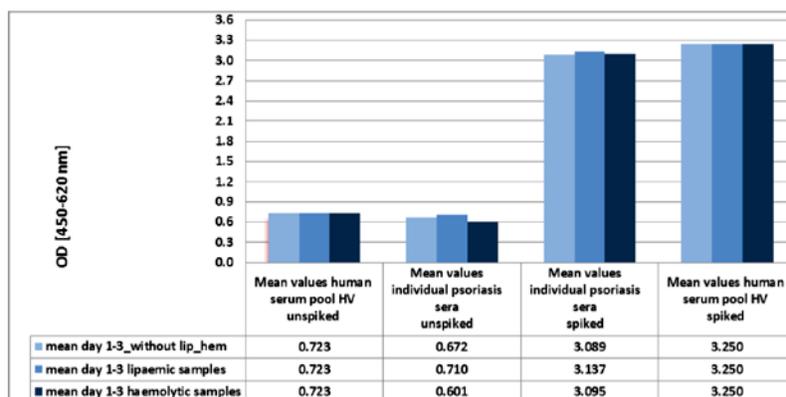
Ten individual human psoriasis patient serum samples were evaluated for potential matrix-related interferences that could prevent detection of neutralizing ADAs. The individual serum samples were spiked three times independently with the LPC concentration of the polyclonal positive control antibody. Samples were diluted 1:3 in matrix buffer and were analyzed in duplicate against a calibration curve prepared in HV human serum pool. Each individual serum was measured without spiking GP2015 during the second neutralizing step to measure the individual background signal. Two sets of QC samples were run to verify the suitability of the assay. Mean OD values for the samples spiked with LPC and analysis of % inhibition are shown in data tables in Appendix 4 of the validation report. The CV of mean OD values ranged from 1% to 6% and each LPC sample was measured above the cut-point (i.e., 32% to 54%).

Reviewer Comment: *Matrix effects from psoriasis patient serum did not interfere with consistent detection of the LPC above the assay cut-point. Similar to the selectivity experiments performed for the ECL method, matrix effects were evaluated between serum of healthy volunteers and psoriasis patients. Because the above experiment doesn't evaluate the impact of matrix components from serum in comparison to assay buffer in detection of ADAs, the IR that was communicated to the sponsor included a comment for the sponsor to provide data that supports the ability of the assay to accurately detect ADA levels in the presence of serum components, such as lipids and hemoglobin.*

Matrix components

In response to the IR, the sponsor provided pre-validation data that support a lack of matrix-related interferences, e.g., lipids and hemoglobin, influencing assay performance. Nine individual psoriasis sera were tested on three different days by the CLB assay. The OD readings of spiked and unspiked individual psoriasis patient serum samples and unspiked and spiked HV human serum pool samples, in addition to hemolytic or lipaemic serum samples, were similar (Figure 3-1 of the IR response, see below).

Figure 3-1 Hemoglobin and lipids do not influence the detection of neutralizing anti-etanercept antibodies



Pre-existing antibodies

In response to the IR with respect to pre-existing antibodies, the sponsor clarified that individual sera were selected from the vendor that excluded psoriasis patients that received etanercept or any other biologic. Additionally, raw data from serum of healthy volunteers and psoriasis patients spiked with GP2015 or unspiked were compared to determine a potential influence of pre-existing antibodies in serum samples that were used to make the psoriasis serum pool (Table 3-7 of the IR response). No significant differences in OD readings from HV sera compared to psoriasis sera were observed.

Reviewer Comment: *The additional information provides support that the psoriasis patient serum pool is representative of the psoriasis patient population with no matrix-related interferences that would impact assay performance. The serum samples used in the method validation are suitable for their intended purpose and will allow for the calculation of meaningful values.*

Precision and Accuracy

Intra-assay precision

Five sets of validation samples (VS1 to VS3) of the positive control antibody were prepared independently in HV human serum pool. The acceptance criteria of back-calculated concentration values for CV, accuracy, and total error were met: CV values were NMT 9%, the accuracy of values were between 83% and 92%, and the total error was NMT 19% (Appendix 5 of the validation report).

Inter-assay precision

One set of validation samples (VS1 to VS3) was prepared in 1:3 diluted psoriatic serum pool and was measured together with a calibration curve prepared in HV human serum pool on six different days. Different analysts, plate readers, and washers were used to evaluate inter-assay precision. The acceptance criteria of back-calculated concentration values for CV, accuracy, and total error were met; CV values were NMT 15%, accuracy values were either 89% or 94%, and total error was NMT 24% (Appendix 06 of the validation report).

Reviewer Comment: *The assay can be performed with high intra- and inter-assay precision and accuracy for detection of anti-etanercept antibodies in the range of 7,500 ng/ml to 1,500 ng/ml.*

Robustness

Robustness of the method was analyzed by using two different washers and two different microtiterplate readers. The results regarding robustness are shown as the results for the inter-assay precision experiment (see above).

Reviewer Comment: *Different washers and readers did not impact the detection of a broad range of ADA concentrations.*

Linearity

The mean, standard deviation, and %CV were calculated for all concentrations of the calibration curves from the inter-assay precision experiments (Appendix 06 of the validation report). The acceptance criteria were fulfilled; CV values were NMT 9% and the coefficient of correlation was 0.9997 (Appendix 7 of the validation report).

Reviewer Comment: *The assay is linear between 500 ng/ml and 10,000 ng/ml in 100% HV human serum pool. These data indicate that the assay performs well across a wide range of ADA concentrations.*

Stability

The stability of the polyclonal antibody is discussed in section 1a of the review ([see Stability section](#)). The serum stability of monoclonal mouse anti-TNFR2 antibody was not assessed since antibody dilutions in serum were only used (b) (4) prepared for evaluation of drug interference and specificity.

Drug Interference

The assessment of drug interference (i.e., GP2015 and EU-approved Enbrel) was investigated using both positive controls (i.e., polyclonal rabbit anti-etanercept antibody and neutralizing monoclonal mouse anti-human TNFR2 antibody). The drug tolerance of the assay at the respective anti-etanercept antibody concentration was defined as the highest concentration of drug that did not alter the classification of the test samples, i.e., prevented the detection of the VS1 or VS3 signal above the cut-point. Results of the experiment for the polyclonal positive control antibody and the monoclonal positive control antibody are displayed in Appendix 9 and Appendix 10, respectively, of the validation report and are summarized below.

Drug tolerance limits for the polyclonal antibody:

- Drug concentrations above 10 µg/ml (GP2015) and 20 µg/ml (EU-approved Enbrel) interfere with the detection of 7,500 ng/ml of ADAs
- Drug concentrations above 0 µg/ml (GP2015) and 1 µg/ml (EU-approved Enbrel) interfere with the detection of 1,500 ng/ml of ADAs

Reviewer Comment: *Because the measured trough serum levels of GP2015 are between 4,000 – 10,000 ng/ml, the drug tolerance results (see above and Appendix 9 of the validation report) demonstrate that high levels of ADAs (i.e., 7,500 ng/ml) can be detected in presence of drug concentrations up to 10,000 ng/ml, while lower levels of ADAs (i.e., 1,500 ng/ml) cannot be detected in the presence of trough levels of drug. The data do not support that the CLB method can*

detect low levels of ADAs in the presence of trough levels; however, the sponsor used an additional positive control antibody to repeat these experiments that would presumably reflect a more specific neutralizing antibody response in humans (see below).

Monoclonal Antibody

As the polyclonal antibody was generated by hyper-immunization of rabbits using GP2015, the development of high amounts of non-neutralizing anti-Fc antibodies is expected. The sponsor claimed that these antibodies cannot be adequately measured in the neutralizing CLB assay format, and therefore, the amount of neutralizing antibodies at the tested low concentration (i.e., 1,500 ng/ml) is expected to be considerably lower and the resulting drug tolerance of the CLB assay higher than reported. Therefore, the sponsor evaluated the drug tolerance of the assay using a neutralizing monoclonal mouse anti-human TNFR2 antibody. Results are shown in Appendix 10 of the validation report. Drug concentrations above 20 µg/ml (i.e., GP2015 or EU-approved Enbrel) do not interfere with the detection of 7,500 ng/ml and 1,500 ng/ml of ADAs.

Reviewer Comment: *The neutralizing antibody response (i.e., 1,500 ng/ml and 7,500 ng/ml of anti-etanercept antibodies) could be detected in the presence of trough levels of drugs. Although the monoclonal positive control antibody used in this experiment at the VS3 concentration (1,500 ng/ml) is not near the assay sensitivity (935 ng/ml, original; 629 ng/ml, updated), the assay can detect 1,500 ng/ml of ADAs in the presence of trough levels of drugs, which is in the USP recommended range of assay sensitivity for a neutralization assay.*

Target Interference

In addition to the drug, the target of etanercept (i.e., TNF-α) may also interfere in the assay as it is able to bind to etanercept in the serum and compete with bound TNF for the binding to GP2015, resulting in false positives. The tolerance level of the assay to target interference was determined by performing a 1:2 dilution series of human TNF from 1,000 pg/ml to 15.6 ml in 100% human serum pool (healthy volunteers). HV human serum pool was used for the determination of target interference because psoriasis serum might contain a larger quantity of TNF, which could lead to uninterpretable results. Samples were tested in duplicates in one run together with a calibration curve prepared in 100% human serum pool (HV). The maximal concentration of target which leads to a signal below the cut-point was defined as the target interference of the assay. None of the TNF concentrations used in the study lead to a signal below the cut-point (i.e., % signal inhibition values were NMT 8%; Appendix 11 of the validation report).

Reviewer Comment: *TNF-α, a mediator of disease in psoriasis patients, is likely to not interfere with assay performance because the target tolerance limit of the assay is at least 1,000 pg/ml of TNF in 100% serum and well above levels of TNF-α typically detected in the serum of psoriasis patients (~25 pg/ml)¹.*

¹ Arican O, et al., Serum Levels of TNF-α, IFN-γ, IL-6, IL-8, IL-12, IL-17, and IL-18 in Patients with Active Psoriasis and Correlation with Disease Severity. *Mediators Inflamm.* 2005 Oct 24; 2005(5): 273-279.

Specificity

The specificity of the CLB assay was not evaluated in validation report; however, the sponsor provided assay depletion curves in the IR response, which demonstrate that inhibition of the assay signal is similarly depleted with increasing concentrations of GP2015 or EU-approved Enbrel when using the polyclonal antibody (Figure 4-1 of the IR response) and the monoclonal antibody (Figure 4- of the IR response).

Reviewer Comment: *Because the detection of a low concentration of ADAs (1,500 ng/ml, polyclonal and monoclonal preparations) can be similarly depleted with EU-approved Enbrel and GP2015 at concentrations of drug below, at, or above trough levels, the assay is suitable to detect both neutralizing ADAs against the proposed biosimilar and the comparator.*

Section II – Clinical Immunogenicity Assessment

The immunogenicity assessment consisted of data evaluation from four clinical studies in healthy volunteers (GP15-101, GP15-102, GP15-103, and GP15-104) and one clinical study in the indicated population, psoriasis patients (GP15-302). Studies in healthy volunteers used single doses during treatment periods 1 and 2, while dosing of psoriasis patients in the GP15-302 study was twice a week during treatment period 1 and once a week during treatment 2. These studies also included a single transition from EU-approved Enbrel to GP2015. As shown in Table 1, all healthy volunteer subjects in studies GP15-101, GP15-102, and GP15-103 were negative for confirmed positive binding anti-etanercept antibodies. In study GP15-104, a total of three healthy volunteer subjects had confirmed positive binding anti-etanercept antibodies at the follow-up visit. All of these subjects had negative samples at the end of Period 1 and had a treatment sequence of GP2015 to EU-approved Enbrel. These ADAs were near the detection limit and none were determined to be neutralizing. While psoriasis patients that received GP2015 did not induce confirmed positive binding anti-etanercept antibodies, five out of 250 serum samples (1.9%) from psoriasis patients administered with EU-approved Enbrel resulted in confirmed positive results for binding anti-etanercept antibodies at week 4. Analysis of these antibodies demonstrates that they have a low titer and are non-neutralizing, and because anti-etanercept antibodies were not detected at weeks 8, 12, 18, and 30 in these patients, it can be concluded that the response was transient. Collectively, these results suggest that (i) a single transition from EU-approved Enbrel to GP2015 does not increase the incidence of anti-etanercept antibodies and (ii) GP2015 induces lower levels of anti-etanercept antibodies in the patient population in comparison with EU-approved Enbrel. Because this difference is not clinically meaningful, it can be concluded that the immunogenicity of GP2015 and EU-approved Enbrel is similar.

Table 1 – Immunogenicity assessment of GP2015, US-licensed Enbrel and EU-approved Enbrel

Study Population	Study ID	Comparison	Subjects	Groups	Confirmed positive binding ADAs	Study Period of Detection	Neutralizing ADAs (#)
Healthy volunteers	GP15-101 PK/Safety	GP2015 vs. EU-Enbrel	54	GP→Enbrel	0	n/a	n/a
				Enbrel→GP	0		n/a
	GP15-102* PK/Safety	GP2015 vs. US-Enbrel	57	GP→Enbrel	0	n/a	n/a
				Enbrel→GP	0		n/a
	GP15-103 PK/Safety	auto-injector vs. PFS	51	PFS	0	n/a	n/a
				Autoinjector			
GP15-104 PK/Safety	GP2015 vs. EU-Enbrel	54	GP→Enbrel	3	Follow-up	n/a	
			Enbrel→GP	0			
Psoriasis patients	GP15-302* Efficacy Safety Immuno.	GP2015 vs. EU-Enbrel	267	Enbrel	5/250 (1.9%)	Treatment Period 1 (2-4 weeks)	0
			264	GP	0/285 (0%)		n/a

*Pivotal study, Immuno = immunogenicity, PFS= pre-filled syringe, n/a = not applicable. This table was made by the reviewer. Refer to the Study Report Body folder of each clinical study listed above for referenced data (Section 5 of the BLA) and the study design.

Reviewer Comment: Although the immunogenicity of GP2015 was evaluated in healthy volunteers, the GP15-302 clinical study is the more relevant study for immunogenicity assessment because it uses a patient population for one of the indications being sought in this 351(k) application (i.e., psoriasis patients) and includes analyzed data from psoriasis patients exclusively receiving GP2015 or EU-approved Enbrel throughout the entire treatment regimen (up to 30 weeks). Based on the product quality review, an adequate analytical bridge between US-licensed Enbrel and EU-approved Enbrel has been established. As a result, the immunogenicity data generated based on the comparison between GP2015 and EU-approved Enbrel would support a finding that there are no clinically meaningful differences between GP2015 and US-licensed Enbrel.



Brian
Janelins

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HUMAN FACTORS, LABEL, LABELING, AND PACKAGING 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:	July 21, 2016
Requesting Office or Division:	Division of Pulmonary, Allergy, and Rheumatology Products (DPARP)
Application Type and Number:	BLA 761042
Product Name and Strength:	Erelzi (GP2015)* Injection 25 mg/0.5 mL Prefilled Syringe (PFS) 50 mg/mL Prefilled Syringe (PFS) 50 mg/mL Autoinjector (AI)
Product Type:	Single Ingredient Combination Product
Rx or OTC:	Rx
Applicant/Sponsor Name:	Sandoz
Submission Date:	July 30, 2015
OSE RCM #:	2015-1845 and 2015-2148
DMEPA Primary Reviewer:	Carlos M Mena-Grillasca, RPh
DMEPA Team Leader:	Mishale Mistry, PharmD, MPH
OMEPRM Deputy Director:	Kellie Taylor, PharmD, MPH

*Erelzi has been developed as a proposed biosimilar to US-licensed Enbrel (etanercept). Since the proper name for Erelzi has not yet been determined, GP2015 is used throughout this review in place of the nonproprietary name for this product.

1 REASON FOR REVIEW

This review evaluates the applicant's Human Factors evaluation, the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Erelzi (GP2015)* injection (BLA 761042) for areas of vulnerability that could lead to medication errors. The Division of Pulmonary, Allergy, and Rheumatology Products (DPARP) requested this review to inform their evaluation of the 351k submission for Erelzi. The reference product, US-licensed Enbrel (BLA 103795), was approved in November 2, 1998.

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
ISMP Newsletters	D (N/A)
FDA Adverse Event Reporting System (FAERS)#	E (N/A)
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

We evaluated the proposed container label, carton labeling, Prescribing Information (PI), and Instructions for Use (IFU) for Erelzi (GP2015)* injection, BLA 761042.

The applicant is proposing the same indications, dosing, and route of administration as the reference product, US-licensed Enbrel (BLA 103795). Sandoz proposes to market a 25 mg and 50 mg pre-filled syringe (PFS) and a 50 mg autoinjector. While these presentations follow the same presentations marketed by the reference product, (b) (4)

We note that the review team is considering a Post Marketing Requirement to introduce a presentation that could service pediatric patients treated for JIA under Pediatric Research Equity Act (PREA), and we defer to the review team's decision on this. Furthermore, (b) (4)

¹ IND 114187 - Biosimilar Biologic Product Development (BPD) Type 2 Meeting; Teleconference; May 18, 2016 from 3:00 pm

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With regard to the proposed autoinjector, the applicant uses the human factors study data gathered for the Cosentyx Sensoready pen (b) (4). The BLA for Cosentyx (secukinumab) is held by Novartis and the Sensoready pen (b) (4) was approved as part of BLA 125504 on January 21, 2015. We note that Sandoz is a Novartis company. Because the Cosentyx human factor study included the same disease state and patient populations as those proposed for Erelzi (with the exception of JIA), as a scientific matter, DMEPA finds that the Cosentyx Sensoready pen human factors validation data referenced in this submission can be appropriately relied on to support the development of the Erelzi autoinjector.

Given that the applicant is relying on data in the Cosentyx Sensoready Pen application, we would, as a scientific matter, expect that the device specific steps on Erelzi Sensoready Pen's IFU closely follow that of Cosentyx. Product specific information on Erelzi Sensoready Pen's IFU must follow US-licensed Enbrel's IFU. However, in our review, we identified that there are some minor differences between the Instructions for Use for Cosentyx Sensoready Pen and US-licensed Enbrel autoinjector and the Erelzi Sensoready Pen. Therefore, we will provide recommendations to the Erelzi Sensoready Pen IFU to follow all device specific steps from Cosentyx IFU and product specific information from US-licensed Enbrel, or ask that the sponsor provide a scientific justification to support the variation.

The Erelzi proposed pre-filled syringes include a passive needle guard safety mechanism to prevent needle stick injuries after injection; whereas the US-licensed Enbrel pre-filled syringes do not include a needle guard. Therefore, to accurately represent the Erelzi PFS, the IFU for Erelzi PFS differs from the US-licensed Enbrel IFU. We find this variation necessary and acceptable. We also note that the plunger rod for Erelzi 25 mg PFS is (b) (4) and for the Erelzi 50 mg PFS is (b) (4). The CDRH reviewer deferred to DMEPA with regards to proper differentiation between the two Erelzi prefilled syringes based on the colors of the plunger rods. However, the prefilled syringes are packaged in a blister tray inside a carton; hence, the tray and carton labeling would be expected to be the primary means for identification and differentiation of the products. In addition, for the indications proposed, it is unlikely that patients be prescribed both strengths concomitantly and therefore patients would not need to differentiate between strengths when using these at home.

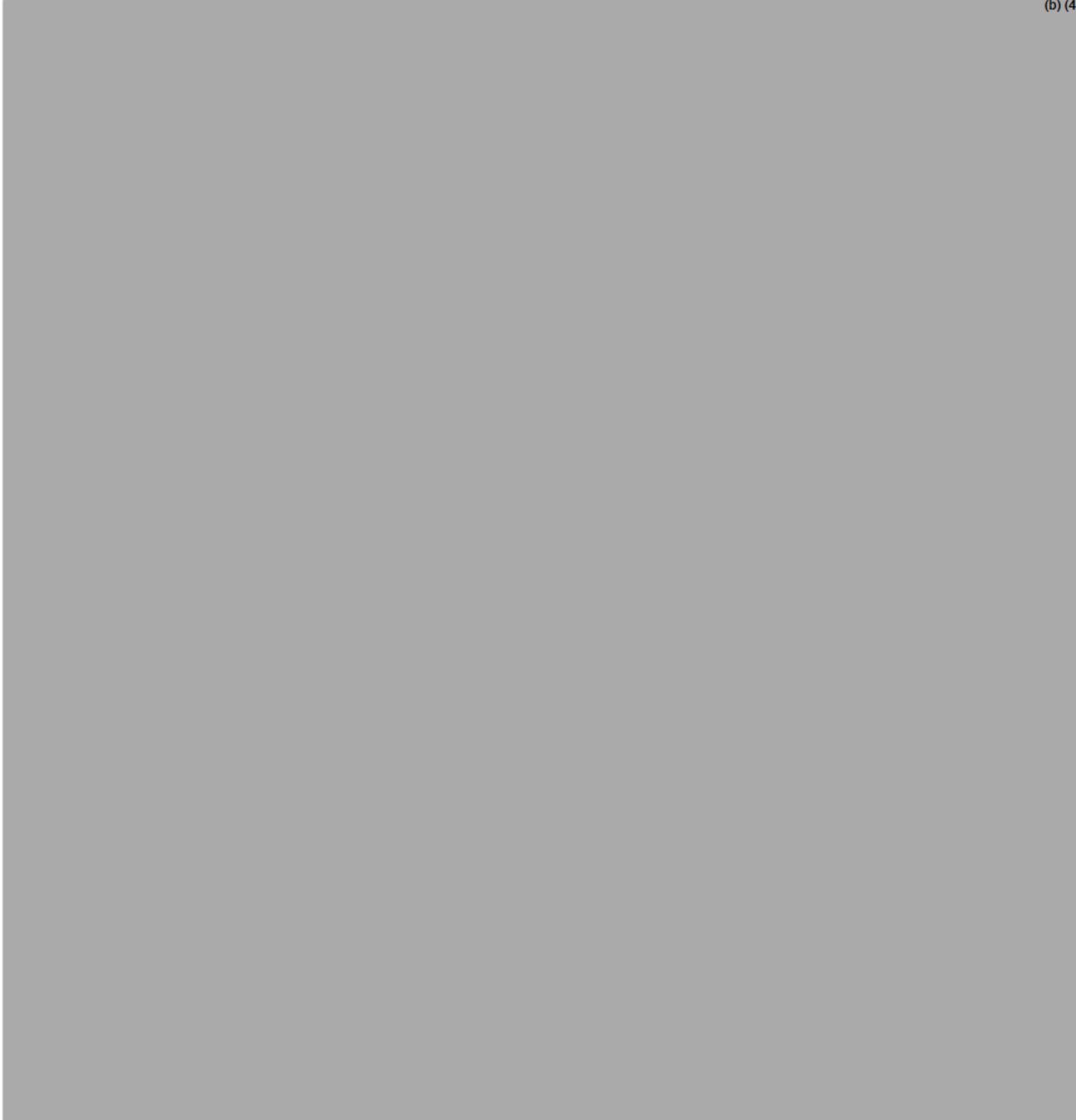
In addition, we note that the proposed color scheme used in the presentation of the strength statements on the labels and labeling (b) (4) color scheme of the reference product, US-licensed Enbrel (see table below for examples). (b) (4)

A table with two rows of redacted content, likely showing color schemes for different strengths of the reference product, US-licensed Enbrel.

to 4:00 pm.

*Erelzi has been developed as a proposed biosimilar to US-licensed Enbrel (etanercept). Since the proper name for Erelzi has not yet been determined, GP2015 is used throughout this review in place of the nonproprietary name for this product.

GP2015 Proposed Labels (not to scale)	US-licensed Enbrel Labels (not to scale source: Annual Report 8/29/13)
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(b) (4)

We note that the storage conditions for the US-licensed Enbrel multiple-dose vial and diluent syringe allows for storage at room temperature [68°F to 77°F (20°C to 25°C)] for a maximum of 14 days. The applicant is proposing a maximum of 28 days of storage at room temperature (b) (4) for the Erelzi

*Erelzi has been developed as a proposed biosimilar to US-licensed Enbrel (etanercept). Since the proper name for Erelzi has not yet been determined, GP2015 is used throughout this review in place of the nonproprietary name for this product.

pre-filled syringes and Erelzi Sensoready Pen. Although the length of time will vary for these two products and we defer to OBP on the scientific support for the statement, we do not have reason to believe that this variation in the statements would be a source of medication errors for the following reasons: (1) US-licensed Enbrel limits the room temperature storage conditions to only one presentation (i.e. vial), which can be confusing to patients, whereas the applicant's proposal for room temperature storage conditions include all marketed presentations (i.e. PFS and Sensoready Pen), and (2) the applicant's proposal for storage at room temperature is inclusive of that of the reference product.

We also note that the statement "single-^{(b) (4)}" is used throughout the labels and labeling. However, we defer to Office of Biological Products (OBP) labeling reviewers for the determination of the appropriate package type term on labels and labeling. In addition, the container labels and carton labeling can be improved to increase the visibility of the route of administration statement and storage information.

Finally, we acknowledge that there are two outstanding items (the nonproprietary name for this product and product strength) that are still under consideration and therefore we defer any comments on these aspects of the labeling at this time.

4 CONCLUSION & RECOMMENDATIONS

Our review identified areas for improvement with regards to the visual display of the strength on the container labels and carton labeling of the proposed product, as it uses ^{(b) (4)} color scheme than the US-licensed Enbrel color scheme and ^{(b) (4)}. Additionally, we identified other aspects of the labels and labeling that should be revised to improve readability of important information and promote the safe use of the product. We provide recommendations for the Division in Section 4.1 and recommendations for Sandoz in Section 4.2 below, prior to approval of BLA 761042.

4.1 RECOMMENDATIONS FOR THE DIVISION

A. Prescribing Information

1. Update the trade name on the labeling to display Erelzi in place of ^{(b) (4)}.

4.2 RECOMMENDATIONS FOR SANDOZ

A. General Comments (All container labels, foil, and carton labeling)

1. Update the trade name on the container labels, foil and carton labeling to display Erelzi instead of ^{(b) (4)}.
2. Ensure the presentation of the proper name is at least ½ the size of the proprietary name taking into account all pertinent factors, including typography, layout, contrast, and other printing features per CFR 201.10(g)(2). As currently presented, the proprietary name and proper name are not commensurate in prominence due to the larger bold font used for proprietary name.
3. Increase the prominence of the route of administration statement by bolding.
4. As currently presented your proposed labels and labeling, you have used ^{(b) (4)}

*Erelzi has been developed as a proposed biosimilar to US-licensed Enbrel (etanercept). Since the proper name for Erelzi has not yet been determined, GP2015 is used throughout this review in place of the nonproprietary name for this product.

(b) (4)

B. Container Label (Prefilled syringe: 25 mg and 50 mg)

1. Revise the statement (b) (4) to read "For Subcutaneous Use Only". To ensure adequate space, we recommend relocating the "Rx Only" statement to the upper right hand corner of the principal display panel.

C. Carton labeling (All package sizes; Prefilled syringe: 25 mg and 50 mg; Sensoready Pen)

1. On the principal display panel, revise the statement (b) (4) to read "Must be refrigerated".

D. Sensoready Pen Instructions for Use

In reviewing your IFU, which is supported by validation data in the Cosentyx BLA, we noted that your proposed IFU has certain differences from the Cosentyx IFU. We outline these differences below to harmonize this IFU with the validated Cosentyx IFU for your consideration. In addition, we recommend that certain product specific information that would be expected to be relevant to the safe use of your biosimilar product be harmonized with the IFU of the reference product, US-licensed Enbrel. If you determine that some of these recommendations are not supportable for Erelzi, we recommend that you provide justification in your response to our comments.

1. Consistently refer to the product as Erelzi Sensoready Pen throughout the IFU. As currently presented you use the names "Erelzi Sensoready Pen" and (b) (4), which can be confusing.
2. Revise to consistently use the word "carton" instead of (b) (4) throughout the IFU. As currently presented you are using both terms, which can be confusing.
1. Revise the word (b) (4) to read "Erelzi Sensoready Pen" in the statement "Keep (b) (4) and all medicines out of the reach of children".
2. Include the statement "Do not try to warm the Erelzi Sensoready Pen by using a heat source such as hot water or microwave" following the statement "Take the Erelzi Sensoready Pen out to the refrigerator 15-30 minutes before injecting to allow it to reach room temperature."
3. Step 1 – First bulleted statement
 - a. Revise the statement to read "Look through the viewing window. The liquid should be clear and colorless. It is ok if you see small white particles in the liquid.
DO NOT USE the Erelzi Sensoready Pen if the liquid is cloudy or discolored or contains large lumps, flakes, or colored particles."
4. Step 2 – Fourth bulleted statement
 - a. Revise the statement to read "If a caregiver or healthcare professional is giving you your injection, they may also inject into your outer upper arm (see Figure F).
5. Step 8 – First bulleted statement
 - a. Revise the word (b) (4) to read "healthcare provider".

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E. Prefilled Syringes IFU

1. Prepare the Erelzi prefilled syringe Section – Step 2

- a. Include the statement “Do not try to warm the Erelzi prefilled syringe by using a heat source such as hot water or microwave” following the revised statement “Take the (b) (4) containing the Erelzi prefilled syringe out to the refrigerator and leave it unopened on your work surface for about 15-30 minutes before injecting to allow it to reach room temperature.”

*Erelzi has been developed as a proposed biosimilar to US-licensed Enbrel (etanercept). Since the proper name for Erelzi has not yet been determined, GP2015 is used throughout this review in place of the nonproprietary name for this product.

APPENDICES: METHODS & RESULTS FOR EACH MATERIALS REVIEWED

APPENDIX A. PRODUCT INFORMATION/PRESCRIBING INFORMATION

Table 2 presents relevant product information for Erelzi that Sandoz submitted on December 11, 2015, and the reference product.

Table 2. Relevant Product Information for Erelzi and the Reference Product		
Product Name	Erelzi	US-licensed Enbrel
Initial Approval Date	N/A	January 31, 2002
Active Ingredient	GP2015*	etanercept
Indication	<ul style="list-style-type: none"> • Rheumatoid Arthritis (RA) • Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years and older • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Plaque Psoriasis (PsO) 	<ul style="list-style-type: none"> • Rheumatoid Arthritis (RA) • Polyarticular Juvenile Idiopathic Arthritis (JIA) in patients aged 2 years and older • Psoriatic Arthritis (PsA) • Ankylosing Spondylitis (AS) • Plaque Psoriasis
Route of Administration	Subcutaneous	Subcutaneous
Dosage Form	Injection, solution	Injection, solution
Strength	25 mg/0.5 mL 50 mg/mL	25 mg/vial 25 mg/0.5 mL (0.51 mL) 50 mg/mL (0.98 mL)
Dose and Frequency	<p>Erelzi is administered by subcutaneous injection.</p> <ul style="list-style-type: none"> • Adult RA and PsA 50 mg once weekly with or without methotrexate (MTX) • AS 50 mg once weekly • Adult PsO 50 mg twice weekly for 3 months, followed by 50 mg once weekly • JIA 0.8 mg/kg weekly, with a maximum of 50 mg per week 	<p>US-licensed Enbrel is administered by subcutaneous injection.</p> <ul style="list-style-type: none"> • Adult RA and PsA 50 mg once weekly with or without methotrexate (MTX) • AS 50 mg once weekly • Adult PsO 50 mg twice weekly for 3 months, followed by 50 mg once weekly • JIA 0.8 mg/kg weekly, with a maximum of 50 mg per week
How Supplied	<ul style="list-style-type: none"> • 25 mg/0.5 mL single-use PFS with BD UltraSafe Passive needle guard • 50 mg/mL single-use PFS with BD UltraSafe Passive needle guard • 50 mg/mL single-use Prefilled Sensoready Pen 	<ul style="list-style-type: none"> • 25 mg/vial multiple-use vials • 25 mg/0.5 mL (0.51 mL) single-use PFS • 50 mg/mL (0.98 mL) single-use PFS • 50 mg/mL (0.98 mL) single-use

*Erelzi has been developed as a proposed biosimilar to US-licensed Enbrel (etanercept). Since the proper name for Erelzi has not yet been determined, GP2015 is used throughout this review in place of the nonproprietary name for this product.

		Prefilled SureClick AI
Storage	Refrigerated at 36°F to 46°F (2°C to 8°C). Do not shake. Store in the original carton to protect from light or physical damage. Individual syringes or autoinjectors may be stored at room temperature for a maximum single period of 28 days.	Refrigerated at 36° to 46°F (2° to 8°C). Do not shake. Store in the original carton to protect from light or physical damage. Individual syringes or autoinjectors may be stored at room temperature for a maximum single period of 14 days.

*Erelzi has been developed as a proposed biosimilar to US-licensed Enbrel (etanercept). Since the proper name for Erelzi has not yet been determined, GP2015 is used throughout this review in place of the nonproprietary name for this product.

APPENDIX B. PREVIOUS DMEPA REVIEWS

B.1 Methods

On December 21, 2015, we searched the L:drive using the term, Erelzi and (b) (4) 1***, to identify reviews previously performed by DMEPA.

B.2 Results

Our search did not identify any previous relevant reviews.

APPENDIX C. HUMAN FACTORS STUDY

The (b) (4) autoinjector (AI) has been developed as a (b) (4) device suitable for a range of dosage forms and / or drug formulations by (b) (4) on behalf of Novartis. (b) (4)

Novartis performed and documented HF studies with their products, in line with FDA's Draft Guidance "Applying Human Factors and Usability Engineering to Optimize Medical Device Design" (June 22, 2011) (see Section 16.1).

The development of the (b) (4) GP2015_50 AI is (b) (4)

Based on an assessment including technical characteristics, route of administration, anticipated indications, targeted groups, and risks associated with the use of the devices, Sandoz considers the human factors study performed for (b) (4) 02-AIN457 resp. (b) (4) 01 (b) (4) to be sufficiently applicable to (b) (4) GP2015_50 AI. It is therefore not deemed necessary to perform additional human factors validation activities specifically for (b) (4) GP2015_50 except for the box handling study due to a different folding box being used.

6.7.2 Applicability of Novartis Human Factor studies for (b) (4) GP2015_50

The following sections provide a comparison between (b) (4) GP2015_50 and (b) (4) 02 AIN457, and where appropriate (b) (4) 01 (b) (4) regarding technical aspects, indications, target populations and IFU which could have an influence on the handling of the product.

Comparison of technical features and product configuration

A comparison of technical characteristics of (b) (4) 02 AIN457 and (b) (4) GP2015_50 is provided in below table.

¹ (b) (4) *** was a proposed proprietary name for this BLA found unacceptable by DMEPA.

Table 6-5 Comparison of technical characteristics

Technical characteristics	(b) (4) GP2015_50	(b) (4) 02 AIN45
Rear subassembly total length		77.1 mm ± 1.0 mm
Total length		165.3 mm ± 0.5 mm
Outer (b) (4) AI shape including cap		Same (triangular) shape
Cap removal torque		≤ (b) (4) Nm
Activation force		(b) (4) N
Injection time		< (b) (4) Sec
Dose accuracy	(b) (4) mL (95% CI with (b) (4) P)	
Needle cover safety (displacement at 80N)		≤ (b) (4) mm
Storage conditions		Drug dependent
Prefilled syringe		Same (BD (b) (4) 1 mL long)
Rigid needle shield		Same (BD design)
Needle gauge*		27G x ½"
Injection depth		Same ((b) (4) mm)
Filling volume	(b) (4)**	(b) (4)
Injection frequency	Weekly or twice weekly (for up to 12 weeks in Plaque Psoriasis)	Weekly or less frequently

* Not visible to the user at any time

** (b) (4) filling volume was used for simulated use handling study

The above table provides evidence that the technical characteristics of both AI are considered equivalent. According to the patients self-injection frequency with the (b) (4) 02 AIN457 described as a less frequent handling (due to lower frequency of injections) the validation study which included a one week and four week training decay is considered as a worst case handling study in comparison to the (b) (4) GP2015_50.

The cap removal torque of (b) (4) Nm is based on a further usability study. This study was commissioned by Novartis to determine the appropriate torque limit specification for the specified target user groups. Initial feedback from clinical trials with Psoriasis patients showed that there were no issues for devices with opening torque up to (b) (4) Nm.

Comparison of indications and target groups

A comparison of indications and target groups, which were validated by Novartis Pharma for (b) (4) 02 AIN457, with the ones for (b) (4) GP2015_50 is provided in Table 6-6 and Table 6-7. The anticipated indications and target groups for both drug products are almost identical.

Table 6-6 Comparison of anticipated indications

(b) (4)



Table 6-7 Comparison of target groups

Characteristics	Characteristics of target groups of GP2015 compared to AIN457 as well as the coverage in the studies
Indications	See previous table; GP2015 specific indication Polyarticular Juvenile Idiopathic Arthritis causes comparable dexterity problems in patients as in patients suffering from rheumatoid arthritis and is therefore covered in the simulated use handling study. In terms of patient impairment, rheumatoid arthritis could be considered as more frequently affecting small joints of fingers and hands if compared to the 2 forms of axial spondyloarthritis. For patients younger than 12 years, the injection is assumed to be performed by a caregiver. Caregivers formed also a distinct user group in the simulated use handling studies.
Age**	Same; three different age groups were analyzed in the simulated use handling studies for all indications (12-17; 18-64; ≥ 65 for AIN HF studies (for (b) (4) HF study target group aged ≥ 75 years)*
Gender**	Same; a minimum of 40% of each gender was included in the simulated use handling studies
Ethnicity**	Same; Caucasian, African-American, Hispanic and Asian people were included in the simulated use handling studies
Injection site**	Same
Hand size**	Same; subjects with very small hands and very big hands and with same impaired dexterity were included in the simulated use handling studies
Educational attainment**	Same; subjects with an education of high-school or lower and college or higher were included in the simulated use handling studies
	Patients, HCPs and professional as well as non-professional caregivers

Characteristics	Characteristics of target groups of GP2015 compared to AIN457 as well as the coverage in the studies
-----------------	--

Training level of users	Same; trained and un-trained subjects were included in the handling studies*
-------------------------	--

* Same; compared to the (b) (4) Usability Study for (b) (4) with the (b) (4) 01 Device.

** Relevant for self-administration / administration to patient

Comparison of the IFU

The IFU for (b) (4) GP2015_50 is based on the IFU for (b) (4) 01 (b) (4) which represents the modified version that was established (and verified in the IFU-Retest) based on the results from the handling studies with trained and untrained users. The descriptions and the step by step technique to use and administer the product is the same except for drug product specific information (e.g. storage requirements; criteria for visual inspection of drug product solution).

Comparison of product label and secondary packaging

The secondary packaging, including the tamper evident seal which is part of the product labeling (indicating product name, volume etc.), is an important factor in the handling experience of a user.

The device seal is a tamper evident perforated label, which is put by the manufacturer on the surface of the device front subassembly and cap. When removing the cap prior to an injection, the tamper evident (perforated) seal has to be broken. The same label as used for the AIN 457 project is used for the (b) (4) GP2015_50 project. Therefore no further handling studies on the cap opening torque including the label are required.

The secondary packaging needs to be opened by the user prior to performing an injection. Depending on the industrial design and the user's physical ergonomics and cognitive capabilities, this process may be more or less cumbersome. The secondary packaging of (b) (4) GP2015_50 will be different from the secondary packaging of (b) (4) 02 AIN457. Therefore Sandoz defined additional verification and box handling usability activities (see Section 6.7.4).

Risks associated with the use of the device

Since the design, intended use and patient population of (b) (4) GP2015_50 and (b) (4) 02 AIN457 are identical also device related risks are comparable. Furthermore it was confirmed by experts from clinical development that drug related risks are comparable between AIN457 and GP2015. Therefore the same hazards were used as a basis for the analysis of risks regarding the use of the device.

Based on the fact that also the indications, the target groups and the instructions for use (except for the first and last tile that contain drug-specific information) are comparable, it was possible to base the Application / Usability Risk Assessment on human factors analysis for AIN457 (b) (4) 02).

APPENDIX D. ISMP NEWSLETTERS

N/A

APPENDIX E. FDA ADVERSE EVENT REPORTING SYSTEM (FAERS)

N/A

APPENDIX F. OTHER

N/A

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

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

/s/

CARLOS M MENA-GRILLASCA
07/21/2016

MISHALE P MISTRY
07/21/2016

KELLIE A TAYLOR
07/21/2016



DEPARTMENT OF HEALTH AND HUMAN SERVICES M E M O R A N D U M

Food and Drug Administration
Office of Device Evaluation
White Oak Building 66
10903 New Hampshire Ave.
Silver Spring, MD 20993

Intercenter Consult Memorandum

Device Constituent Part Design Review: CDER BLA761042- CDRH ICC1500500

Date: April 19, 2016

To: Peter Adams
Division of Biotechnology Review and Research I (DPRRI)
Office of Biotechnology Products (OBP)
Office of Pharmaceutical Quality (OPQ)
Center for Drug Evaluation and Research (CDER)

From: Sarah Mollo
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Center for Devices and Radiological Health (CDRH)

Subject: Device Constituent Part Design Review – BLA 761042, subcutaneous injection of (b) (4)
(etanercept) via pen injector or prefilled syringe

I. **Recommendation**

Recommend approval of the combination product based on review of the device constituent with three post-market commitments.

1. The sponsor provided a response to a request for information for essential performance requirements for release specifications on March 11, 2016 which states that break loose and glide force will be included in release specifications of the GP2015 (b) (4) PFS. The sponsor has recently validated a method for measurement of BLGF (break loose, glide force) and plans to generate additional data from commercial batches to define specifications. The sponsor has committed to implementing the specifications based on those data. Generated data and the updated [Module 3.2.P.5.1] will be submitted with the annual report. For additional information, please see the lot release testing section under pre-filled syringe with needle safety device engineering performance (pp. 18, 19).
2. The sponsor has committed to include the injection depth and the test items related to the audible and visual feedback into the lot release testing for commercial batches of (b) (4) GP2015_50. Methods for confirming the audible feedback (i.e. occurrence of second click) and visual feedback (i.e. plunger fills the window and stops moving) applicable for release testing will be

developed and specifications will be defined. Once established, these test items will be included into the lot release testing and implemented prior to launch. For additional information, please see the lot release testing section under autoinjector engineering performance (pp. 32, 33).

3. In response to IRs sent on December 18, 2015 and February 22, 2016, the sponsor provided information that a new design of folding box and transport carton was defined and successfully passed test runs of mechanical stress application and indicated that additional transport validation will be performed after introduction of these changes. The sponsor has stated that transport validation will be completed successfully prior to the launch of the product, and the final transport validation report will be available by the end of August 2016. For additional information, please see the transportation section under autoinjector engineering performance (pp. 27,28)

II. Review Summary

CDRH performed an evaluation of the design of the device constituent parts of the pre-filled syringe with needle safety device and the autoinjector configurations. This evaluation covered the intended design and design control information for the subject device constituent parts. This review did not cover the following elements:

- Review of drug product
- Review of primary container closure-drug product interaction or biocompatibility/toxicology
- Usability and Human Factors of the combination product
- Manufacturing of the drug product
- Manufacturing of the device constituent part of the combination product

This review did cover the following elements:

- Inspection of sponsor's design input activities
- Inspection of sponsor's design verification activities
- Confirmation of standards conformance where relied upon
- Inspection of test methods and results of bench top testing completed
- Inspection of stability testing completed on the device constituent part
- Review of risk analysis documentation and conclusions of safety
- Review of biocompatibility of needle safety device and autoinjector (patient contacting components)

Relevant findings within this review included:

- Design controls are adequate
- Design verification activities are adequate
- The devices conform with the referenced international and FDA-recognized consensus standards
- The devices meet the sponsor defined essential performance requirements
- The devices meet the ISO 11608-1 Dose Accuracy Specifications
- The devices maintain essential performance after exposure to shipping conditions
- The devices maintain essential performance after exposure to aging conditions
- The sponsor has established and conducted appropriate device design risk management activities
- The devices were demonstrated to be biocompatible according to the level of patient contact

III. Consult Purpose

The Center for Drugs Evaluation and Research (CDER) requested a consult from CDRH/ODE for a device constituent part design review of BLA 761042, which is a combination product consisting of GP2015, a biosimilar to Enbrel, and three configurations of the device constituent: two pre-filled

syringes with needle safety device (25 mg/0.5 mL and 50 mg/1.0 mL) and an autoinjector (50 mg/1.0 mL). This NDA has been submitted by Sandoz.

IV. Coverage of Review

CDRH/ODE reviews content related to the design of device constituent parts for combination product submissions. This review is limited to design requirements and verification/validation information to support the device constituent part, including essential performance of the device constituent part and reliability of the device constituent part over time and after expected environmental exposures. This review does not cover review of the primary “container closure” (i.e. cartridge), manufacturing or process validation of the device, nor usability studies for the device.

V. Background

GP2015 (Etanercept) is a TNF α inhibitor used for the treatment of various autoimmune diseases. GP2015 is a biosimilar to Enbrel with the same intended use. This biosimilar is not seeking an interchangeable claim. Therefore, CDRH did not evaluate any attributes of the device constituents for interchangeability. The present marketing authorization application seeks licensure for all indications for which the US licensed reference product Enbrel[®] is approved. Full information on the indications being applied for is provided in [Module 2.7.3].

The submission contains information on 3 devices: 2 PFS with needle safety device (25 mg and 50 mg) and an autoinjector with 50 mg PFS.

Pre-filled syringe with Needle Safety Device (PFS with NSD)

The intended use of the combination product GP2015_PFS_25_50 in (b) (4) is the delivery of a subcutaneous (s.c.) injection of GP2015 drug formulation whereas the needle safety device (NSD) constituent part is intended to prevent needlestick injuries (NSI). The NSD gets activated once the complete contents of the prefilled syringe (PFS) have been ejected.

The GP2015_PFS_25_50 in (b) (4) is available in two strengths, 25 mg/0.5 mL and 50 mg/1.0 mL. The drug product is filled in a PFS, which is not a marketable product by itself (e.g. it does not have a plunger rod). Both strengths use the identical primary container materials. They only differ in the filling volume and are identified by a (b) (4). After assembly the strength can be differentiated amongst others by the label, the color of the device constituent parts and the secondary packaging (see Module 1.14.1.1).

Autoinjector (AI)

The Sponsor is proposing to market their drug with an auto-injector that is based off of the (b) (4) (b) (4) developed by (b) (4) on behalf of Novartis Pharma. The specific model name given to the subject device of this submission is (b) (4) GP2015 50. The following information was provided by the Sponsor in regard to the (b) (4) auto-injector (b) (4)

The (b) (4) AI has been developed as a (b) (4) device suitable for a range of dosage forms and / or drug formulations by (b) (4) on behalf of Novartis. (b) (4)

(b) (4). One drug thereof, AIN457 (INN: secukinumab) was developed for indications largely similar to those of Enbrel[®], e.g. (b) (4), psoriatic arthritis, psoriasis, and ankylosing spondylitis. AIN457 was recently approved as Cosentyx[®] by the Agency (BLA 125504 (see Section 16.1)).

(b) (4) AI (b) (4) was also used by Sandoz to develop an administration device specifically for GP2015, (b) (4)

(b) (4) Therefore several documents compiled as well as activities or investigations performed by Novartis Pharma or (b) (4) for other drug products (i.e. AIN457) are equally applicable to the (b) (4) GP2015_50 combination product.

Reviewer Comment

The autoinjector components for GP2015 and AIN457 (b) (4) differing in the drug product and fill volume specification. Therefore, the sponsor repeated only those tests which could be impacted by the drug/fill volume. Additionally, the indications for AIN457 are largely similar to those of Enbrel®, e.g. (b) (4), psoriatic arthritis, psoriasis, and ankylosing spondylitis. The reviewer agrees with the sponsor's assessment of tests that were not considered to be influenced by the drug product and therefore tested with water or in an empty syringe.

The single function of the (b) (4) AI is to deliver a single, fixed dose, subcutaneous injection of GP2015. The (b) (4) AI is composed of a main outer body and a prefilled syringe (PFS) carrier assembly inside; the device is spring powered and is designed to administer the entire contents of the PFS in one dose. The (b) (4) AI does not have a fluid path and does not have any contact with the drug or biologic contained within the prefilled syringe.

VI. Device Description

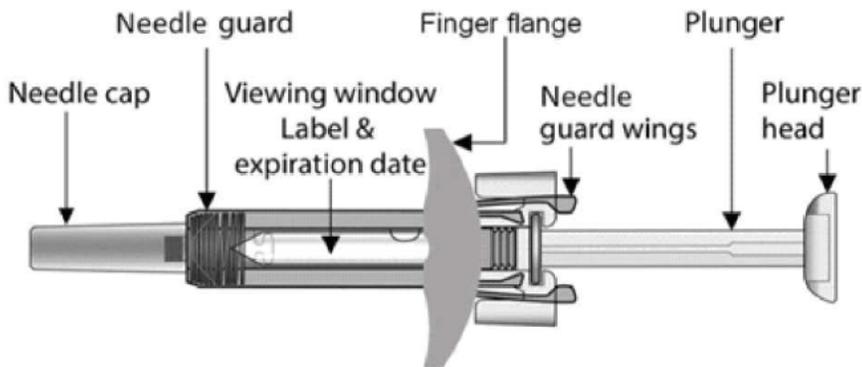
Pre-filled syringe with Needle Safety Device (PFS with NSD)

The GP2015_PFS_25_50 in (b) (4) combination product has two commercially available device components:

- 1 mL long syringe with staked 27G ½ inch needle, needle shield, and rubber stopper
- Needle safety device: BD UltraSafe Passive Needle Guard (b) (4) consisting of the needle guard assembly, the plunger rod and an add-on finger flange

The container closure system and the NSD of the combination product are depicted in Figure 4-1 below.

Figure 4-1 Schematic figure of the combination product (exemplary design, not final commercial design)



GP2015_PFS_25_50 in (b) (4) is a single-use, fix dose product. It is intended for the safe delivery of a single subcutaneous dose of GP2015. Two strengths, i.e. 25 mg/0.5 mL and 50 mg/1.0 mL have been developed which only differ by filling volume. The strengths are identified by the color of the plunger rods in addition to the labeling.

GP2015 25 mg/0.5 mL and 50 mg/1.0 mL solution for injection is (b) (4) filled in the glass syringe barrel and stoppered with the rubber plunger. A rubber needle shield encapsulates the needle; the rigid shell (b) (4). The syringe barrel, needle and plunger stopper are (b) (4).

Table 2-1 GP2015 25 mg/0.5 mL and 50 mg/1.0 mL solution for injection in PFS: Identity of materials of construction

Component	Description	Identity of material	Supplier	DMF number ³⁾	Compliance status
(b) (4) Syringe with staked needle (sold as sterile and non-pyrogenic)					
Syringe barrel	1 mL long, colorless	(b) (4)	(b) (4)	(b) (4)	Complies with Ph. Eur. and USP requirements for type I glass (b) (4) Stainless steel
Staked hypodermic needle	27 G x 1/2"				
(b) (4) Plunger stopper					
Plunger stopper	Grey rubber stopper	(b) (4)	(b) (4)	(b) (4)	Complies with Ph. Eur. and USP requirements
	Rubber formulation				
	Piston (plunger)				
Rigid needle shield					
Rigid shell	Plastic shell	(b) (4)	(b) (4)	(b) (4)	Not applicable as not product contacting Complies with Ph. Eur. and USP requirements
Rubber needle shield	Grey rubber needle shield				
	Rubber formulation				

¹⁾ The rubber formulation for the plunger stopper is provided to (b) (4)

²⁾ The rubber formulation for the rubber needle shield is provided to (b) (4)

³⁾ Letters of authorization (LoA) to the DMF are provided in [Module 1.4.1]

Table 4-2 Strengths of GP2015_PFS_25_50_in (b) (4)

	GP2015 (25 mg / 0.5 mL)	GP2015 (50 mg / 1.0 mL)
Strength	25 mg / 0.5 mL	50 mg / 1.0 mL
Filling volume	0.5 mL	1.0 mL
Plunger Rod	(b) (4) (b) (4)	(b) (4) (b) (4)
Finger Flange	Grey – (b) (4)	Grey – (b) (4)

Reviewer Comment

The engineering consultant was concerned that colors differentiating the two strengths of the drug are too similar and could be confused by the user, resulting in an under or over delivery of the drug. The lead reviewer sent an email to the RPM, Jessica Lee, to bring this to the attention of DMEPA or appropriate CDER division. Marjorie Shapiro in OPQ provided additional information (email attached appendix) that the 25 mg syringes have a (b) (4) label and the 50 mg syringes have a (b) (4) label. The issue appears to have been addressed; however, CDRH defers the acceptability of this mitigation to DMEPA.

Syringe barrel, needle shield, and rubber stopper

The syringe barrel is colorless made of borosilicate glass type I (Ph. Eur., USP/NF). The syringe is assembled with a staked stainless steel needle and a rigid needle shield. The needle shield consists of a rubber needle shield (with product contact) in (b) (4) rubber formulation and a rigid shell (no direct drug product contact). The rigid shell is made of (b) (4) and (b) (4).

Needle

27 ½ Gauge stainless staked steel needle

Needle Safety Device

BD UltraSafe Passive™ Needle Guard (NSD) consists of the needle guard assembly, plunger rod and add-on finger flange. They form together the single-use device constituent parts of the combination product GP2015_PFS_25_50_in (b) (4)

The needle guard assembly is a three-component assembly of a plastic body, plastic guard and metal spring. Once combined with a suitable 1 mL long ISO syringe, this needle guard forms an interlocked needle shielding system which allows delivering a medicine in a controlled fashion. The add-on finger flange enlarges the grip area, and thus, provides additional

the drug fluid path nor does it provide any protection to the drug product.

The needle safety device is indicated for single use to aid in the protection of users from accidental sharps injuries. It was developed by Safety Syringes Inc. (SSI) which was later on acquired by Becton Dickinson Medical - Pharmaceutical Systems (BDM-PS). The NSD has been 510(k) cleared in the US under K011369 and K060743 (see Section 16.2) (Regulation Number: 880.5860, Product Code MEG).

NSD Operational principles

After removal of the needle cap, the solution for injection is manually injected by pressing down the plunger as far as it will go, so that the plunger head is completely between the needle guard wings. The user is instructed to wait for at least 5 seconds prior to removing the needle from the skin.

Releasing the plunger, once the full content has been expelled and the syringe is removed from the skin, activates the safety device, which automatically extends and covers the exposed needle. Thereafter, the syringe shall be discarded in a sharps container.

The add-on finger flange enlarges the grip area and assists users in gaining purchase on the finger flange area.

Reviewer Comments

1. The Sponsor states that the NSD has been cleared under K011369 and K060743, however upon review of these 510(k) submissions, it does not appear that the submission followed “Guidance for industry and FDA Staff: Medical Devices with Sharps Injury Prevention Features” issued in 2005. Therefore, CDRH recommended that the Sponsor be asked to verify that it has complied with all aspects of the Guidance regarding Risks to Health, Bench Testing, Simulated Clinical Use Testing, Labeling, Microbial Ingress Tests, Sterilization, and Biocompatibility. The sponsor responded on 12/28/15 demonstrating that the NSD has undergone bench testing and simulated clinical use studies to verify that the device adheres to the Sharps Injury Prevention Guidance. The response was adequate, the deficiency has been resolved.
2. An IR was issued to address the engineering consultants concern that unintentional activation prior to administration of entire dose resulting in under dosing. The sponsor provided a response on 12/28/15 that consisted of a justification as to why unintentional activation is not a concern based on human factors data and the inclusion of an additional risk mitigation of including a warning on the instructions for use. The information provided was adequate; the deficiency has been resolved.
3. An IR was sent to address the engineering consultant’s concern that there were no clear feedback to the user that the entire contents of the device have been expelled. The sponsor provided a response on 12/28/15, clarifying that there is tactile feedback at the end of injection when the user is unable to push the plunger rod any further. Additionally, the needle guard will only activate at the end of delivery. The sponsor has included statements within their instructions for use that specify the user should continue to press on the plunger for an additional 5 seconds after the plunger is as far as it will go. The human factors studies demonstrated users were able to successfully administer the entire dose. The information provided was adequate; the deficiency has been resolved.

Conditions of Use

After removal of the needle cap, the solution for injection is manually injected by pressing down the plunger as far as it will go, so that the plunger head is completely between the needle guard wings. The user is instructed to wait for at least 5 seconds prior to removing the needle from the skin.

Releasing the plunger, once the full content has been expelled and the syringe is removed from the skin, activates the safety device, which automatically extends and covers the exposed needle. The

add-on finger flange enlarges the grip area and assists users in gaining purchase on the finger flange area.

The injection can be performed by the patient him-/herself, a healthcare professional (HCP) or by a trained caregiver. Administration is weekly or twice weekly in accordance with the prescribing information (see [Module 1.14.1.3]).

Dose Administration

The GP2015_PFS_25_50_in (b) (4) is intended for s.c. application of GP2015. Thus, the GP2015 formulation is administered through a needle into the fatty tissue just under the skin.

The recommended site is the front of the thighs and the lower abdomen, except for the area of 2 inches (5 cm) around the navel. If a caregiver of HCP is administering the injection, the outer upper arms may also be used.

The injection should be at least 1cm from the previously used injection site and areas of injection should be rotated.

Autoinjector(AI)

The (b) (4) GP2015_50 is a single use drug-device combination product consisting of an administration device and a drug product constituent part. The device constituent part is a single-use autoinjector ((b) (4) AI), and the drug component is a 50 mg / 1 mL solution of GP2015 provided in a prefilled syringe with a staked needle. The prefilled syringe is assembled into the autoinjector and forms a single unit with the autoinjector which is not to be separated.

The (b) (4) GP2015_50 is a disposable, fix dose, single dose needle-based injection system with automated functions according to ISO 11608-1 (see Section 16.1) and ISO 11608-5 (see Section 16.1). The corresponding system designation is D1.

The (b) (4) GP2015_50 consists of the following parts (as shown in Figure 4-4)

- Cap (protects the needle before use)
- Cap Seal (tamper evidence feature)
- Rigid Needle Shield (RNS) (protects needle before use) – part of the PFS
- Needle (inserts into the skin)
- Needle Cover (Sharps Injury Prevention Feature (SIPF))
- AI Body (contains the injector mechanism)
- Inspection Window (allows user to check the progress of the injection (green indicator) and check the appearance of the drug before use)
- Green Indicator (shows the progress of the injection as it slowly progresses through the inspection window during injection)

Figure 4-4 Graphical depiction of the (b) (4) GP2015_50 and its key components

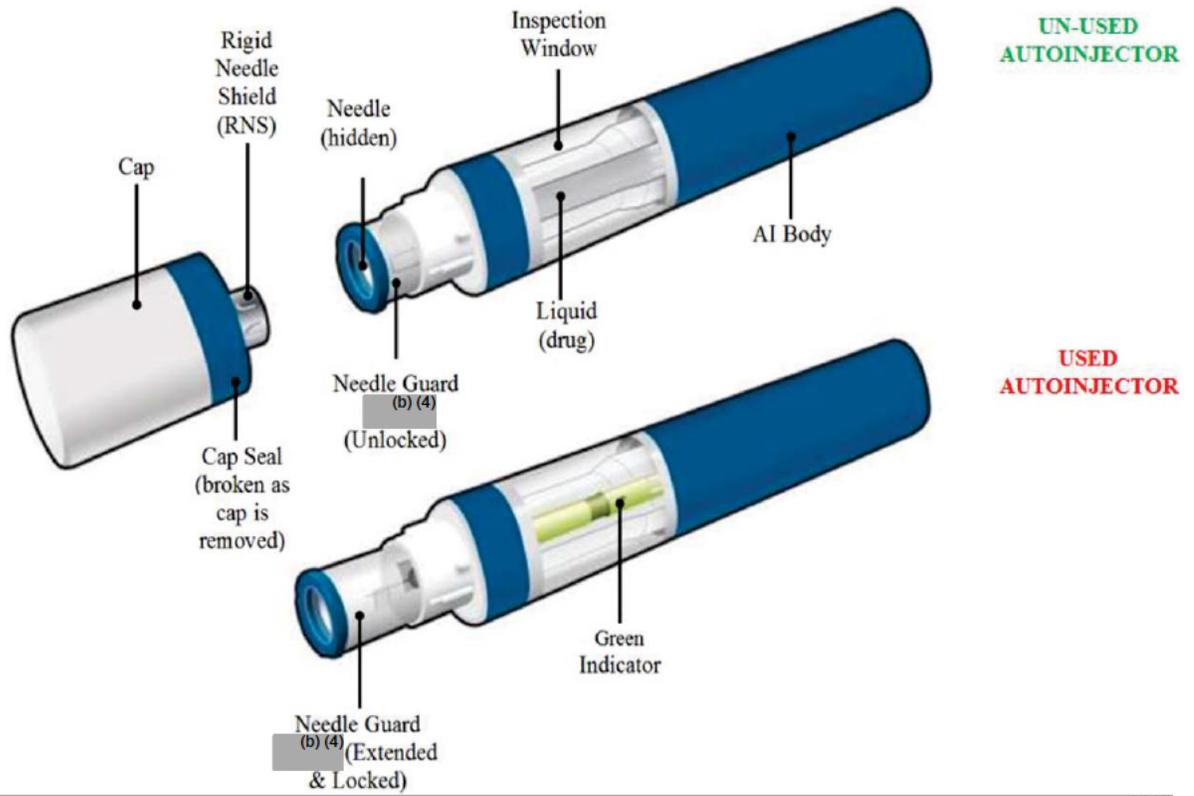


Figure 4-1 Composition of (b)(4) GP2015_50 (exploded view)



(b)(4)



Conditions of Use

The injection process starts with the removal of the cap. Whilst twisting the cap off, the rigid needle shield of the syringe is removed. Once the cap is removed, the needle remains covered and completely hidden by the needle cover. When the autoinjector is pressed gently against the skin, the extended Needle Cover is pushed back into the front subassembly and the device will activate. By actuating the process, the needle is inserted automatically into the patient's skin, and following the needle insertion the injection process starts automatically. The start of the injection process is indicated by a first click.

During the injection, the plunger rod drives the rubber stopper emptying the content of the syringe. The injection process can be monitored through an inspection window on the autoinjector. When the injection is almost finished a second click will sound and then the plunger rod stops. When the device is removed from the injection site, the needle cover automatically extends to completely cover the needle and irreversibly locks in the extended position to prevent inadvertent needle stick injuries. It is not possible to re-attach the cap.

The needle-based injection mechanism is spring powered and designed to administer the entire content of the prefilled syringe in one dose. The entire content of the prefilled syringe is delivered to

the patient at the fixed rate. The volume i.e. dosage is defined by the fill volume of the prefilled syringe.

Dose Administration

(b) (4) GP2015_50 is a disposable, fix dose, single dose needle-based injection system. The needle-based injection mechanism is spring powered and designed to administer the entire contents of the prefilled syringe in one dose. Thus each injection delivers the single full dose of 50 mg. No dose setting can be done with the (b) (4) GP2015_50.

(b) (4) GP2015_50 is intended for patient self-administration of therapy and for administration by caregivers or healthcare professionals (HCPs). (b) (4) GP2015_50 is intended to be used by (b) (4) and adults. (b) (4), the injection will be performed by a caregiver. Administration is weekly or twice weekly in accordance with the prescribing information (see [Module 1.14.1.3]).

The (b) (4) GP2015_50 is intended for s.c. application of GP2015. Thus, the GP2015 formulation is administered through a needle into the fatty tissue just under the skin. The recommended site is the front of the thighs and the lower abdomen, except for the area of 2 inches (5 cm) around the navel. If a caregiver of HCP is administering the injection, the outer upper arms may also be used.

VII. Design Requirements

Pre-filled syringe with Needle Safety Device (PFS with NSD)

Requirement	Specification	Verification	After Aging/Preconditioning/Shipping? (Intended shelf-life = 24 months)
Injection Force	Results indicated (b) (4)N with plunger speed set to (b) (4) mm/min	Stability Testing	Aging – Yes, (b) (4) months
Dose Accuracy / Extractable Volume for final finished combo product	NLT (b) (4) mL or (b) (4) mL for 1 mL and 0.5 mL PFS respectively	Transport Validation (3.2.P.3.5) Stability Testing (3.2.P.8.3)	Shipping/Transport Validation – Yes, included transport temperature, mechanical stress, and low air pressure Aging – Yes, (b) (4) months
Injection Time	NLT (b) (4)seconds, based on user injection force	Instructions for Use	N/A
Needle Length/Gauge	0.5 inch / 27 G Stainless Steel	DMF (b) (4) 3.2.R. Technical Summary NSD	N/A

Manufacturing In-Process Control	Specification
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Break Loose and Glide Force	(b) (4) syringes tested as described in 3.2.P.5.6 DP control strategy
Extractable Volume	NLT (b) (4) mL or NLT (b) (4) mL

Reviewer Comment
The design requirements for the pre-filled syringe with needle safety device are adequate.

Autoinjector (AD)

2.1 Functional/Performance Requirements (Ambient Conditions: 18°- 28°C, 25%-75% RH)

DIR Item No.	Requirement(s)	Equivalent Item in DIR 0154-002 and DIR 0154-004	Included in GP2015 (b) (4)-50 Design Verification (Yes/No)	Justification for Exemption
4.1	The injection time in air shall be less than or equal to (\leq) (b) (4) seconds. The average injection time shall be typical value (b) (4) seconds	2.1	Yes	N/A
4.2	The delivered volume shall be equal or larger than (\geq) (b) (4) ml calculated according to the dose accuracy requirements specified in ISO11608-1 ((D1, N=60, one side tolerance limit factor k at 95% CI with (b) (4)P).	2.2	Yes	
4.3	The needle injection depth shall be (b) (4) mm.	2.3	No	This property is not influenced by the difference of the pre-filled syringe content
4.4	The displacement of the Needle Cover before activation shall be between (b) (4) mm (excluding initial play).	2.4 A	No	
4.5	The activation shall occur at a minimum distance of (b) (4) mm between the Needle cover extension and the Front end cover	2.4 B	No	
4.6	The needle point shall be at least (b) (4) mm inside the edge of the needle cover after completed injection, when the Needle Cover is exposed to a force of, at least (b) (4) N.	2.5	No	
4.7	The force on the Needle cover to trigger activation shall be between (b) (4) N. (\geq) (b) (4) N and (\leq) (b) (4) N).	2.6	No	
4.8	The Needle Cover override force after injection shall be at least (b) (4) N (instantaneous) with less or equal to (\leq) (b) (4) mm displacement of the Needle Cover.	2.7	No	
4.9	The separation force between Front Shell and Rear end Cover shall be at least (b) (4) N (Typical value (b) (4) N).	2.8	No	
4.10	The separation force between Front Shell and Front end Cover shall be at least (b) (4) N.	2.9	No	

DIR Item No.	Requirement(s)	Equivalent Item in DIR 0154-002 and DIR 0154-004	Included in GP2015 (b)(4)-50 Design Verification (Yes/No)	Justification for Exemption
4.11	The device shall give an audible feedback at the start of the injection stroke.	2.10	Yes	See Note 1
4.12	The device shall give an audible feedback signalling "end of injection" as late in the injection stroke as practically possible.	2.11	Yes	
4.13	The device shall have a visible end of injection indicator.	2.12	Yes	
4.14	It shall be possible to monitor the Plunger Rod movement during the injection stroke.	2.13	Yes	
4.15	The device shall allow for visual inspection of the drug product, i.e. the formulation and the pre-filled syringe.	2.14	No	This property is not influenced by the difference of the pre-filled syringe content
4.16	The separation force between the Cap and the RNS Remover shall be \geq (b)(4)N.	2.15	No	
4.17	The separation force between the RNS Remover and the RNS shall be \geq (b)(4)N.	2.16	No	Identical device components and syringe components are used
4.18	When the Cap is twisted off from the device, any potential rotation of the RNS may not cause coring (cut out of rubber particles).	2.17	No	
4.19	The needle must be hidden before use.	2.18	Yes	See Note 1
4.20	The rotation torque should be \leq (b)(4) Nm when twisting off the Cap from device with label.	2.19	No	This property is not influenced by the difference of the pre-filled syringe content
4.21	The separation force between the Cap and the Front end cover (plastic parts only) shall be (b)(4)N. (\geq (b)(4)N).	2.20	No	
4.22	The noise level and tactile response during activation and injection shall be acceptable by the customer	2.21	Yes	See Note 1
4.23	The syringe needle shield must not be moved outwards from the syringe during handling/ assembly in a way that the needle is exposed to microbiological contamination	2.22	No	This property is not influenced by the difference of the pre-filled syringe content

DIR Item No.	Requirement(s)	Equivalent Item in DIR 0154-002 and DIR 0154-004	Included in GP2015: (b) (4) 50 Design Verification (Yes/No)	Justification for Exemption
4.24	The assembly of the PFS must be facilitated by sufficient guiding and chamfers in Front sub-assembly	2.23	No	This property is not influenced by the difference of the pre-filled syringe content NOTE: this requirement is verified by the Qualification of the (b) (4) assembly line at Novartis. Ref report number: WST_303_B_821_1_QB_001
4.25	The overall weight of the device, including filled 1 ml syringe, must not exceed (b) (4) g	2.24	Yes	N/A
4.26	Total length: 165 mm – 167 mm. Cap length: 30 mm ±0.5 mm Max diameter: 21.5 mm	2.25	No	This property is not influenced by the difference of the pre-filled syringe content
4.27	The device must automatically insert the needle and inject the medication	2.26	Yes	N/A
4.28	The design of the device shall be adopted for delivery of one dose with Pre filled syringe fill volume lower than (b) (4) ml.	2.27	No	This property is not influenced by the difference of the pre-filled syringe content
4.29	The device must comprise no more than two sub-assemblies that are to be assembled with the pre-filled syringe in a final assembly step	2.28	Yes	See Note 1
4.30	The device must have a (b) (4) cross section, as described in the Industrial design report	2.29	Yes	

DIR Item No.	Requirement(s)	Equivalent Item in DIR 0154-002 and DIR 0154-004	Included in GP2015-(b)(4)-50 Design Verification (Yes/No)	Justification for Exemption
4.31	The outer shape of the device must not have any sharp edges	2.30	Yes	See Note 1
4.32	The body of the device must have a straight shape, without curves	2.31	Yes	
4.33	The device must be actuated by pressing the needle cover against the injection site only, without additional trigger button	2.32	Yes	
4.34	The device must have a protective Cap, to be removed prior to injection	2.33	Yes	
4.35	The Cap must be possible to remove by a rotational movement, using a cam curve as described in Industrial design report	2.34	Yes	
4.36	The device must have a needle cover that locks in its outer position, protecting the needle, after injection	2.35	Yes	N/A
4.37	The device shall be free from visual and functional defects after vibration testing according to ISO 11608-1:2012	2.36	No	This property is not influenced by the difference of the pre-filled syringe
4.38	Front subassembly: Cap (b)(4); Needle cover extension (b)(4); Front end cover (b)(4); Rear subassembly: Plunger rod (b)(4); Rear end cover (b)(4)	New requirement in GP2015 (b)(4)-50	Yes	See Note 1
4.39	The cap must be designed to prevent accidental activation when removed and the user must not be able to activate the device without removing the cap	New requirement in GP2015 (b)(4)-50	Yes	

NOTE 1: The items which shall be verified by "Assessment by project team" and visual inspection based on the Design Input Requirements, are already verified in the 0154-002 (b)(4)-01A (same device as GP2015-(b)(4)-50) and 0154-004 (b)(4)-02A (same device as GP2015-(b)(4)-50) and are therefore not considered relevant to verify again for the (b)(4) project team. The Assessment will be applicable for the Sandoz project team; (b)(6), Device core team leader (b)(4) and (b)(6), Quality Assurance, except for the items 4.28 and 10.3 which are considered covered by the already performed (b)(4) team assessment.

Reviewer Comments

- The design requirements for the autoinjector are adequate for the intended use of the combination product.
- An IR was sent to the sponsor (March 18, 2016) asking for validation of the acceptance criteria of < (b)(4) seconds for the injection time of the autoinjector. The sponsor stated that acceptability of the acceptance criteria of < (b)(4) seconds for the injection time of the (b)(4) autoinjector was validated with the summative human factor studies for (b)(4) 02 AIN457, using the (b)(4) autoinjector and the same syringe

with a different drug product. The studies demonstrated that the intended user population was able to use the autoinjectors. Additionally, the injection time is not communicated in the IFU, the completion of injection time is indicated by audible and visual cues. The reviewer confirmed with the DMEMPA reviewer (Carlos Mena-Gillasca) that the patient population in the human factors study for (b) (4) 02 AIN457 was appropriate for this combination product (ie. included RA patients) and that DMEMPA did not have any concerns about the (b) (4) second injection time based on the results of that study.

3. The sponsor was asked to provide validation for the acceptability of the injection depth. The (b) (4) GP2015_50 needle length is 12.7 mm whereas the predetermined injection depth (exposed part of the needle) is less. The sponsor provided a summary of the literature that supports the range chosen for this syringe. Additionally, there was adequate delivery of drug dose to the target tissue with the (b) (4) GP2015_50 in comparison to GP2015 PFS has been shown in the clinical study G15-103.

VIII. Engineering Performance

Pre-filled syringe with Needle Safety Device (PFS with NSD)

Design Verification of Needle

The requirements for the syringe needle were based on ISO 7864 Sterile Hypodermic Needles for Single Use. Additionally, the 1 mL BD (b) (4) syringe with 27G X ½ staked hypodermic needle was validated in the pre-filled syringe with NSD and autoinjector presentations in clinical studies (see clinical acceptability section below). No adverse events were recorded concerning the needle.

Design Verification Tests on combination product

Table 2-1 Design Verification Tests performed by BD on the combination product

BD Mechanical Test	BD internal Test Protocol	BD internal Test Report	Result
Activation force	LTP430	TR20152080	Pass
Triggering force*	LTP430	TR20152080	Pass
Compression force	LTP430	TR20152080	Pass
Separation force	LTP430	TR20152080	Pass
Syringe insertion force**	LTP430	TR20152080	Pass
Syringe retention force**	LTP430	TR20152080	Pass
Syringe Spin test**	LTP430	TR20152080	Pass

*test performed with water filled syringes

**test performed with empty syringes

As the tests mentioned above are not considered to be influenced by the specific drug product as long it is filled in an ISO 11040-4 compliant 1mL syringe, these tests are considered also applicable for the proposed GP2015 PFS in NSD combination. The tests also include component separation.

However, additional tests on the final combination product have been and are being performed including resistance to, drop testing, freedom from unacceptable damage to or loss of medication volume due to mechanical forces exerted by the system (container closure integrity test (CCIT)), resistance of system components to damage from shipping in the following test programs:

1. Transport Validation of the combination product in final packaging - mechanical and physicochemical testing. For further details refer to section 12, Response to question 5.
2. Ongoing stability study of the combination product including mechanical and physicochemical testing. Details are described in the stability protocol:
 - BP027615, Stability Protocol – Study no. GP2015_DP_031 (see [Module 1.11.1 - RFI 08 – Answer to Question 1 to 18 - Attachment 24])

Reviewer comment

The engineering performance review found the above verification tests acceptable. The reviewer agreed with the sponsor’s assessment of tests that were not considered to be influenced by the drug product and therefore tested with water or in an empty syringe.

Table 6-2 Functional Requirements

ID	Design input	R/W	Requirement Ref.
DIR2.1	To ensure that the PFS with NSD and add-on finger flange is suitable for delivery of subcutaneous injection, a 1 mL long ISO standard glass syringe with a ½" long staked needle shall be selected.	R	URS2.1
DIR2.2	The selection of the off-the-shelf components must ensure that the PFS with NSD and add-on finger flange are suited for safe removal of the rigid needle shield.	R	URS2.2
DIR2.3	The selection of the NSD and add-on finger flange must ensure that the user is able to activate the needle safety device feature when fully depressed.	R	URS2.3
DIR2.4	The final products two strengths must be clearly distinguishable, visibly by virtue of colour, design and labelling description.	R	URS2.4
DIR2.5	It must be possible for the user to open the packaging that contains the combination product. Secondary packaging must provide means for opening by perforation or peel off strap suitable for the intended patient population.	R	URS2.5
DIR2.6	The blister must be wide enough to provide enough space to easily retract the syringe from the blister by providing minimum (b) (4) mm space on each side of the combination product body.	R	URS2.6
DIR2.7	The selection of off-the-shelf components must ensure that the safety feature does not activate prior to the end of the injection.	R	URS2.7
DIR2.8	The selection of the safety device must ensure that it is suitable for the use with a 1 mL long ISO standard glass syringe.	R	URS2.8
DIR2.9	The selection of the add-on finger flange must ensure that is suitable for the use with the NSD.	R	URS2.9

Extractable volume was tested as part of in-process controls, aging, and transportation studies. The reviewer agrees that dose accuracy has adequately been addressed.

Reviewer Comment

1. Extractable volume was tested as part of in-process controls, aging, and transportation studies. The reviewer agrees that dose accuracy has adequately been addressed.
2. During the Summative AIN457 Human Factors study, a trained participant did not release the cap prior to injection, thus releasing some medication when the cap became forced off via the plunger. An IR was sent to address the engineering consult’s concern the force required to move the cap was too low. The sponsor provided a response clarifying that the incident the human factors study was actually a result of the cap not coming off as easily as the user expected, but that he immediately recognized his error and was able to correct his mistake upon second injection. The minimum force of (b) (4) N is needed to retain integrity during plunger rod assembly, in environments with minor pressure fluctuations, and prevent unintentional cap removal by the user. There are clear instructions in the IFU specifying cap removal prior to injection. The findings of the human factors study supports that users are able to successfully complete an injection when flowing IFU. The deficiency has been resolved.

Design Verification Tests on bulk pre-filled syringes

Break loose and gliding force will be included in release testing for (b) (4) DP in syringes for routine use as described in the (b) (4) DP control strategy (Module 3.2.P.5.6). Break loose and gliding forces testing is not considered needed for fully assembled GP2015 25 mg/0.5 mL and 50 mg/1.0 mL solution for

through; therefore, the NSD is not expected to impact the gliding or break loose force and the gliding or break force is not expected to impact the functionality of the NSD.

The sponsor provided a letter of authorization for the NSD the 510(k) K011369. The sponsor has also included the design verification requirements of the NSD of the combination product within the Technical Summary Needle Safety Device. The essential performance requirements and specifications are summarized below:

Table 2-2 Essential performance requirements, specifications, and traceability

Essential Performance Requirement	Specification	Verification
Activation force	Spring reaction force \geq (b) (4) N during activation all the way through the lockout	Pass (see BD test: TR20152080)
Triggering	Correct triggering along with full activation into locked position	Pass (see BD test: TR20152080)
Compression force	Force required to override the activated locked guard to the un-activated position: \geq (b) (4) N	Pass (see BD test: TR20152080)
Separation force	Force required to separate the guard from the body when the assembled device has been activated in its locked position: \geq (b) (4) N	Pass (see BD test: TR20152080)
Syringe Spin test	Syringe spins freely at least in one direction	Pass (see BD test: TR20152080)

Lot Release Testing:

The Sponsor has provided the following release specifications to be tested for the syringe (Table 2-2) and rubber stopper (Table 2-3):

Table 2-2 Specifications

Parameter	Specification	Method
Dimensions	In accordance with size specific drawing (see Figure 2-1)	Dimension testing with suitable measuring equipment
Appearance (syringe with needle and protection cap) ¹⁾	Free from process defects	Visual examination
Cleanliness	Free from glass splinters, fibres, dust, hair and insects	Visual examination
Identification	Corresponds qualitatively to the reference spectrum	IR spectroscopy
Material quality ¹⁾	Complies (needle shield and glass)	Current Ph. Eur./USP
Bacterial endotoxins ²⁾	(b) (4) EU/syringe	Current Ph. Eur./USP

¹⁾ Tests can be omitted if the supplier of the packaging material is qualified and certifies compliance with the requirement.

²⁾ Bacterial endotoxin testing is performed periodically by the drug product manufacturer. Routine testing by a qualified supplier is also accepted for inclusion on the Certificate of Analysis.

Table 2-3 Specifications

Parameter	Specification	Method
Dimensions	In accordance with size specific drawing (see Figure 2-2)	Dimension testing with suitable measuring equipment
Appearance – Cleanliness	Grey, clean and free from processing defects and mold flashing	Visual examination
Identification	Corresponds qualitatively to the reference spectrum	IR spectroscopy
Material quality	Complies with the requirements of Ph. Eur./USP	Current Ph. Eur. monograph/ USP for ‘Rubber closures for containers for aqueous preparations for parenteral use’

¹⁾ Bacterial endotoxin testing is performed periodically by the drug product manufacturer. Routine testing by a qualified supplier is also accepted for inclusion on the Certificate of Analysis.

The following information was provided by the Sponsor regarding the inspection and testing completed prior to release of the final combination product in regards to the PFS and NSD:

Release testing of the final combination product GP2015_PFS_25_50 in (b) (4) includes visual inspection as well as functional testing. The functional testing includes the following test items:

- (b) (4)
- (b) (4)
- (b) (4)
- (b) (4)

The following IR was sent to the sponsor on March 10, 2016

The lot release testing requirements for the pre-filled syringe does not appear to include the essential performance requirements. Include the dose accuracy (i.e., extractable volume), break loose and gliding force within the lot release specifications.

Sponsor Response received March 11, 2016

The release specifications applicable for the GP2015 (b) (4) pre-filled syringe (PFS) are provided in [Module 3.2.P.5.1].

Essential performance requirement ‘extractable volume’:

Extractable volume is included in the release specifications for the GP2015 (b) (4) PFS. Release specifications for the (b) (4) PFS are ‘not less than (NLT) (b) (4) mL’ for the 50 mg strength and ‘NLT (b) (4) mL’ for the 25 mg strength, see also [Module 3.2.P.5.1].

In addition, dose accuracy is part of autoinjector (AI) release specification since this confirms the device functionality. The release specification for dose accuracy is ‘NLT (b) (4) mL’ (see [Module 3.2.R Technical summary (b) (4) device]).

Essential performance requirement ‘Break loose and gliding force’:

Break loose and gliding force (BLGF) are considered as quality attributes of high criticality due to the potential impact on the combination product’s performance and therefore will be included in release specifications of the GP2015 (b) (4) PFS for routine use as described in the control strategy [Module 3.2.P.5.6].

For BLGF a method for measurement at a speed of 300 mm/min has been validated recently and will be used for routine release testing of the GP2015 (b) (4) PFS in order to ensure a robust function in the autoinjector as well as with the needle safety device.

In order to define robust release specifications, Sandoz proposes to generate additional data from commercial batches and to define specifications based on those data.

Sandoz herewith commits to implement the specifications as soon as data from 10 commercial batches per strength (25 mg and 50 mg) are available. Generated data and the updated [Module 3.2.P.5.1] will be submitted with the annual report.

Reviewer Comment

The sponsor has stated that break loose and glide force will be included in the release specifications and that they plan to implement new specifications based on the validations of the new method. The reviewer agrees that the sponsor can provide the lot release specifications as a post-market commitment.

(b)(4). See post-market commitments under the Recommendation section at the top of this memo.

Shelf-life/Stability

The defined shelf life of the final, assembled GP2015_PFS_25_50 in (b)(4) is based on the shelf life of the drug product constituent part as described in Stability Summary and Conclusion document located in 3.2.P.8.1. The product has to be stored at 36°F to 46°F (2°C to 8°C). A risk assessment of the assembly process considering the impact of the addition of the Needle Safety Device was conducted which determined that the assembly process of the needle safety device will not impact the shelf-life of the drug product.

The sponsor provided a Stability Protocol (Study No.: GP2015_DP_031). The objective of this registration stability study is to evaluate the stability of the combination product 'GP2015 PFS with Needle Safety Device and Finger Flange produced during the assembly validation at (b)(4) (b)(4). Three batches of the combination product will be investigated in this study (see Table 3-1), including both the 50 mg / 1 mL and the 25 mg / 0.5 mL strengths.

The shelf life of the combination product is determined by the manufacturing date (b)(4) and is 24 months. Therefore the assembled product will be tested only until the actual end of shelf life of the (b)(4) PFS. Additionally, the device functionality will be confirmed after 24 months in order to confirm the maximal possible shelf life for the combination product (i.e. assuming a worst-case batch assembled directly after syringe filling).

(b)(4)

4 Test methods

Table 4-1 Test methods

Test	Analytical method	Reference	Comment
Appearance (combination product)	Visual check	CP 7516	Not tested in this study
Functional testing (combination product)			
Free rotation of the syringe in the NSD	Manual check	CP 7516	Performed according to release specifications
Activation of NSD	Manual check	CP 7516	Performed according to release specifications
Assembly of the finger flange controls	Manual check	CP 7516	Performed according to release specifications
Comparison of the (b) (4) label and plunger rod	Manual check	CP 7516	Performed according to release specifications
FDF control (combination product)	Visual check	CP 7516	Not tested in this study
Description (PFS)			
Color of solution	Visual evaluation	CP 7399 / 7449	
pH (potentiometric)	Potentiometry	CP 7399 / 7449	
Clarity	Ratio turbidimetry	CP 7399 / 7449	
Extractable volume	Weighing	CP 7399 / 7449	Performed with the assembled combination product
Appearance of container	Visual evaluation	CP 7399 / 7449	Not tested in this study
CCIT (dye ingress)	Visual inspection for discoloration	CP 7399 / 7449 SOP AP 92.404	Performed at Sandoz (b) (4), shipping at (b) (4) °C Syringes are removed from the safety device before testing
Identity / purity (PFS)			
Identity / Product related substances and impurities I	SEC	CP 7399 / 7449 SOP AP 83.179	

6.1 Storage conditions and pull points

Samples are stored at (b) (4) °C until the start of the study. Storage conditions during the study are defined as follows:

Table 6-1 Overview of storage conditions and pull points

Condition	Temperature / relative humidity (r.h.)	Scheduled pull points [months]
Intended	(b) (4) °C	0 (initial time point does not include all allowed OOF times)
Out-of-fridge (OOF)	(b) (4)	2, 3, 6 (measured within (b) (4) PFS shelf life of 24 months) 9, 12 (measured after (b) (4) PFS expiry; nevertheless, results are expected to be within specifications and will be used for linear regression analyses) 24 (maximal combination product shelf life, only functional testing is performed)

Transportation (packing and shipping)

The Sponsor provided the following information regarding the shipping/packaging/transportation of the subject device:

The transport validation plan (see Section 16.2) identifies potential risks, and includes all applicable user requirement specifications (URS) and acceptance criteria as well as the requirements to fulfill mechanical stress tests according to relevant ISTA test requirements. The transport validation will be completed before launch of the product.

The following parameters are evaluated after mechanical stress testing:

- Physical damage to product
e.g. transportability, damage to transport cartons, folding boxes and blisters
- Product integrity,
e.g. activation status of the NSD, peeling off of the blister foil from the blister tray and detachment of syringe from the NSD.
- Quality and container closure integrity
A head to head analytical comparison of mechanically stressed versus unstressed samples is performed for physico-chemical characteristics as well as container closure integrity testing (see Table 9-4 below).

Two GP2015 drug product in PFS batches and one placebo batch were shipped as part of these validation shipments.

Reviewer comment

The functional testing for the PFS with NSD performed after shipping and aging studies was adequate.

Risk Analysis

The sponsor provided an overview of their risk management activities (see below). No unacceptable risks were identified after implantation of risk mitigation measures. The sponsor states that the overall residual risk, the risk control measures and benefit-risk profile are considered acceptable for GP2015_PFS_25_50 at this stage

Figure 8-1 Overview of risk management activities and responsibilities



The activities to be performed as part of the risk management process include:

- Risk management plan and updates
- Hazard identification (HID)
- Application / usability risk assessment applying a Failure Mode and Effect Analysis (FMEA)
- Process Failure Mode and Effect Analysis (PFMEA):
- Human Factor study: please refer to Section 6.7 Human factors design considerations
- Risk management report and updates

A hazard analysis was performed for the prefilled syringe and the NSD, respectively. The identified hazards together with the approved instructions for use (IFU) and findings of the usability study were used to perform a usability risk assessment for the GP2015_PFS_25_50 in (b) (4) combination product. The usability risk assessment utilizes a FMEA and follows the steps of the IFU.

Reviewer Comment

The engineering consult requested that the sponsor submit the Risk management and usability and engineering plan, hazard identification, and usability risk assessment referred to within the submission. The Sponsor provided the requested information which contained an appropriate risk mitigation strategy for the identified hazards.

Autoinjector (AI)

(b) (4) AI (b) (4) was also used by Sandoz to develop an administration device specifically for GP2015, whereby the (b) (4) AIN457 respectively (b) (4). Therefore several documents compiled as well as activities or investigations performed by Novartis Pharma or (b) (4) for other drug products (i.e. AIN457) are equally applicable to the (b) (4) GP2015_50 combination product.

Table 7-1

Comparison of technical characteristics

(b) (4)

-02 AIN457 -

(b) (4)

Technical characteristics	(b) (4) 02 AIN457	(b) (4) GP2015-50
Cap Removal torque		≤ (b) (4) Nm
Activation Force		(b) (4) N
Injection time		< (b) (4) sec
Dose Accuracy	(b) (4) mL (95% CI with	(b) (4) P)
Needle cover safety (displacement at 80N)		≤ (b) (4) mm
Prefilled syringe		Same (BD (b) (4) 1 mL long)
Rigid needle shield		Same (BD design)
Needle gauge*		27G x ½"
Injection depth		Same ((b) (4) mm)
Filling volume	(b) (4)	(b) (4)**
Injection frequency	Weekly or less frequently	Weekly or twice weekly (for up to 12 weeks in Plaque Psoriasis)

* Not visible to the user at any time

** (b) (4) filling volume was used for simulated use handling study

The Sponsor notes that the technical and functional performance of the auto-injector was tested and verified as part of the design verification testing within (b) (4) GP2015_50_ (b) (4) _02 and (b) (4) GP2015_50_ (b) (4) . Parts 1 and 5 of ISO 11608 were taken into account throughout the design verification process and testing. Testing included preconditioning such as cool, standard and warm atmosphere testing as well as free fall testing, vibration testing, dry heat and cold storage testing was performed in accordance with ISO 11608-1.

The following Performance Testing activities were performed: dose accuracy, injection time, reliability (number of activations without failure), injection depth, activation and overriding forces, and cap removal torque.

While the performance information of the AI is provided within MAF (b) (4) , the Sponsor should have a listing of essential system level requirements for the AI and all the information that verifies the essential system level requirements within their BLA submission as the owner of the combination product. The following IR was sent on December 18, 2015:

To support performance of the autoinjector presentation, you appear to rely on data contained within MAF (b) (4) . While this approach is acceptable, the Agency expects that you as the combination product developer will provide record of combination product requirements along with evidence that those requirements have been verified within the 351(k) BLA.

Update the 351(k) BLA with the following information:

- A listing of essential system level requirements for the autoinjector.*
- Information which verifies the essential system level requirements (see bullet 16a. above) using final finished batch release combination product.*

The sponsor provided the following response to 16b:

Design verification has been performed on the combination product level and on component level. All verification tests passed. An overview regarding which verification report covers which design input requirement is provided in the "Reference information for each test requirement" (see MAF (b) (4) , Attachment 8). Since these tests were conducted by (b) (4) the data were included in the MAF (b) (4) .

Some performance requirements of the autoinjector were assessed to be dependent on the drug product, thus specific to the GP2015 combination product. These requirements were tested with a fully assembled combination product including GP2015 drug product and include:

- Dose accuracy (in standard, cool and warm atmosphere according to ISO 11608-1)*

- Dose accuracy (after pre-conditioning according to ISO 11608-1o)
- Injection time
- Drop tests according to ISO 11608-1
- Attribute testing
- Weight

Other performance requirements of the combination product are not dependent on the drug product within the assembled syringe (e.g. assembly separation force). Therefore verification data obtained for combination products, consisting of the identical auto-injector components, are considered applicable for the GP2015 combination product. A justification as well as all applicable protocols and reports are provided in the Attachment 8 of the MAF (b) (4).

Reviewer comment

The sponsor has included the essential performance requirements and specifications within the NDA. The performance requirements performed on the combination product were chosen based on the ability of the drug to impact the result. Evaluation of requirements that are not impacted by the drug (ie. separation force) were leveraged from the (b) (4) autoinjector ((b) (4) AIN457. This approach is acceptable.

Dose Accuracy

The sponsor conducted the dose accuracy testing according to ISO 11608-1 including storage and environmental conditioning.

Reviewer Comment

The labeling states that the autoinjector will be (b) (4) for 15 minutes before injection. The design input requirements included completed injection (dose accuracy testing) in a cool atmosphere ((b) (4) °C). The testing is performed after a minimum of 4 hours storage.

The Sponsor indicated that the subject device does not require any dose setting or transferring a certain volume from a cartridge or vial into a syringe because the device incorporates a single dose prefilled syringe. Therefore, the dose which the patient receives is based on the filling volume of the PFS. The Sponsor indicates in Table 7-1 of Technical Summary (b) (4) Device that the dose accuracy of the subject device is (b) (4) mL (95% CI with (b) (4) P).

The Sponsor notes that according to ISO 11608-1 the subject device is a system D1 and so the device must maintain a 95% confidence that at least the probability content of all doses are above the lower specification limit. The Sponsor states that for manufacturer-filled containers, the applicable one-sided lower specification limit for the minimum deliverable dose is determined from the drug labeling.

The following summary of verification dose accuracy testing was provided in MAF (b) (4)

Dose accuracy

(b) (4)

The lead reviewer sent to an email to CDER/CMC conveying the engineering consultants concern that the information found in the device master file (MAF (b) (4) indicated that the dose accuracy results were below the specification and consequently deemed to fail in dose accuracy testing. The low dose accuracy was not considered a result of the autoinjector but due to low fill volume. The sponsor provided a new syringe batch after fill volume correction. Design verification of dose

accuracy then passed. CDRH provided a draft IR, but wanted to get CMC's input because the error centered around fill volume.

In your Technical Summary (b) (4) Device under 3.2.R, you state that the PFS is (b) (4)

Dr. Marjorie Shapiro provided the following feedback:

During the process validation (b) (4), one of the lots, S002 (as described in the excerpt below) had OOS results for extractable volume. This occurred in syringes at the end of filing this lot after routine IPC testing (b) (4)

(b) (4). The type of event that happened here had not been observed before for this product or others filled on this line.

The root cause was identified (b) (4). The preventive action changed the SOP to include a (b) (4). Since this happened, there have been no extractable volume failures and this step is included in the continued process verification plan.

Reviewer comment

The root cause has been identified and a mitigation strategy has been implemented. CDRH defers the acceptability of this mitigation step to CDER/CMC.

Mechanical Safety

The following tests were performed by (b) (4) within MAF (b) (4) on the subject device to ensure specifications were met for the separation of device components:

3.1 Component tests

Item	Test item	Output/ unit	DIR item	Test document#	Specification limit	Amounts
Test 1A	Rear end cover and front shell separation force	N	DIR 2.8	0154-002-TI-C004r01	\geq (b) (4) N	60 pcs
Test 1B	Rear end cover and front shell separation force	N	DIR 2.8	0154-002-TI-C004r01	\geq (b) (4) N	Refer to (b) (4) 02A ageing protocol ATP20120217
Test 2A	Front end cover and front shell separation force	N	DIR 2.9	0154-002-TI-C005r01	\geq (b) (4) N	60 pcs
Test 2B	Front end cover and front shell separation force	N	DIR 2.9	0154-002-TI-C005r01	\geq (b) (4) N	Refer to (b) (4) 02A ageing protocol ATP20120217
Test 3	Cap and RNS remover separation force	N	DIR 2.15	0154-002-TI-C006r01	\geq (b) (4) N	60 pcs
Test 4	Shield remover removal force	N	DIR 2.16	0154-002-TI-C007r01	\geq (b) (4) N	60 pcs
Test 5	Cap pull off force from front end cover	N	DIR 2.20	0154-002-TI-C014r01	(b) (4) N	60 pcs

The following Device Drop Tests were performed by (b) (4) in MAF (b) (4) on the autoinjector:

5.3 Device drop test (Test 4)

Direction	Height	Device-state
Horizontal (new NISs in a non-turbulent way)	100cm height	Cap on With label
Vertical-A (new NISs in a non-turbulent way)		
Vertical-B (new NISs in a non-turbulent way)		

Test item	Output	DIR item	Test document#	Specification limit	Amounts	
Device drop test	Three directions	Pass/ Fail	#7.2	ISO 11608-1:2012	All NIS shall be visually examined and must not have defects after the free-fall conditioning.	60 pcs
	Injection time	second		0154-002-TI-F013r3.0	(b) (4) sec (All individual values shall fall within this limit)	60 pcs
	Dose accuracy	ml			<ul style="list-style-type: none"> Each data must fulfill $\bar{x} - (k*s) \geq (b) (4) \text{ ml}$ Refer to ISO 11608-1 Annex B, the NIS system D1, one side tolerance limit factor k at 95% CI with (b) (4)p. $k_{\text{net}} \geq k$ 	

Test 4 Three directions	
Number of Pass = 60pcs	Yield Rate = 100%
Number of Fail = 0pcs	Defect Rate = 0%
Result	PASS

Reviewer comment

The auto-injector met all mechanical safety requirements.

Shelf-Life/Stability

The subject device was tested during the aging study to verify the functionality and reliability of the subject device after accelerated aging. The Sponsor notes that all durability requirements specified in the accelerated aging test protocol were successfully fulfilled. Attachment 7 of MAF (b) (4) contains the accelerated aging and preconditioning test protocol and report for the subject device. Tests performed after accelerated aging included: drop tests, environmental tests, storage environment tests, and transportation tests were conducted by (b) (4) and demonstrated that the subject device maintained dose accuracy and injection time requirements after conditioning. All tests were shown to pass. In addition to the aging tests performed during design verification, the autoinjector functionality was also tested for a maximum shelf life of 2 years during stability testing of the drug product.

Reviewer comment

The stability testing was adequate to demonstrate the two-year shelf-life for the autoinjector.

Transportation (packaging and shipping)

A transportation validation for the GP2015 autoinjector combination product was performed with regard to mechanical stress. The impact of mechanical stress (vibration, shock, low air pressure) was evaluated by applying the ISTA 3A (International safe Transit Association) procedure including the test of vibration under low air pressure with regard to integrity of components and physico-chemical characteristics as well as container closure integrity testing.

Integrity of components included any deformation or other physical damage to the overall shipment configuration, defects of drug product components like damages to folding boxes and perforation of folding boxes and functionality of the autoinjectors.

The transport validation regarding mechanical stress was successful for quality of drug product, container closure integrity and functionality of the autoinjectors but revealed issues regarding the folding box design and transportability of transport cartons. Three parameters that did not comply after application of mechanical stress:

1. Transportability of cartons
2. Integrity of folding boxes
3. Functionality of the folding box

The sponsor stated that a comprehensive development program was successfully performed to solve the three issues listed above. A new design of the folding box was designed which successfully passed test runs of mechanical stress application. After induction of these changes and manufacture of additional test samples including the new folding box and transport carton, additional transport validation regarding mechanical stress will be performed before launch.

IR sent February 22, 2016

In response to the Information Request (IR) dated, Dec 18, 2015, you provided information that a new design of folding box and transport carton was defined and successfully passed test runs of mechanical stress application. You indicated that additional transport validation will be performed after introduction of these changes. Clarify when the report will be submitted.

Sponsor response received February 26, 2016

Activities for the additional transport validation regarding mechanical stress with the new design of the folding box and the transport carton for the GP2015 autoinjector presentation are currently ongoing. An interim report will be provided by 20 May 2016. This interim report will contain data related to the transportability of transport cartons and to integrity and functionality of folding boxes. These data are intended to address the parameters which did not comply in the initial transport validation, and demonstrate suitability of the modified folding box and transport carton. In addition, the interim report will also contain data regarding the functionality of the autoinjector.

The physico-chemical testing and container closure integrity testing will be performed for completeness. Transport validation will be completed successfully prior to the launch of the product, and the final transport validation report will be available by the end of August 2016.

Reviewer Comment

The verification of the container closure integrity and functionality of the autoinjector have been successfully completed after transportation. The sponsor is performing additional testing for the transportability, integrity, and functionality of the carton and folding boxes. The reviewer recommends that this information is submitted by the sponsor upon completion.

Process Validation Testing:

Release testing of the final combination product is performed including visual inspection as well as functional testing. The release tests are outlined below:

Table 13-2 Release testing of the final combination product (b) (4) GP2015_50

Test item	Criteria	Test principle
Dose accuracy	Not less than (b) (4) mL	Gravimetric determination of the amount of liquid (calculated with the density for GP2015) released from the (b) (4) AI (method is based on ISO 11608-1(see Section 16.1))
Appearance	<ul style="list-style-type: none"> • autoinjector cap and label present • syringe present inside autoinjector assembly • syringe not damaged (as viewed through the window) • seal bridges on label not broken 	Visual control of the appearance of the assembled autoinjector
Identification of syringe	The assembled color code of the prefilled syringe complies to specification	Visual control of the color of the ring code label on the syringe after partial removal of label

The Sponsor states that additional testing of the final combination product (b) (4) GP2015_50 was completed during process validation in order to ensure that the subject device met certain functional requirements after assembly. The following tests were performed on 3 batches ranging in size from approximately (b) (4) pieces up to (b) (4) pieces:

Table 13-5 Additional testing of the final combination product (b) (4) GP2015_50 during process validation

Test item	Criteria	Test principle
Cap removal torque	Not more than (b) (4) Nm	Measure the peak torque needed to rotate the cap and the shield remover from the autoinjector (final assembled device including the label)
Activation force	Between (b) (4) N	Measure the peak force on the needle cover to trigger actuation
Needle cover displacement at activation	Between (b) (4) mm	Measure the displacement of the needle cover before actuation
Injection depth	Between (b) (4) mm	Measure the needle length exposed during injection
Injection time	Not more than (b) (4) seconds	Measure the time required to complete the injection into air.
Needle cover safety, displacement at (b) (4) N	Not more than (b) (4) mm	Verify that a force greater than or equals to (b) (4) N load cannot push the needle cover back into the front sub-assembly after injection, and the needle cannot be seen after the needle cover withstood (b) (4) N force.
Rear end cover safety, displacement at (b) (4) N	Not more than (b) (4) mm	Verify that a force of (b) (4) N load on the needle cover after injection cannot push the rear end cover out of the autoinjector body.

Lot Release Testing- AutoInjector

The sponsor provided the following table in response to the Agency's request for documentation that the essential performance requirements have been included in the lot release specifications.

Table 8-1 Lot release testing of the final combination product (b) (4) GP2015_50

Criteria	Test principle	Rationale
Identity		
The assembled color code of the prefilled syringe complies to specification	Visual control of the color of the (b) (4) label on the syringe after partial removal of label	The test 'Identity' ensures that the correct syringe is assembled into the autoinjector
Appearance		
<ul style="list-style-type: none"> • autoinjector cap and label present • syringe present inside autoinjector assembly • syringe not damaged (as viewed through the window) • seal bridges on label not broken 	Visual control of the appearance of the assembled autoinjector	The test 'Appearance' ensures that the autoinjector has been assembled completely and without any obvious damages.
Dose accuracy		
Not less than (b) (4) mL	Gravimetric determination of the amount of liquid (calculated with the density for GP2015) released from the (b) (4) AI (method is based on ISO 11608-1)	The test ensures the proper device functionality and dosing.

Reviewer Comment

In response to question 2 (Information Request dated, March 18, 2016), in which the Agency requested validation for the acceptability of the acceptance criteria of \leq (b) (4) seconds for the injection time for the autoinjector, the sponsor included the following statement:

“The injection time is not communicated in the Instructions for User (IFU). Completion of injection is indicated to the user via audible and visual means (i.e. second click and green indicator fills the window and stops moving). Correct use of the autoinjector, as indicated in the IFU, is therefore independent of injection time.”

The Agency sent a follow-up IR on April 4, 2016 requesting that the audible and visual feedback mechanisms of the autoinjector be included within the essential performance and lot release specifications. The sponsor responded that the audible and visual feedback mechanisms have been verified as part of the Design Input Requirements; however, they do not feel that it is necessary to include the audible and visual feedback within the lot release specifications. The sponsor included the following statement:

“Therefore, for lot release testing, complete injection i.e. dose accuracy was selected as a functional test. Meeting the dose accuracy specification of \geq (b) (4) mL depends on successful completion of previous sequences such as audible and visible feedback (i.e. the plunger has to completely fill the window and is thus visible, and audible feedback must have occurred). Thus dose accuracy inherently ensures meeting audible and visual feedback requirements.”

The performance testing has verified the requirements for the audible and visual feedback attributes; however, including the audible and visual feedback mechanisms within the lot release specifications will assure that all manufactured batches meet the essential performance requirements. The sponsor has stated that the audible and visual cues and not injection time are necessary for the patient to administer a complete dose. CDRH recommends that the sponsor add the audible and visual feedback mechanisms as part of their lot release criteria as a post market commitment.

The following IRs were sent to the sponsor on April 12, 2016:

1. On March 18, 2016, the Agency requested documentation that the essential performance requirements have been included in the lot release specifications. You provided a summary of your lot release testing of (b) (4)

included is dose accuracy. The Agency considers the needle extension to be an essential requirement, as it impacts the ability of the device to deliver the drug to the correct anatomical site. Please include needle extension within the lot release criteria. Alternatively, please provide a justification for why the depth of the needle is not considered an essential performance requirement.

The sponsor provided a response on April 19, 2016 stating that they commit to including the test item “injection depth” into the lot release testing for the commercial batches of (b) (4) GP2015_50. The specification used is the value defined in the design input requirements and verified in the design verification.

Table 1-1 Injection depth specification for lot release of (b) (4) GP2015_50

Test Item	Specification	Test principle
Injection depth	Between (b) (4) mm	Measure the needle length exposed during injection

Reviewer Comment

The deficiency has been resolved. The sponsor has committed to including this specification within the lot release testing.

2. On March 18, 2016 the Agency requested validation of the acceptability for the acceptance criteria of \leq (b) (4) seconds for the autoinjector injection time. In response, you stated that completion of injection is indicated to the user via audible and visual means (i.e. second click and green indicator fills the window and stops moving) and that correct use of the autoinjector is therefore independent of injection time. The Agency sent a follow-up IR on April 4, 2016 requesting that the audible and visual feedback mechanisms of the autoinjector be included within the essential performance and lot release specifications. You have responded that the audible and visual feedback mechanisms have been verified as part of the Design Input Requirements; however, you do not plan to include the audible and visual feedback mechanisms with the lot release criteria. You state that “meeting the dose accuracy specification of \geq (b) (4) mL depends on successful completion of previous sequences such as audible and visible feedback (i.e. the plunger has to completely fill the window and is thus visible, and audible feedback must have occurred). Thus dose accuracy inherently ensures meeting audible and visual feedback requirements.” The injection time will affect the ability of the patient to receive the entire dose and is not captured by dose accuracy testing. You have stated that the injection time is not communicated to the patient but that the patient is to rely on the audible and visual feedback mechanisms. Therefore, CDRH recommends that you include the audible and visual feedback mechanisms to your lot release criteria.

The sponsor provided a response on April 19, 2016 stating that in alignment with the Agency’s recommendation, Sandoz commits to include test items related to the audible and visual feedback into the lot release testing for commercial batches of (b) (4) GP2015_50. Methods for confirming the audible feedback (i.e. occurrence of second click) and visual feedback (i.e. plunger fills the window and stops moving) applicable for release testing will be developed and specifications will be defined. Once established, these test items will be included into the lot release testing and implemented prior to launch.

Reviewer Comment

The deficiency has been resolved. The sponsor has committed to including this specification within the lot release testing. This has been included within the recommending post-market commitments at the top of the memo.

Risk Analysis

Sandoz has included their Risk Management and Usability Engineering Plan based on ISO 14971 in section 8 of the Technical Summary (b) (4) Device in SN0000 under 3.2.R. The risk management plan was signed by Sandoz and submitted as attachment 5 under 3.2.R.

The activities to be performed as part of the risk management process include:

- Risk management plan and updates
- Hazard identification (HID)
- Application / usability risk assessment applying a Failure Mode and Effect Analysis (FMEA)

- Process Failure Mode and Effect Analysis (PFMEA)
- Application & Usability Specification
- Human Factor study: please refer to Section 6.7 Human factors design considerations
- Risk management report and updates

A hazard analysis was performed considering device related hazards and drug related hazards. The identified hazards and feedback from human factor studies together with the approved instructions for use (IFU) are used to perform a usability risk assessment for the (b) (4) GP2015_50 combination product. The usability risk assessment utilizes a Failure Mode and Effect Analysis (FMEA) and follows the steps of the IFU.

(b) (4) uses FMEA methodology (severity vs. probability of occurrence vs. detection level) for evaluation and control of design and manufacturing risks related to the manufacturing of the (b) (4) autoinjector subassemblies. Risk assessments were performed for the manufacturing process of the (b) (4) GP2015_50 combination product at (b) (4). The risk assessments follow the risk management process at (b) (4) and utilize a Failure Mode and Effect Analysis (FMEA). After all risk control measures from risk management activities have been implemented and successfully verified and/or validated, it will be assessed if the overall residual risk posed by the device is acceptable and documented in the Risk Management & Usability Engineering Report.

In response to an information request on March 10, 2016, the sponsor provided additional information on their hazard identification in the Risk Estimation and Evaluation Report (REER).

The hazard identification list generated by Sandoz was used as a basis for the severity assessment by (b) (4) in the REER. In the REER (b) (4) evaluated all risks, and based on the evaluation classified the risk as acceptable or not acceptable. The REER identified one (1) risk as unacceptable, and implemented risk mitigation to reduce the risk to an acceptable level. This is documented in the REER. All other risks were evaluated to be acceptable. The acceptable risks in the table do not reference mitigations; however, the risks have been evaluated to determine if any mitigation can be implemented to lower the risk. Since no mitigations have been deemed necessary, no specific risk control measure has been referenced in the table (refer to [Module 1.11.1 - RFI 13 – Answer to Question 1 - Attachment 1] for detailed information).

For some risks, the REER refers to Sandoz' risk management activities. These risks have been addressed in Sandoz' risk management activities, and are summarized in the Risk Management and Usability Engineering report. Risks were mitigated as reasonably practicable and presenting state of the art. The Risk Management and Usability Engineering report concludes that all risks, including risks identified by (b) (4) are in the acceptable area and the overall benefit outweighs any remaining risks.

No unacceptable risks were identified after implementation of risk mitigation measures. The overall residual risk, the risk control measures and the benefit-risk profile are considered acceptable for the (b) (4) GP2015_50 (see [Module 3.2.R Technical summary (b) (4) device - Attachment 5])

Reviewer Comment

The sponsor's Risk Management and Usability Engineering Report, documents the risk evaluation and implementation of risk control, concluding that there was no residual unacceptable risks. The risk analysis information for the autoinjector is acceptable.

IX. Biocompatibility

Pre-filled syringe with Needle Safety Device (PFS with NSD)

Becton Dickinson (BD) conducted Biocompatibility testing on all parts of the needle safety device (NSD). These parts are the needle guard, which consists of the body, the guard and the spring, the plunger rod and the finger flange. The results of all biocompatibility studies meet established criteria for preclinical toxicological safety evaluation and are therefore considered passed. The test selection and the protocol design was performed in accordance with ISO 10993:1 standard. In particular, components are tested either from final assembled devices (e.g. test article 14-0502-025) or after the molding process.

A summary on tests performed and their results are presented in Table 28-1 as provided by BD. The applicable test protocols and reports are considered confidential by BD, and thus not shared with Sandoz. BD sent the documents to the FDA. The submitted information was adequate; the test results were negative.

Device materials

2.2 Identity of components and materials of construction

Primary packaging components are constructed of the materials defined in Table 2-1.

Table 2-1 GP2015 25 mg/0.5 mL and 50 mg/1.0 mL solution for injection in PFS: Identity of materials of construction

Component	Description	Identity of material	Supplier	DMF number ³⁾	Compliance status	
(b) (4)* Syringe with staked needle (sold as sterile and non-ovrogenic)						
Syringe barrel	1 mL long, colorless	(b) (4)	(b) (4)	DMF- (b) (4)	Complies with Ph. Eur. and USP requirements for type I glass	
Staked hypodermic needle	27 G x 1/2"		(b) (4)	DMF- (b) (4)	(b) (4) Stainless steel	
(b) (4) Plunger stopper						
Plunger stopper	Grey rubber stopper Rubber formulation Piston (plunger)		(b) (4)	(b) (4)	DMF- (b) (4) Volume 23 Volume 9 Volume 10	Complies with Ph. Eur. and USP requirements
Rigid needle shield						
Rigid shell	Plastic shell	(b) (4)	(b) (4)	DMF- (b) (4)	Not applicable as not product contacting	
Rubber needle shield	Grey rubber needle shield		(b) (4)	DMF- (b) (4) ²⁾	Complies with Ph. Eur. and USP requirements	
	Rubber formulation		(b) (4)	DMF- (b) (4) Record 030		

¹⁾ The rubber formulation for the plunger stopper is provided to (b) (4)
²⁾ The rubber formulation for the rubber needle shield is provided to (b) (4)
³⁾ Letters of authorization (LoA) to the DMF are provided in [Module 1.4.1]

Table 28-1 Summary on biocompatibility testing performed

(b) (4)			
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Autoinjector (AI)

The autoinjector has direct contact with intact skin. The required testing includes cytotoxicity, sensitization, and irritation. The testing was performed according to ISO 10993. The test protocols and test reports are in MAF (b) (4). The submitted information was adequate.

Endpoint	Test Method	Extraction and Test Method	Test Result
(b) (4)			

		Acceptability	
Cytotoxicity	MEM Elution	Acceptable	Grade 0; Pass
Sensitization	ISO Guinea Pig Maximization Sensitization Test	Acceptable	Grades NS-0; SO-0; Pass
Irritation	ISO Primary Irritation Test	Acceptable	Grades NS-0; SO-0; Pass

Reviewer Comment

The patient contacting components of the needle safety device and autoinjector were demonstrated to be biocompatible according to the level of patient contact, surface contact with intact skin.

X. Clinical Acceptability

The pre-filled syringe (i.e. container closure system) used in the mentioned three PK studies, GP15-101, GP15-102 and GP15-104, as well as the one intended for commercial use is identical. Detailed information on the pre-filled syringe (PFS) is provided in [Module 3.2.P.7] and the respective Letters of Access (LoAs) are provided in [Module 1.4.1].

A comparison of the pre-filled syringes used in the four PK studies is provided in Table 18-1. The pre-filled syringe used in the GP15-103 study was assembled with a (b) (4). Whereas, the pre-filled syringe used in the GP15-104 study had, in addition to the (b) (4). This configuration was selected to allow blinding between GP2015 and Enbrel/EU. In the GP15-101 and GP15-102 studies, drug product was transferred from the pre-filled syringe to an application syringe in the pharmacy of the single study site outlined in Table 18-1.

Bioequivalence was demonstrated when PK concentrations of GP2015 50 mg were compared between the administration using an autoinjector ((b) (4) GP2015_50) and the administration using a PFS. In a randomized, open label, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 following a single subcutaneous injection by an autoinjector and by a pre-filled syringe in healthy male subjects.

During the clinical development program of GP2015, a phase 1 PK study had the secondary objective to evaluate and compare the overall safety, tolerability, and local tolerance of GP2015 administered by (b) (4) GP2015_50 and GP2015_PFS_25_50 in (b) (4) as a single s.c. injection of 50 mg. The following information was provided by the Sponsor:

In conclusion study GP15-103 showed that a single dose of GP2015 50 mg administered by an autoinjector ((b) (4) GP2015_50) and by a PFS in this study was safe and well tolerated by healthy male subjects with no unexpected adverse events (AEs). Overall, the type and incidence of treatment-emergent adverse events (TEAEs) was similar for the autoinjector (b) (4) GP2015_50 and PFS. There were no notable trends or clinically relevant changes observed in the clinical laboratory parameters, vital signs, ECGs or local tolerance at injection site. All subjects had negative anti -drug antibodies (ADA) results on Day 1 of both treatment periods and at follow-up. Thus, none of the subjects developed ADAs upon treatment with GP2015 [27] (see chapter 12).

A clinical evaluation of the Auto-Injector was completed by the Sponsor with a description of the following general essential requirements:

- Ease of use
- Durability
- Ergonomic design and usability
- Dose accuracy
- Microbial contamination
- Choice of material
- Packaging
- Risk assessment and control
- Labeling and instructions for use

Table 18-1 Comparison of PFS Presentations

	GP15-101 & GP15-102	GP15-103 ⁽¹⁾	GP15-104	GP2015 PFS with NSD ⁽²⁾ (as intended for commercial use)
Pre-filled Syringe (see [Module 3.2.P.7] Container closure system)	1mL BD (b)(4) ⁽³⁾ syringe with 27G x 1/2"staked hypodermic needle with rigid needle shield (b)(4) plunger stopper			
Constituent components	BD (b)(4) ⁽³⁾ - Plunger rod 1mL (b)(4)	BD (b)(4) ⁽³⁾ - Plunger rod 1mL	BD (b)(4) ^(3,4) - Plunger rod 1mL (b)(4)	BD UltraSafe ⁽³⁾ Passive™ (b)(4) - Needle guard 1mL - Plunger rod 1mL - Add-on Finger Flange 1mL

¹ For sake of completeness all PK studies are presented in this table.

² The term "needle safety device" (NSD) is used to refer to the complete device "BD UltraSafe Passive™ (b)(4)" (i.e. needle guard, plunger rod and an add-on finger flange).

³ BD (b)(4) and BD UltraSafe Passive™ are trademarks owned by Becton Dickinson (BD).

⁴ Reflects constituent parts used by reference product Enbrel/EU

Reviewer Comment

The pre-filled syringe with NSD and the autoinjector were used in the clinical evaluations of the drug. The devices have been validated for the intended use.

XI. Digital Signatures

Digital Signature Concurrence Table	
Reviewer Sign-Off	Sarah B. Mollo -S Digitally signed by Sarah B. Mollo -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, cn=Sarah B. Mollo -S, 0.9.2342.19200300.100.1.1=2001712033 Date: 2016.04.19 15:18:29 -04'00'
Branch Chief Sign-Off	Alan M. Stevens -S Digitally signed by Alan M. Stevens -S DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People, 0.9.2342.19200300.100.1.1=130018921, cn=Alan M. Stevens -S Date: 2016.04.20 08:29:37 -04'00'

APPEARS THIS WAY ON ORIGINAL

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

/s/

LEILA P HANN

06/27/2016

Checked in on behalf of Sarah Mollo (CDRH)

Clinical Inspection Summary

Date	June 14, 2016
From	Roy Blay, Ph.D., Reviewer, GCPAB\OSI Janice K. Pohlman, M.D., M.P.H., Team Leader, GCPAB\OSI Kassa Ayalew, M.D., M.P.H., Branch Chief, GCPAB\OSI
To	Leila Hann , Regulatory Project Manager Rachel Glaser, M.D., Medical Officer Gary Chiang, M.D., Medical Officer Nikolay Nikolev, M.D., Medical Team Leader Division of Dermatology and Dental Products Division of Pulmonary, Allergy, and Rheumatology Products
NDA/BLA #	BLA #761042
Applicant	Sandoz, Inc.
Drug	Erelzi (etanercept, GP2015)
NME (Yes/No)	No (biosimilar)
Therapeutic Classification	Standard Review
Proposed Indication(s)	Treatment of plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, polyarticular juvenile idiopathic arthritis
Consultation Request Date	September 14, 2015
Summary Goal Date	June 15, 2016
Action Goal Date	August 30, 2016
BsUFA Date	August 30, 2016

1. OVERALL ASSESSMENT OF FINDINGS AND RECOMMENDATIONS

The clinical sites of Drs. Kingo, Weglowska and Pulka were inspected in support of this NDA. In addition, a sponsor inspection of Hexal, Inc., a subsidiary of Sandoz, Inc., was also conducted. Based on the results of the clinical investigator and sponsor inspections, OSI is unable to confirm the reliability of reported concomitant psoriasis treatment and adherence to the protocol-specified randomization stratification scheme. Otherwise, the study was conducted according to the protocol and other data generated by these sites appear acceptable in support of the respective indication.

The causes of the stratification scheme errors and inadequate reporting of previous psoriasis medications appear to be multifactorial: the lack of a specific eCRF section to indicate prior psoriasis therapy; the provision of unclear protocol instructions defining concomitant therapy (any past psoriasis therapy at any time was defined as concomitant treatment); the failure of the clinical study team members and CRO monitors to understand the protocol definitions of timelines to be used for the reporting of prior psoriasis therapy; and the delayed recognition of erroneous reporting of concomitant psoriasis therapy by the sponsor during preparation of a clinical site for inspection.

The stratification scheme errors and inadequate reporting of previous psoriasis medications was communicated to the review division. The review team statistician informed OSI reviewers that a primary efficacy endpoint analysis (using the initial sponsor-proposed analysis) that did not rely upon prior psoriasis treatment categorization, was used to demonstrate non-inferiority of the proposed etanercept biosimilar (GP2015) to a currently marketed product. Based upon communication with the review division, an analysis has confirmed that the proposed biosimilar is clinically non-inferior to a marketed formulation when prior treatment is not considered.

2. BACKGROUND

The Applicant submitted this BLA to support the use of a biosimilar etanercept (GP2015) for the treatment of plaque psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and polyarticular juvenile idiopathic arthritis.

Protocol GP 15-302 entitled “A randomized, double-blind, multicenter study to demonstrate equivalent efficacy and to compare safety and immunogenicity of a biosimilar etanercept (GP2015) and Enbrel® in patients with moderate to severe chronic plaque-type psoriasis” was inspected in support of this application.

The sites of Drs. Kingo, Weglowska, and Pulka were chosen for inspection as only foreign data were submitted in support of the application. These sites were among the larger enrolling along with the presence of site-specific protocol violations. As this application was among the first of the “biosimilar” applications, an inspection of the sponsor, Hexal, was also conducted.

Protocol GP15-302 was conducted at 71 study centers worldwide encompassing the treatment of 531 subjects with moderate to severe chronic plaque-type psoriasis. The first patient visit was June 24, 2013, and the last patient completed the study (12-week analysis) on Jun 24, 2014. Following screening, subjects were randomized 1:1 to either GP2015 or Enbrel® as stratified by weight and prior systemic therapy, and received subcutaneous injections twice weekly for the first 12 weeks. The Psoriasis Area Severity Index 75 (PASI 75) was the primary efficacy variable; i.e., that proportion of subjects demonstrating 75% improvement after 12 weeks of treatment. The primary objective of the study was to demonstrate equivalent efficacy of GP2015 and Enbrel® in patients with moderate to severe chronic plaque-type psoriasis with respect to PASI 75 response rate at Week 12. The sponsor concluded from its efficacy analyses that GP2015 and Enbrel® were therapeutically equivalent as based on the pre-specified confidence interval. In addition, the results of the subgroup analyses (i.e., body weight stratum [<90 kg and ≥ 90 kg] and previous systemic therapy [yes/no]) also showed no differences between treatment groups.

3. RESULTS (by site):

Site #/ Name of CI/ Address	Protocol #/ # of Subjects (enrolled)	Inspection Dates	Classification
3704/ Kulli Kingo, M.D., Ph.D. Tartu University Hospital Dermatology Department, Raja 31 Tartu, Estonia 50417	GP15-302/ 30/	15-19 Feb 2016	VAI
4813/ Jolanta Weglowska, M.D., Ph.D. Wojewodzki Szpital Specjilistyczny we Wroclawiu Oddzial Dermatologiczny Ul. Kamienskigo 73a 51-124 Wroclaw, Poland	GP15-302/ 26/	8-12 Feb 2016	NAI
4809/ Graznya Pulka, M.D., Ph.D. Specjalisiyczny Osrodek "All-Med" Ul. Sw. Marka 31/1 31-024 Krakow, Poland	GP15-302/ 35/	1-5 Feb 2016	NAI
Hexal (Sponsor) Mark McCamish, M.D., Ph.D. Hexal AG IndustrieStr. 25 Holzkirchen, Bavaria 83607	GP15-302/ N/A	15-19 Feb 2016	NAI

Compliance Classifications

NAI = No deviation from regulations.

VAI = Deviation(s) from regulations.

OAI = Significant deviations from regulations. Data unreliable.

Pending = Preliminary classification based on information in 483 or preliminary communication with the field; EIR has not been received from the field, and complete review of EIR is pending. Final classification occurs when the post-inspectional letter has been sent to the inspected entity.

1. Kulli Kingo, M.D., Ph.D.

At this site for Protocol GP15-302, 37 subjects were screened, 30 subjects were randomized, two subjects discontinued, and 28 subjects completed the study.

The study records of 12 subjects were reviewed in detail. Source data was compared to line listings. Records reviewed included, but were not limited to, site deviation, ethics committee correspondence, financial disclosure, electronic systems training, monitoring reports, and test article accountability and storage.

The study records of 12 subjects were reviewed in detail. Signed informed consent was obtained from these subjects prior to study entry. The primary efficacy endpoint was verified for all enrolled subjects. A Form FDA 483 was issued at the conclusion of the inspection with a single observation regarding failure to follow the investigational plan. The protocol in Section 5.5.7 under “Concomitant treatment” required that previous topical, systemic, and phototherapy treatments for psoriasis administered prior to screening be entered into the electronic Case Report Form (eCRF). This information was not entered into the eCRFs for any of the 30 subjects randomized to treatment at this site. According to Dr. Kingo, there were no specific eCRF worksheets available for entering prior psoriasis treatments. Stratification of subjects per protocol was to be based on subject weight (either more or less than 90 kg) and by prior systemic psoriasis treatment; i.e., “no prior systemic therapy”, “any prior systemic therapy including biologic immunomodulating agents but no prior treatment with a TNF antagonist”, and “prior treatment with a TNF antagonist”. Subsequently, prior psoriasis treatment was also to be used in analysis of efficacy.

Dr. Kingo, in her written response dated March 10, 2016, stated that she misunderstood protocol requirements and did not enter into the eCRF topical, systemic and phototherapy treatments for psoriasis administered prior to screening for 30 out of 30 subjects. This misunderstanding was not corrected by the clinical research associates (CRAs) during monitoring visit discussions. According to Dr. Kingo, subjects were stratified correctly as source data referring to prior psoriasis treatment were used to randomize subjects in IVRS.

Other than the failure to include subjects’ psoriasis therapy prior to screening for subjects in the concomitant medication section of the eCRF, study conduct was in reasonable compliance with good clinical practices and data generated by this site appear to be acceptable in support of the indication.

The final classification of the inspection of Dr. Kingo was Voluntary Action Indicated (VAI) for failure to adhere to protocol; specifically, the clinical investigator did not include prior psoriasis therapy on the eCRF since there was no designated section of the eCRF to do so. However, according to the investigator, subjects were stratified correctly according to the protocol-specified classification for prior psoriasis therapy using source documentation (office charts).

2. Jolanta Weglowska, M.D., Ph.D.

At this site for Protocol GP15-302, 36 subjects were screened, 26 subjects were randomized to treatment, and ten subjects were screen failures.

The records of 13 subjects were reviewed in detail. Records reviewed included, but were not limited to, ethics committee approvals, financial disclosure, sponsor and monitor correspondence, training, adverse events, and drug accountability and storage.

Review of all study subject records indicated that informed consent forms were completed prior to any study-related testing. The primary efficacy endpoints (PASI and IGA scores) were also verified for all study subjects. Subject 011 died of cardio-respiratory failure during the study. This serious adverse event was not suspected of being related to treatment with the study medication. Subject 005 had not received prior systemic psoriasis treatment but was stratified to the incorrect group (treatment with systemic medications). Although not specified in the protocol, the CI considered phototherapy to be systemic, while the sponsor did not. Other stratification issues were not noted for the other 12 subjects whose records were reviewed.

A Form FDA 483 was not issued at the conclusion of the inspection. Other than the incorrect stratification of Subject 005 which would not appear to have a significant effect on safety or efficacy considerations, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

3. Graznya Pulka, M.D., Ph.D.

At this site for Protocol GP15-302, 42 subjects were screened, 35 subjects were enrolled, three subjects were discontinued, and 32 subjects completed the study.

The study records of 18 subjects were reviewed in depth. Records reviewed included, but were not limited to, ethics committee approvals, financial disclosure, sponsor and monitor correspondence, training, adverse events, and drug accountability and storage.

Review of all study subject records indicated that informed consent forms were completed prior to any study-related testing. Based upon the ORA investigator's review of the protocol deviation listing submitted by the sponsor to the BLA and source documents, Subjects 003, 012, 020, 025, 026, 032, 037, and 042 were stratified incorrectly to the "no prior systemic medications" group when all had actually received prior systemic medications and should have been stratified to that group. Although a copy of the protocol deviation listing from the site was included with the inspection report, copies of the source documentation from the IWRS and subject's records and medication listings were not included with the inspection report and therefore could not be verified by OSI. Subject 032 was hospitalized for four days post-randomization for treatment of infection of the leg due to eczema. This hospitalization was considered a serious adverse event (SAE), and the subject was treated with the following protocol-prohibited medications: tacrolimus (for four days), hydrocortisone cream (for seven days), and phototherapy (for three days). The subject was not discontinued from the study nor was the treatment reported as a protocol deviation since the medical monitor stated that the treatment of an SAE with protocol prohibited medications was not to be considered a protocol deviation.

At Dr. Pulka's site, multiple stratification errors were reported by the sponsor to the BLA based upon prior systemic psoriasis treatment, although evidence to substantiate this was not submitted with the inspection report.

The final classification of the inspections of Dr. Pulka was No Action Indicated (NAI). Although no Form FDA 483 was issued, the inspection reports indicate that there were problems with stratification for randomization based upon prior therapy at the site. OSI did not upgrade the classification of inspection to VAI, since the evidence supporting the mis-stratification was not included with the inspection report.

The stratification and reporting of prior or concomitant systemic psoriasis treatments was discussed with the review team statistician. The statistician used the sponsor's initially proposed primary efficacy analysis that did not rely on prior treatment stratification to demonstrate non-inferiority of the biosimilar etanercept (GP2015). Other than the stratification issue that the review division is aware of and appears to have been factored into their review, the study appears to have been conducted adequately, and the data generated by this site appear acceptable in support of the respective indication.

4. Hexal AG

This sponsor was inspected with respect to the conduct of Protocol GP15-302 performed in support of BLA #761042 and focused on the following clinical investigators: Drs. Kingo, Pulka, and Weglowska.

The inspection reviewed the following which included, but was not limited to, study initiation approvals, investigational product labeling, investigational product disposition, study investigator and monitor selection, study investigator communications, study monitoring, adverse event evaluation and reporting, record keeping, and progress report and final study result submissions.

The final classification of the inspection of the sponsor, Hexal, was NAI. The inspection of the sponsor confirmed that erroneous reporting of prior psoriasis treatment for some subjects at select sites had been reported in the original BLA submission. The sponsor had notified FDA of this issue prior to the sponsor inspection by way of an information amendment submitted to the BLA on January 19, 2016. This issue was attributed to misinterpretation by some clinical study team members of inclusion of any prior psoriasis treatment irrespective of timing of such therapy relative to baseline. Based upon the information amendment submitted to the BLA, the sponsor conducted a database check to assess deletions of psoriasis treatments from the eCRF; for 67 of 82 subjects, prior therapy had been deleted erroneously and 12 of these 67 subjects required changes to their prior systemic therapy categorization. The sponsor's subsequent sensitivity analysis revealed no clinical or statistical differences on the primary endpoint when "prior systemic therapy" was excluded as a factor.

A Form FDA 483, Inspectional Observations, was not issued at the conclusion of the inspection; however there was discussion of the sponsor's lack of a data capture process to specifically document previous psoriasis treatment(s) of study subjects. The protocol specified the need for prior psoriasis treatment data to enable a stratified randomization and analysis of subject treatment outcome based on the presence and nature of prior treatment. The electronic data capture (EDC) system used in this study was intended to capture information regarding the use of concomitant medications. The protocol defined concomitant medications as any medication used up to six months prior to baseline. The protocol further defined all previous topical, systemic, and phototherapy medications for psoriasis as concomitant medications, irrespective of date of treatment. The sample electronic Case Report Form (eCRF) included in the BLA submission and intended to collect this information was entitled, "Ongoing and Concomitant Medications/Therapies".

The sponsor submitted a six-page information amendment to the BLA prior to the inspection. This amendment, dated January 14, 2016, and submitted to the BLA on January 19, 2016, stated that some members of the clinical team misunderstood the protocol's definition of concomitant medications to include all psoriasis treatments irrespective of date of treatment. As a result of this misunderstanding, some clinical sites were asked by the data management CRO to remove psoriasis treatments administered more than six months prior to baseline. Removal of this information resulted in the sponsor receiving incomplete or erroneous reports of psoriasis treatments for some subjects. This reporting deficiency appears to have been exacerbated by the sponsor's failure to provide an EDC form specifically designed to capture this data.

Subject stratification was to be based on documentation of prior psoriasis treatment; however, some sites misunderstood the protocol's definition of concomitant medication to include prior psoriasis treatment at any time. Because of this misunderstanding, subjects may have been stratified incorrectly with subsequent potential impact on the efficacy analyses.

To assess the impact of the inadequate reporting of prior psoriasis treatment, the sponsor conducted a sensitivity analysis on the primary endpoint which excluded the stratification factor "prior systemic therapy" from the statistical model. According to the sponsor, this sensitivity analysis revealed no clinical or statistical differences when excluding this factor. The review division may wish to consider the effect, if any, of the inadequate reporting of prior psoriasis treatments in its assessment(s) of study outcome; otherwise, the studies appear to have been conducted adequately, and the data submitted by the sponsor may be used in support of the respective indication.

{See appended electronic signature page}

Roy Blay, Ph.D.
Good Clinical Practice Assessment Branch
Division of Clinical Compliance Evaluation
Office of Scientific Investigations

CONCURRENCE:

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Kassa Ayalew, M.D., M.P.H
Branch Chief
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Central Doc. Rm.\BLA 761042
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DPARP\Division Director\Badrul Chowdhury
DDDP\Team Leader\David Kettl
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DDDP\Medical Officer\Gary Chiang
DPARP\Medical Officer\Rachel Glaser
DPARP\Project Manager\Leila Hann
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OSI\ DCCE\GCPAB\Team Leader\Janice Pohlman
OSI\ DCCE\GCPAB\Reviewer\Roy Blay
OSI\ DCCE\Program Analysts\Joseph Peacock\Yolanda Patague
OSI\Database Project Manager\Dana Walters

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/s/

ROY A BLAY
06/14/2016

KASSA AYALEW
06/14/2016

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

DATE: January 30, 2015

TO: Curtis Rosebraugh, M.D., M.P.H.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II (ODEII)
Office of New Drugs

FROM: Xingfang Li, MD, RAC
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

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

SUBJECT: Inspections at

PAREXEL Early Phase Clinical Unit
Harrow, UK

Covance Clinical Research Unit (CRU) Ltd.
Leeds, UK

covering the following application:

BLA 761042 (GP2015, a biosimilar to US Enbrel
(etanercept) sponsored by Sandoz Inc., USA)

Reviewer Recommendations:

The OSIS clinical EIR reviewer defers to the OSIS bioanalytical EIR reviewers, and PK and immunogenicity reviewers, to evaluate the impact of protocol deviations related to clotting and centrifuging blood samples at 2-8°C, instead of room temperature for studies **GP15-101 and GP-102**.

This reviewer recommends that results from study **GP15-104** supporting **BLA 761042** should not be accepted for further Agency

review, because PAREXEL did not retain original blinding codes for the products assessed in the studies.

The inspections were conducted by ORA Investigators at these sites:

1. **Covance Clinical Research Unit (CRU) Ltd. Leeds LS2 9LH, UK was inspected** for studies **GP15-101 and GP15-102** by Richard Berning from 1/18/2016 to 1/22/2016.
2. **PAREXEL Early Phase Clinical Unit, Harrow HA1 3UJ UK was inspected for study (GP15-104)** by Joyce Wong from 12/01/2015 to 12/07/2015.

The following studies were audited during the inspections:

Study#: GP15-101
Study Title: "A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel® (EU-licensed) following a single subcutaneous injection in healthy subjects"
Study Period: 11/21/2011 - 4/20/2012
Study Site: Covance Clinical Research Unit (CRU) Ltd.
Leeds, UK

Study#: GP15-102
Study Title: "A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel® (US-licensed following a single subcutaneous injection in healthy subjects"
Study Period: 02/28/2011 - 08/23/2012
Study Site: Covance Clinical Research Unit (CRU) Ltd.
Leeds, UK

Study#: GP15-104
Study Title: "A randomized, double blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel (EU-licensed) following a single dose of 50 mg subcutaneous injection in healthy male subjects"
Study period: 06/30/2014-11/19/2014
Clinical Site: PAREXEL Early Phase Clinical Unit
Harrow, UK

Inspection of the **bioanalytical portions** of these studies was conducted at **HEXAL AG, Oberhaching, Germany** from **January 18, 2016**

to **January 22, 2016**, by OSIS Pharmacologists **Hasan A. Irier, Ph.D.** and **Kara Scheibner, Ph.D.** The EIR review for this bioanalytical inspection will be submitted as a separate memo.

Inspection at **PAREXEL Early Phase Clinical Unit:**

The audit at PAREXEL included a thorough review all elements of the bioequivalence compliance program including but not limited to review of records for 54 enrolled subjects and 100% review of informed consent forms. IRB approval was obtained prior to subjects being enrolled into the study. The principal investigator (PI) and sub-investigators recorded that informed consent was obtained prior to beginning study-related procedures on source documentation. On 12/10/2015, during the inspection, the sponsor sent a copy of the blinding codes to the firm, because PAREXEL had not retained the original blinding codes on-site. Therefore, Ms. Wong could not properly un-blind the treatment codes to verify that study subjects received the intended products. Ms. Wong performed drug accountability by reference to the substituted codes and observed no problems. Subject dosing logs appeared to be accurate, except for the absence of original blinding codes. The regulatory binders, subject CRFs, record binders, and source documents were maintained, organized, in good condition, complete and legible. There were no discrepancies noted.

At the conclusion of inspection on 12/11/2015, Form FDA 483, Inspectional Observations, was not issued. Mr. (b) (4)

[REDACTED] attended the inspection close-out meeting by telephone. A discussion was held regarding the fact that PAREXEL did not retain original blinding codes due to instructions from the sponsor stating that the sealed envelope should be returned to the sponsor upon study completion.

Discussion item: Failure to retain original blinding codes.

Parexel's management stated at the close-out meeting (12/11/2015) that they would reply to this discussion item in writing within 15 business days. OSIS has not received this response.

Maintenance of blinding codes in biosimilar studies is not required by regulation. However, failure to retain the original codes prevented verification of study events. We cannot assure that subjects received the correct study drug as randomized. This is a concern because OSIS (previously DSI and OSI) documented

accidental and deliberate alterations of blinding codes in unrelated bioequivalence studies at unrelated CROs for NDAs and ANDAs.

In this reviewer's opinion, the original blinding code is critical to verifying data integrity. Its absence at the PAREXEL site is uncorrectable, because correct dosing could not be verified at the inspection. The voluntary reserve samples (also not required by current regulation) do not establish identity of dosed products, because they too were blinded. We recommend that the clinical data for study **GP15-104** not be accepted for further agency review.

Inspection at **Covance Clinical Research Unit (CRU)**:

Please note that as of this writing, OSIS has not received the EIR for the inspection at Covance Clinical Research Unit (CRU), Ltd. U.K. ORA investigator Richard Berning conducted this inspection from 1/18/2016 to 1/22/2016 for studies (**GP15-101 and GP15-102**). This review is based on email correspondence received from Mr. Berning. Once the EIR with exhibits is received and evaluated, we will update DPARP if our recommendation changes.

Mr. Berning did not issue Form FDA 483 and only discussed the following protocol violation. Instead of clotting and centrifuging blood samples for PK and immunogenicity evaluations at room temperature, the firm clotted and centrifuged blood samples at refrigerated temperatures. The protocol-specified temperature is not subject to a regulation or guidance. The protocol violation is discussed on p. 50 of the pharmacokinetic method validation report BA12008-R from Hexal AG, the firm that conducted bioanalytical assessment of study samples.

In this reviewer's opinion, the potential problem with clotting and centrifuging sample at 2-8°C versus room temperature is incomplete clotting, with later formation of fibrin in the serum samples. Presence of fibrin strands could have caused incomplete recovery of entrapped analytes, and variable positive or negative interferences from light scattering. Note: Some "gel separation" and "Serum Separation Tubes" from vendors contain clot activators like ground glass, and they may have accelerated clotting. We defer to the OSIS bioanalytical EIR reviewers, PK and immunogenicity reviewers to evaluate the impact of this protocol deviation. In addition, inaccuracies may have arisen from precipitation or co-precipitation of etanercept, its anti-drug antibodies, or their complexes, with rheumatoid factor, specific

or nonspecific IgM, complement, or cryoglobulins, or from activation of cold agglutinins (and release of hemoglobin-peroxidase). These other species are much less likely to occur in blood of normal young and healthy subjects than in blood of patients with certain pathologic conditions like rheumatoid arthritis. The potential inaccuracies, and further effects on Minimum Required Dilution before assay, are hypothetical and cannot be evaluated with available information. In particular, the experiments on temperature dependence of recovery of etanercept added to blood are not useful in evaluating these possibilities.

Conclusions:

Studies GP15-101 and GP15-102 (Covance Clinical Research Unit (CRU) Ltd. Leeds, UK): This EIR reviewer defers to the OSIS bioanalytical EIR reviewers, and PK and immunogenicity reviewers, to evaluate the impact of clotting and centrifuging blood samples at refrigerated temperatures instead of room temperature.

Study GP15-104 (PAREXEL Early Phase Clinical Unit, Harrow, UK): This EIR recommends that the failure to retain the original blinding codes at PAREXEL prevents assuring that subjects received the intended products during the study. It is not possible to verify correct dosing. **Study GP15-104 should not be accepted for further Agency review.**

Final Classifications:

PAREXEL Early Phase Clinical Unit. Harrow, UK: **VAI**
(FEI: 3009032622)

Covance Clinical Research Unit (CRU) Ltd. Leeds, UK: **NAI**
(FEI: 3000244766)

Email cc:

OSIS/Kassim/Taylor/Fenty-Stewart/Nkah/Miller
OSIS/DNDBE/Bonapace/Dasgupta/Cho
OSIS/DGDBE/Haidar/Skelly/Choi/Li
CDER/OND/ODEII/DPARP/Rosebraugh
ORA/Joyce Wong
ORA/Richard Berning

Draft: XFL 01/30/2016

Page 6 - Inspection of PAREXEL Early Phase Clinical Unit,
Harrow,UK) and Covance Clinical Research Unit (CRU)
Ltd. Leeds, UK

Edits: MFS 2/1/2016; SK 2/3/2016; IH 2/3/2016

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ Covance Clinical Research Unit (CRU) Ltd. Leeds, UK

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ PAREXEL Early Phase Clinical Unit., Harrow, UK

OSIS file #: **BE 6966**

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Date: 2016.02.09 08:03:52 -05'00'

Skelly signing on behalf of Dr. Haidar

Michael F. Skelly, Ph.D.
Team Leader
Division of Generic Drug Bioequivalence Evaluation
Office of Study Integrity and Surveillance (OSIS)

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/s/

XINGFANG LI
02/09/2016

SAM H HAIDAR
02/12/2016

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 5, 2016

TO: Curtis Rosebraugh, M.D., M.P.H.
Director
Division of Pulmonary, Allergy, and Rheumatology
Products
Office of Drug Evaluation II (ODEII)
Office of New Drugs

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

and

Hasan A. Irier, Ph.D.
Pharmacologist
Division of Generic Drug Bioequivalence Evaluation
(DGDBE)
Office of Study Integrity and Surveillance

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

SUBJECT: Inspection of Hexal AG (Hexal), Oberhaching, Germany
covering: BLA 761042 (GP2015, a biosimilar to US
Enbrel [etanercept]), sponsored by Sandoz Inc.

Summary:

At the request of the Division of Pulmonary, Allergy, and Rheumatology Products, the Office of Study Integrity and Surveillance (OSIS) conducted an inspection of analytical portions of the following clinical studies conducted by Hexal, Oberhaching, Germany. Please note that during this inspection, studies from another submitted application, BLA (b)(4), were also reviewed; these findings will be discussed in a separate EIR review. Also, please note that we have not received an

official response to the Form FDA-483 from Hexal. We will update this review if necessary upon receipt of the firm's response.

Based upon the results of the inspection, we recommend that the PK and immunogenicity reviewers consider the potential impact of clotting and centrifugation of study samples at 2-8°C instead of room temperature as specified in the protocol in studies GP15-101 and GP15-102. We recommend that data for study GP15-104 be accepted for further review, but note that the reported titer for Subject 189/Day 29/672hr may not be accurate.

Study Number: GP15-101
Study Title: "A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel® (EU-licensed) following a single subcutaneous injection in healthy subjects"
Study Dates: November 21, 2011 through April 20, 2012

Study Number: GP15-102
Study Title: "A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel® (US-licensed) following a single subcutaneous injection in healthy subjects"
Study Dates: February 28, 2102 through August 23, 2012

Study Number: GP15-104
Study Title: "A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel (EU-licensed) following a single dose of 50 mg subcutaneous injection in healthy male subjects"
Study Dates: June 30, 2014 through November 19, 2014

Inspection of the analytical portion of the studies was conducted by OSIS/DGDBE Pharmacologists [REDACTED] (b)(6) [REDACTED] at Hexal in Oberhaching, Germany from January 18 through January 22, 2016.

The audit included a thorough examination of facilities and equipment, review of SOPs and training records, review of method validation and study records including correspondence, and interviews and discussions with Hexal's management and staff.

Following inspection of the studies, Form FDA-483 was issued (**Attachment 1**). Additional minor observations were discussed

throughout the week, and during the inspection close-out meeting. The Form FDA-483 observations related specifically to this application, discussion items, and an evaluation of observations and discussions with Hexal's management follow.

OBSERVATION 1

1. Exclusion of data values without established criteria or formal justification in validations BA-12008-R, and studies BA-12018, and BA14021. Specifically:

- a. In method validation BA-12008-R, 1 of 2 duplicate values was excluded from calibration standards (Run 120404-3_mask), long term stability validation samples (Runs 120829-1, 120222-6_(b)(4) and 120327-5), short term stability validation samples (Runs, 120302-2_mask, 120302-3, and 120308-2_(b)(4)), selectivity validation samples (Runs 120403-7, 120403-8, 120404-1, 120404-2_(b)(4), and 120404-4), intra-assay precision and accuracy validation samples (Run 120214-1_(b)(4) and 120216-1_(b)(4)), and endogenous TNF interference (Runs 120216-2_(b)(4) and 120217-4_(b)(4)). There are no formal criteria for exclusion of data points, and reasons for data exclusion were not reported.
- b. In method validation BA-12008-R, select data values were excluded from statistical calculation in Runs 120214-2_(b)(4) (Intra-assay precision and accuracy for GP2015), 120223-3_(b)(4) (Inter-assay precision and accuracy Set 3), 120228-3 (Inter-run precision and accuracy Set 4), 120404-3_(b)(4) (Selectivity) and 120229-2 (freeze/thaw stability of Enbrel EU). The reported justification was a suspected technical error, but there was no accompanying documentation for a processing error in the run preparation sheets or on raw data print outs.
- c. In study BA12018-R, 1 of 2 duplicate values was excluded from calibration standards in Runs 120522-2_mask, 120523-4, and 120613-1-R4_mask without justification.
- d. In study BA-14021-R (GP15-104), valid assay results from Run 20 for Subject 189, Day 29-672 hr (results for titer dilutions 1:1 through 1:8) were deactivated. These samples were repeated, with significantly different results. Assay values from the sample repeats were reported as final with no justification for selecting repeat values over original values.

Evaluation of Observations:

1a. Although these single value exclusions were reported in the original BA-12008-R (PK) method validation and in the sponsor-submitted validation report, there were no established criteria to justify exclusion of one of two duplicate values. We requested that the firm produce new data tables to include all formerly excluded values. Recalculation of precision and accuracy without exclusion of any method validation values resulted in QCs and calibration standards failing acceptance criteria (**Attachment 2**). Hexal acknowledged that exclusion of single assay results without formal criteria was an oversight during method validation for this study. They indicated that for each affected run, at least 75% of calibration standards met their established acceptance criteria, which would have allowed exclusion of both duplicated calibrator values, without resulting in a failed run. Hexal has discontinued the practice of single value exclusion (without formal justification) from standards and QCs in both method validations and study sample analysis, and have updated their SOPs accordingly (**Attachment 3**).

1b. The sponsor-submitted method validation report states that select data points (both duplicate values) were excluded from statistical calculations of assay results. We identified such exclusions from specific runs (listed above in observation **1b**) by reviewing SpectraMax Pro original source data for each method validation run. The source data print-outs had no clear explanation for data exclusion other than a notation that the data would be excluded (**Attachment 4**). During the study audit, Hexal acknowledged this observation and indicated that their current practice is to record justification that exclusions are appropriate (e.g. observed pipetting or technical error). However, during the inspection, Hexal could not provide justification for exclusion of values noted in observation 1b. We have not received a formal response to FDA-483 observations from Hexal; if justification is provided in their response, we will update this review.

1c. Hexal excluded or masked one of two duplicate values of select calibration standards in three BA12018-R (GP15-101) PK study runs without justification. We reviewed source data from the study runs to identify and verify these exclusions (**Attachment 5**). No explanation or justification for exclusion of these data points was recorded in the source documentation. Hexal acknowledged that select data exclusion should not have been done without justification and established criteria. They stated that criteria for data exclusion would be established and

formal justification for excluded values would be recorded in future studies. Because at least 75% of calibration standards for these runs met acceptance criteria, exclusion of these data points from calibration curves did not impact the acceptance of quality control and study sample results.

1d. An initial antibody titer assessment for sample 00189/Day 29/672hr was performed in Run 20 with dilutions of 1:1, 1:2, 1:4 and 1:8. ElectroChemiLuminescence (ECL) values of duplicates were 124 and 122, 114 and 110, 91 and 98, and 90 and 86 respectively. Thus, none of the dilutions resulted in a value below the cut point (86 ECL units), suggesting that further dilutions (1:16 or more) were appropriate to determine the titer. Run 20 was accepted based on established plate acceptance criteria, and all study samples were valid (%CV between duplicates was <20%).

However, the original titer results were "deactivated" (**Attachment 6**), and 1:1, 1:2, 1:4, and 1:8 sample dilutions were reassayed at these and new dilutions 1:16, 1:32, 1:64, 1:128, and 1:256 in Run 22 (**Attachment 7**). The repeat analyses resulted in only the 1:1 sample dilution having an ECL value above the cut point (96/100), in contrast to the original positive results. The results of the second (repeat) analysis were reported as the final titer results.

This observation encompasses several issues: 1) why the original **valid** titer samples were repeated, despite their meeting all acceptance criteria; 2) why the **repeat titer results** were reported over the original results, despite a significant difference between the two runs; 3) there were **no established criteria** to justify selection of the repeat results to report as final; and 4) discrepancy of results between the two assay runs suggests the assay is **non-reproducible** at ECL values around the screening cut point or at the Minimum Required Dilution (MRD).

This observation can partly be attributed to the study using a LIMS system, and that some sample results were deactivated because a valid titer result was not determined. Thus, as these samples were deactivated, they were marked for repeat analysis, and in respect to the LIMS system, were not valid results despite meeting all acceptance criteria. Also contributing to this observation is the fact that Hexal had no established criteria to decide how results like these should be reported.

During the inspection, Hexal acknowledged that this was partly a function of using the LIMS system for a semi-quantitative assay,

and that they would reassess how to manage and report assay results like these.

In regards to **Study GP15-104**, we recommend that DPARP evaluate whether the reported titer for Sample 00189/Day 29/672hr is accurate. In addition, the discrepancy between titer results suggests non-reproducibility of the assay, specifically at low concentrations and near the MRD.

OBSERVATION 2

2. Failure to report all method validation data for BA-12008-R and BA-12013-R. Specifically:

- a. In method validation BA-12008-R, values for calibration standards were reported for only 7 out of 54 total runs performed during the validation; values were reported only for runs 120214-1_ (b) (4), 120214-2_ (b) (4), 120216-1_ (b) (4), 120221-4_ (b) (4), 120222-1_ (b) (4), 120223-3_ (b) (4), and 120301-2.
- b. In method validation BA-12013-R, assay values for three sets of serial antibody dilutions used to determine assay sensitivity were not reported; only the calculated sensitivity concentrations for each dilution set, and the final determined sensitivity concentration were reported.
- c. In study report BA-14021-R, an additional low positive control (LPC - 102 ng/mL) was included as part of the plate acceptance criteria to assess assay performance close to the cut point; however, data from qualification of the new positive control were not reported either in the study report, or as an addendum to the original method validation (BA-12013-R).

Evaluation of Observations:

2a. In method validation BA-12008-R, we noted that values for calibration standards were included in the sponsor-submitted report for only 7 of 54 total validation runs. We requested a table including all calibration standard values for all method validation runs (**Attachment 8**), and verified that the runs listed in the final report were selected from the full list of calibration standard values generated during method validation. We reviewed the calibration standards for all 54 runs, and verified that all non-reported runs met standard curve acceptance criteria to be valid. We also identified the masked and/or excluded values listed under observation 1a and 1b. Hexal acknowledged this observation and informed us that corrective actions will be taken to ensure that any current or future

reports would include a table with calibration standard values for all valid runs.

Hexal has not provided an explanation for why these specific 7 runs were chosen for reporting. We find that this observation has no impact on data integrity as we verified that calibration standards in all runs met acceptance criteria.

2b. We observed that some individual data points were not reported for the serial 1:3 dilutions used in determination of assay sensitivity in the final method validation report or in a subsequent amendment. We collected source data from the three assay runs used to determine sensitivity (**Attachment 9**). The data we collected were comparable to the graphical data presented in Appendix 03 of the method validation. Thus, we find that this observation has no impact on data integrity of sensitivity measurements.

2c. Raw data from three runs used to qualify the new low positive control (LPC - 102 ng/mL) were located within method development data, and provided by the firm during the inspection (**Attachment 10**). The new LPC consistently had ECL values greater than the cut point (Mean ECL value = 124.7, %CV = 7.14), and was more relevant to the cut point ECL value (86 ECL units) and to study sample values compared to QC3 (600 ng/mL).

We discussed the importance of including these data in the study report, or as an addendum to the method validation, in order to establish that 1) the new LPC was accurate and precise in the assay, and 2) it met acceptance criteria. Hexal included two sets of the LPC per plate in study sample analysis for GP15-104. The only acceptance criterion for the LPC was that the ECL value be greater than the selected cut point. Hexal acknowledged that the data should have been reported, and stated that such data will be reported in the future.

In regard to **Study GP15-104**, we find that this observation has no impact on data integrity as we were able to verify that the new LPC was qualified, and that acceptance criteria were met.

Discussion Items:

Addressing impact of protocol violation (clotting and centrifuging sample at 2-8°C versus room temperature) on PK assessment: During inspection of the clinical facility (Covance, Harrogate, UK) for studies GP15-101 and GP15-102, ORA investigator Richard Berning noted a protocol violation during study sample acquisition; it was discussed during the inspection

closing meeting and also mentioned in Dr. Li's EIR Review memo. The protocol called for clotting and centrifugation of blood samples for PK and immunogenicity evaluations to be done at room temperature. However, Covance clotted and centrifuged blood samples at refrigerated temperatures (2-8°C). In the pharmacokinetic method validation report (BA12008-R; pages 50-53; **Attachment 11**), this protocol violation was discussed. Data from experiments at Hexal to evaluate the impact of the temperature deviation on measurement of etanercept were reported. We examined the source data of these experiments, and we verified the data reported to FDA. Run acceptance criteria were met; the concentration ratio of etanercept-spiked control samples clotted and centrifuged at room temperature to control samples clotted and centrifuged at 2-8°C had to be between 0.75 and 1.25, and this criterion had to be fulfilled for at least 80% of the tested samples. Percentage accuracy (not an established acceptance criterion) for spiked etanercept concentration versus detected etanercept concentration failed in almost all etanercept-spiked samples. Hexal explained that whole blood was spiked with etanercept at the clinical site, and thus handling errors could have caused the aberrant values.

We cannot cite regulations, guidance, or technical literature to question or exclude effects of possibly incomplete clotting, precipitation or co-precipitation of etanercept, anti-drug or nonspecific antibodies, rheumatoid factor, or cryoglobulins, or hemolysis of erythrocytes by activated cold agglutinins. Most of these interferences are unlikely in the study samples from normal healthy subjects.

While Hexal assessed the effects of clotting and centrifugation temperature on the ability to quantify etanercept in the PK assay, to our knowledge, comparable experiments were not done to determine the effects on detecting anti-drug or neutralizing antibodies. Thus, while it appears that clotting and centrifugation of samples at 2-8°C did not affect quantitation of etanercept concentrations, we cannot conclude the same regarding anti-drug and neutralizing antibodies. We note that the guideline in USP article 1106.1, "Immunogenicity Assays -- Design and Validation of Assays to Detect Anti-Drug Neutralizing Antibody," not in effect at the time of these studies, recommended that sera from incompletely clotted blood should be evaluated for interference in the assays.

Moreover, Hexal did not evaluate the effects of lipemia or hemolysis on quantification of etanercept, or detection of anti-etanercept antibodies. Hexal did not record whether received

study samples were hemolytic or lipemic, but instead relied on the clinical sites (Covance and Parexel) to document these (**Attachment 12**). Hexal has updated their SOP to ensure sample status and integrity are assessed properly, that any such observations are reported.

Thus, PK data and source documentation available during the inspection do not allow us to conclude whether the protocol violation had an impact on the overall outcome of the study. We recommend that the PK and immunogenicity reviewers assess the information provided here and in the study reports.

Anti-drug antibody (ADA) assay reproducibility: The significant discrepancy in repeat titer results in **Study GP15-104** (discussed under Observation 1d) suggests that results at lower ADA concentrations and sample dilutions may not be consistently reproducible. Supporting evidence was also found in **Study GP15-101**; none of the four study samples that screened positive for ADAs (e.g. had a mean ECL value >86 cutpoint) was reproducible in the confirmatory assay. All four unspiked samples (thus mimicking the screening assay) had ECL values <86 cutpoint.

In **Study GP15-101**, the low QC (600 ng/mL) had a mean ECL value of 311, which is >3 times the cut point. Thus, there was little or no assurance that the assay was consistent in the region near the cut point. In study **GP15-104**, a new LPC (102 ng/mL) was added to study runs. The mean ECL value of the LPC over all study runs was 154.4; this value is substantially closer to the assay cut point, and had a low coefficient of variation (7.1%) suggesting that the assay is performing consistently within this range. Despite this, both studies had results suggestive of reproducibility issues within the low end of the assay range.

Of note, in-study cut points using pre-dose study samples were not determined/assessed in studies GP15-101, GP15-102, or GP15-104, and thus, the suitability of the screening cut point determined during method validation using commercially available individual human serum samples was not confirmed using samples from the study population. It is possible that some of the apparent irreproducibility in these studies would be resolved by study-specific cut points.

Cut Point Assessment:

1. ***Determination of Outliers*** - We confirmed that outliers were not assessed with statistical methodology (e.g. Boxplot method), but instead by visual inspection of data plotted on a histogram. This method excluded no outliers from the

statistical cut point calculations. Implementation of a Boxplot analysis indicated four high outliers (95, 95, 89, and 88). However, removal of these outliers does not significantly alter the screening cut point. Thus, there was no impact on cut point determination. Hexal acknowledged that visual determination of outliers was a historical practice, and that their current practice is to use statistical methodology to determine outliers.

2. **In-study cut point determination** - Hexal did not assess pre-dose study samples to determine in-study cut points.
3. **Confirmatory Cut point** - The confirmatory cut point was calculated at 99.9% (0.1% false positive rate). We discussed that the recommendation in FDA's immunogenicity guidance was 99%; Hexal acknowledged that they received previous feedback in regard to the confirmatory cut point. The confirmatory cut point determined for GP15-101, GP15-102, and GP15-104 was 18% (percent inhibition of assay signal). Calculation of a 1% false positive rate resulted in a confirmatory cut point of 13.1%. However, examination of all subject study sample results in the confirmatory assay suggested that no additional study samples would have confirmed positive with the 13.1% cut point. Thus, using the 0.1% false positive rate had no impact on the outcome of the reported study results.

Decrease in the ECL signal value of controls: The final study sample run (Run 130811) in **Study GP15-102** was completed approximately 6 weeks after the previous study run (Run 121036; July 27, 2012 vs. September 04, 2012). We observed a trend of decreasing control ECL values in Run 130811 compared to all previous study runs, in some cases 20-30% (Table 4-2). Plate acceptance of control samples was based upon back-calculated concentrations compared to the nominal control concentration, rather than a statistically determined range of ECL values. A decrease in ECL signal would not be recognized in the concentration results because values are calculated relative to the standard curve. Decreased control assay signals could be indicative of stability problems in controls or reagents; the positive control used in this study was delivered to Hexal on August 14, 2009 (see Table 3-3). At the time of the study, the positive control used in the assay was over 3 years old.

We discussed that the accepted long term stability of antibodies is at least 2 years when stored at $\leq -20^{\circ}\text{C}$ [European Bioanalytical Forum white paper and the USP guidelines]. However, we recommend that it is best to monitor long term performance of positive control antibodies using raw signal

values in order to recognize trends that would indicate instability. This is particularly important in longer term patient studies.

Conclusion: Based on the observations above, we make the following recommendations, pending receipt of Hexal's response to Form FDA-483:

Studies GP15-101 and GP15-102: We recommend that the PK and immunogenicity reviewers consider the potential impact of clotting and centrifugation of study samples at 2-8°C instead of room temperature as specified in the protocol. While available data suggest that this protocol deviation had no impact on quantification of etanercept concentrations, there is insufficient evidence to evaluate whether detection of anti-etanercept antibodies (binding or neutralizing) was affected.

Study GP15-104: We recommend accepting PK and immunogenicity study data for further review. However, we note that the reported ADA titer for subject 189/Day 29/672hr may be inaccurate.

Kara A. Scheibner, Ph.D.
DGDBE, OSIS

Hasan A. Irier, Ph.D.
DGDBE, OSIS

Final Classification:

**VAI - Hexal AG, Oberhaching, Germany
(FEI# 3011617743)**

DARRTS CC:

OTS/OSIS/Kassim/Taylor/Nkah/Fenty-Stewart

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

OTS/OSI/DNDBE/Bonapace/Dasgupta/Cho

Draft: KAS 02/02/16; HI 02/03/16

Edits: MFS 02/04/16; SHH 02/05/2016

OSI: File#: BE6966

ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good Laboratory Practice Compliance/INSPECTIONS/BE Program/Analytical Sites/Hexal AG, Oberhaching, Germany

FACTS: none

201 Page(s) has been Withheld in Full as b4 (CCI/TS) immediately following this page

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

/s/

HASAN A IRIER
02/08/2016

MICHAEL F SKELLY
02/08/2016
Skelly signing on behalf of Dr. Kara Schreibner (a primary author) and Dr. Sam Haidar.

MEMORANDUM

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

DATE: October 19, 2015

TO: Chief
Medical Products & Tobacco Trip Planning Branch
Division of Medical Products and Tobacco Inspections
Office of Medical Products and Tobacco Operations

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

SUBJECT: **FY 2016, CDER High Priority Pre-Approval Data
Validation Inspection**, Bioresearch Monitoring, Human
Drugs, CP 7348.001

RE: BLA 761042
DRUG: GP2015, a biosimilar to US Enbrel (etanercept)
[PHSA 351(k) route]
SPONSOR: Sandoz Inc.

This inspection memo provides pertinent information to conduct the inspections of the following clinical bioequivalence (BE) studies. Background materials are available in ECMS under the ORA folder. The inspections should be completed and endorsed EIRs submitted to CDER **prior to Feb. 1st, 2016.**

Do not reveal the studies to be inspected, drug names, or the study investigators to the sites prior to the start of the inspections. The sites will receive this information during the inspection opening meeting. The inspection will be conducted under Bioresearch Monitoring Compliance Program CP 7348.001, not under CP 7348.811 (Clinical Investigators).

At the completion of the inspection, please send a scanned copy of the completed sections A and B of this memo to the OSIS POC.

Study #: GP15-101
Study Title: "A randomized, double-blind, two-way cross-over study to determine the pharmacokinetics and safety of GP2015 and Enbrel[®] (EU-licensed) following a single subcutaneous injection in healthy subjects"

Study Period: 11/21/2011-4/20/2012
Investigator: Dr. Joseph Chiesa
Clinical Site: Covance Clinical Research Unit (CRU) Ltd.
Leeds LS2 9LH, UK
Tel: +44 113 2373500
Fax: +44 113 2445600

Study #: **GP15-102**
Study Title: "A randomized, double-blind, two-way cross-over
study to determine the pharmacokinetics and safety
of GP2015 and Enbrel® (US-licensed following a
single subcutaneous injection in healthy subjects"
Study Period: 02/28/2012- 08/23/2012
Investigator: Dr. Joseph Chiesa
Clinical Site: Covance Clinical Research Unit (CRU) Ltd.
Leeds LS2 9LH, UK
Tel: +44 113 2373500
Fax: +44 113 2445600

Study #: **GP15-104**
Study Title: "A randomized, double blind, two-way cross-over
study to determine the pharmacokinetics and safety
of GP2015 and Enbrel (EU-licensed) following a
single dose of 50 mg subcutaneous injection in
healthy male subjects"
Clinical Site: PAREXEL Early Phase Clinical Unit
Level 7, Northwick Park Hospital;
Watford Road
Harrow HA1 3UJ UK
Tel: +44 1895 614851
Fax: +44 20 8422 6070
Study period: 06/30/2014-11/19/2014
Investigator: Dr. Annelize Koch

Please collect a list of bioequivalence studies performed at each
site in the last 5 years that were intended for submission to
FDA. The list should include information on test and reference
reserve samples retained at the sites or at a third party for the
bioequivalence studies. Please refer to **Table 1** for an example.

SECTION A - RESERVE SAMPLES

The protocols for these three studies specify [in accordance with
21 CFR 312.57; 312.59; 312.60; 312.62(a)] that a portion of the
unused drug products should be retained by the clinical sites as
reserves.

Please examine the reserves, and either collect them and ship them to the Division of Pharmaceutical Analysis (DPA), or place them under FDA evidence seal and have the clinical site ship them to DPA, under appropriate conditions (wet ice, dry ice, etc.). **Please collect at least 10 dosage units each of the proposed biosimilar and reference product.**

Please follow the instructions below:

- Verify whether reserve samples were retained, as specified in the study protocols.
- If the reserve samples were stored at a third party site, please verify and collect a written assurance or affidavit to confirm that the third party is independent from the sponsor, manufacturer, and packager, and that the sponsor was notified in writing of the location. In the event the reserve samples were not retained or are not adequate in quantity, please notify the POC immediately.
- Please obtain a written assurance from the clinical investigator or the responsible person at the clinical site that the reserve samples are representative of those used in the specific PK study, and that they were stored under conditions specified in accompanying records. Document the signed and dated assurance either on the facility's letterhead, or Form FDA 463a, Affidavit.
- Samples of the test and reference products in their original containers should be shipped to the Division of Pharmaceutical Analysis, St. Louis, MO, for screening, at the following address:

John Kauffman, Ph.D.
Center for Drug Evaluation and Research
Division of Pharmaceutical Analysis (DPA)
Center for Drug Analysis (HFH-300)
645 S. Newstead Ave
St. Louis, MO 63110

SECTION B - BLINDING CODES

RANDOMIZATION AND BLINDING: Because these are **randomized and double-blinded studies**, it is necessary to break the blinds and use the blinding and treatment codes to verify compliance with the clinical protocols provided by the sponsor, and to confirm

that subjects were dosed according to the treatment randomization
schedules. During the inspections:

- Please collect a complete copy of the study randomization
schedule and blinding codes for the site and the dosing logs
from the firm. Unseal the blinding codes and note the date
and your initials on the envelope. Exhibit a photocopy of
the complete randomization schedule and blinding code in the
EIR. If the blinding code was previously unsealed, determine
the reasons why. If a sealed blinding code is not available,
please notify the OSIS POC immediately.
- Please unblind the treatment codes on the Case Report Forms,
and use the treatment codes to verify that 100% of the
subjects were dosed according to the study randomization
schedule. Please scratch off the label covers on the CRF, if
needed, to reveal the codes. Document the date and time that
you unblind the treatment codes, if applicable.

SECTION C - CLINICAL DATA AUDIT

Please remember to collect relevant exhibits for all findings,
including discussion items at closeout, as evidence of the
findings.

- Confirm that informed consent was obtained for all subjects
enrolled at the site.
- Audit the study records for all subjects enrolled in both
studies.
- Compare the study report submitted to FDA with the original
documents at the site.
- Check for under-reporting of adverse events (AEs).
- Check for evidence of inaccuracy in the electronic data
capture system.
- Check reports for the subjects audited.
 - o Number of subject records reviewed during the
inspection: _____
 - o Number of subjects screened at the site: _____
 - o Number of subjects enrolled at the site: _____
 - o Number of subjects completing the study: _____
- Verify from source documents that evaluations related to the
primary endpoint were accurately reported in the study report.

- Confirm that site personnel conducted clinical assessments in a consistent manner and in accordance with the study protocols.
- Confirm that site personnel followed SOPs during study conduct.
- Examine correspondence files for any applicant or monitor requested changes to study data or reports.
- Include a brief statement summarizing your findings including IRB approvals, study protocol and SOPs, protocol deviations, AEs, concomitant medications, adequacy of records, inclusion/exclusion criteria, drug accountability documents, and case report forms for dosing of subjects, etc.
- Other Comments:

Specific Instructions

Please pay extra attention to the inclusion-exclusion criteria and safety monitoring.

Inclusion-exclusion, safety monitoring, and PK modeling are likely to evaluate creatinine clearance. Please confirm whether the clinical chemistry lab used appropriate methodology to measure serum creatinine concentrations accurately, and to calculate creatinine clearance. Some laboratories fail to exclude interferences from serum proteins, or to adjust for their interference with the assay for creatinine.

Additional instructions to the ORA Investigator:

In addition to the compliance program elements, other study specific instructions may be provided by the OSIS POC prior to the inspection. Therefore, we request that the OSIS POC be contacted for further instructions before the inspection, and also regarding data anomalies or questions noted during review of study records. The ORA investigator should contact the OSIS POC for inspection-related questions or clarifications.

If you issue Form FDA 483, please forward a copy to the OSIS POC (see below). If it appears that the observations may warrant OAI classification, notify the OSIS POC as soon as possible.

**Remind the inspected site of the 15 business-day timeframe for
submission of a written response to the Form FDA 483. In
addition, please forward a copy of the written response as soon
as it is received to the OSIS POC.**

OSIS POC: Arindam Dasgupta, Ph.D.
Lead Pharmacologist
Office of Study Integrity and Surveillance
Tel: 1-301-796-3326
Fax: 1-301-847-8748
E-mail: arindam.dasgupta@fda.hhs.gov

**The endorsed EIR and Form 483 documents should be sent to the
following:**

If electronic: CDER-OSIS-BEQ@fda.hhs.gov
If paper: Ms. Dinah Miller
FDA/CDER/OTS/OSIS
W051 RM5333 HFD-45
10903 New Hampshire Ave.
Silver Spring, MD 20993-0002

Email cc:
ORAHQ/OMPTO/DMPTI
OSIS/Kassim/Taylor/Dejernett/Fenty-Stewart/Nkah/Miller
OSIS/DNDBE/Bonapace/Dasgupta/Cho
OSIS/DGDBE/Haidar/Skelly/Choi/Li

Draft: XFL 10/15/2015
Edit: MFS 10/15/2015; SHH 10/19/2015
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ Covance Clinical Research Unit (CRU) Ltd. Leeds
LS2 9LH, UK
ECMS: Cabinets/CDER_OC/OSI/Division of Bioequivalence & Good
Laboratory Practice Compliance/INSPECTIONS/BE Program/Clinical
Sites/ PAREXEL Early Phase Clinical Unit. HA1 3UJ UK

BE File#: 6966
FACTS: 11572185

Table 1

SL NO.	Study number	Drug Name	Fast/Fed	Sponsor	Submission	Study Conduct Dates	Reserve Samples	Quantity	Lot# for Test and Reference
1	XXXXX	Aspirin + Dipyridamole Capsules	Fast	XXXX	USFDA	Dec 24-Dec 31, 2014	At Site	300 for test, 200 for reference	XXXX and XXX
2	XXXXX	Montelukast	Fed	XXXXX	unknown	XXXXX	Third Party	two kits	XXXX and XXX
3	XXXXX	XXXXXXXX	Fast	XXXXXX	Pilot	XXXXX	Not retained	two bottle for test, two bottles for reference	XXXX and XXX

Xingfang Li, MD, RAC
 Consumer Safety Officer
 Division of Generic Drug Bioequivalence Evaluation (DGDBE)
 Office of Study Integrity and Surveillance (OSIS)

Xingfang Li -S

Digitally signed by Xingfang Li -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
 cn=Xingfang Li -S, 0.9.2342.19200300.100.1.1=2000576511
 Date: 2015.10.19 13:57:57 -04'00'

Sam H. Haidar -S

Digitally signed by Sam H. Haidar -S
 DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
 cn=Sam H. Haidar -S, 0.9.2342.19200300.100.1.1=1300123664
 Date: 2015.10.20 12:17:42 -04'00'

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

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

/s/

XINGFANG LI
01/19/2016

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# 761042	NDA Supplement #: S- BLA Supplement #: S-	Efficacy Supplement Category: <input type="checkbox"/> New Indication (SE1) <input type="checkbox"/> New Dosing Regimen (SE2) <input type="checkbox"/> New Route Of Administration (SE3) <input type="checkbox"/> Comparative Efficacy Claim (SE4) <input type="checkbox"/> New Patient Population (SE5) <input type="checkbox"/> Rx To OTC Switch (SE6) <input type="checkbox"/> Accelerated Approval Confirmatory Study (SE7) <input type="checkbox"/> Labeling Change With Clinical Data (SE8) <input type="checkbox"/> Manufacturing Change With Clinical Data (SE9) <input type="checkbox"/> Animal Rule Confirmatory Study (SE10)
Proprietary Name: (b) (4) Established/Proper Name: GP2015 Dosage Form: Strengths:		
Applicant: Sandoz Agent for Applicant (if applicable):		
Date of Application: July 29, 2015 Date of Receipt: July 29, 2015 Date clock started after UN:		
PDUFA/BsUFA Goal Date: May 29, 2016		Action Goal Date (if different): May 27, 2016
Filing Date: September 27, 2015		Date of Filing Meeting: September 02, 2015
Chemical Classification (original NDAs only) : <input type="checkbox"/> Type 1- New Molecular Entity (NME); NME and New Combination <input type="checkbox"/> Type 2- New Active Ingredient; New Active Ingredient and New Dosage Form; New Active Ingredient and New Combination <input type="checkbox"/> Type 3- New Dosage Form; New Dosage Form and New Combination <input type="checkbox"/> Type 4- New Combination <input type="checkbox"/> Type 5- New Formulation or New Manufacturer <input type="checkbox"/> Type 7- Drug Already Marketed without Approved NDA <input type="checkbox"/> Type 8- Partial Rx to OTC Switch		
Proposed indication(s)/Proposed change(s): psoriatic arthritis, plaque psoriasis, polyarticular juvenile idiopathic arthritis, ankylosing spondylitis, rheumatoid arthritis		
Type of Original NDA: AND (if applicable) Type of NDA Supplement:		<input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)
<i>If 505(b)(2): Draft the "505(b)(2) Assessment" review found at:</i> http://inside.fda.gov:9003/CDER/OfficeofNewDrugs/ImmediateOffice/UCM027499		

Type of BLA	<input type="checkbox"/> 351(a) <input checked="" type="checkbox"/> 351(k)
If 351(k), notify the OND Therapeutic Biologics and Biosimilars Team	
Review Classification:	<input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority
The application will be a priority review if:	
<ul style="list-style-type: none"> • A complete response to a pediatric Written Request (WR) was included (a partial response to a WR that is sufficient to change the labeling should also be a priority review – check with DPMH) • The product is a Qualified Infectious Disease Product (QIDP) • A Tropical Disease Priority Review Voucher was submitted • A Pediatric Rare Disease Priority Review Voucher was submitted 	
Resubmission after withdrawal? <input type="checkbox"/>	Resubmission after refuse to file? <input type="checkbox"/>
Part 3 Combination Product? <input checked="" type="checkbox"/>	<input type="checkbox"/> Convenience kit/Co-package <input type="checkbox"/> Pre-filled drug delivery device/system (syringe, patch, etc.) <input checked="" 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)
If yes, contact the Office of Combination Products (OCP) and copy them on all Inter-Center consults	

<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 (FDCA Section 505B) <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):

List referenced IND Number(s): 114187

Goal Dates/Product Names/Classification Properties	YES	NO	NA	Comment
PDUFA/BsUFA 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 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</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

<i>to the supporting IND(s) if not already entered into tracking system.</i>				
Is the review priority (S or P) and all appropriate classifications/properties entered into tracking system (e.g., chemical classification, combination product classification, orphan drug)? <i>Check the New Application and New Supplement Notification Checklists for a list of all classifications/properties at:</i> http://inside.fda.gov:9003/CDER/OfficeofBusinessProcessSupport/ucm163969.htm <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:</i> http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm <i>If yes, explain in comment column.</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If affected by AIP, has OC 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)/Form 3792 (Biosimilar User Fee Cover Sheet) included with authorized signature?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<u>User Fee Status</u> <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>	Payment for this application (<i>check daily email from UserFeeAR@fda.hhs.gov</i>): <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			
<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>	Payment of other user fees: <input checked="" type="checkbox"/> Not in arrears <input type="checkbox"/> In arrears			
<u>User Fee Bundling Policy</u> <i>Refer to the guidance for industry, Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees at:</i> http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM079320.pdf	Has the user fee bundling policy been appropriately applied? <i>If no, or you are not sure, consult the User Fee Staff.</i> <input checked="" type="checkbox"/> Yes <input type="checkbox"/> No			
505(b)(2) (NDAs/NDA Efficacy Supplements only)	YES	NO	NA	Comment
Is the application a 505(b)(2) NDA? (<i>Check the 356h form,</i>	<input type="checkbox"/>	<input type="checkbox"/>		

cover letter, and annotated labeling). If yes , answer the bulleted questions below:					
• Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA?		<input type="checkbox"/>	<input type="checkbox"/>		
• 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)].		<input type="checkbox"/>	<input type="checkbox"/>		
• 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)]?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>If you answered yes to any of the above bulleted 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 for advice.</i>					
• Is there unexpired exclusivity on another listed drug product containing the same active moiety (e.g., 5-year, 3-year, orphan, or pediatric exclusivity)?		<input type="checkbox"/>	<input type="checkbox"/>		
<i>Check the Electronic Orange Book at: http://www.accessdata.fda.gov/scripts/cder/ob/default.cfm</i>					
If yes , please list below:					
Application No.	Drug Name	Exclusivity Code	Exclusivity Expiration		
<i>If there is unexpired, 5-year exclusivity remaining on another listed drug product containing the same active moiety, 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>					
Exclusivity	YES	NO	NA	Comment	
Does another product (same active moiety) have orphan exclusivity for the same indication? <i>Check the Orphan Drug Designations and Approvals list at: http://www.accessdata.fda.gov/scripts/opdlisting/ood/index.cfm</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>			
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)]?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, consult the Director, Division of Regulatory Policy II, Office of Regulatory Policy</i>					
NDAs/NDA efficacy supplements only: Has the applicant requested 5-year or 3-year Waxman-Hatch exclusivity?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
If yes , # years requested:					
<i>Note: An applicant can receive exclusivity without requesting it;</i>					

<i>therefore, requesting exclusivity is not required.</i>				
NDAs only: Is the proposed product a single enantiomer of a racemic drug previously approved for a different therapeutic use?	<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 checked="" type="checkbox"/>	
BLAs only: Has the applicant requested 12-year exclusivity under section 351(k)(7) of the PHS Act? <i>If yes, notify Marlene Schultz-DePalo, CDER Purple Book Manager</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 type="checkbox"/>	<input checked="" type="checkbox"/>	

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

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

<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.				
BLAs only: Companion application received if a shared or divided manufacturing arrangement?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
If yes, BLA #				
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 (3397/3792), 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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If foreign applicant, a U.S. agent must sign the form [see 21 CFR 314.50(a)(5)].</i>				
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"/>	
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)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<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>				
Clinical Trials Database	YES	NO	NA	Comment
Is form FDA 3674 included with authorized signature?	<input checked="" type="checkbox"/>	<input checked="" type="checkbox"/>		No clinical studies in US
<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>				
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, both 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 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 checked="" 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> <i>Date of consult sent to Controlled Substance Staff:</i>	<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@fda.hhs.gov to schedule required PeRC meeting²</i> <i>Note: NDAs/BLAs/efficacy supplements for new active ingredients</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

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<i>(including new fixed combinations), 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>				
If the application triggers PREA, is there an agreed Initial Pediatric Study Plan (iPSP)?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
If required by the agreed iPSP, are the pediatric studies outlined in the agreed iPSP completed and included in the application?	<input type="checkbox"/>	<input type="checkbox"/>	<input checked="" type="checkbox"/>	
<i>If no, may be an RTF issue - contact DPMH for advice.</i>				
<u>BPCA:</u>				
Is this submission a complete response to a pediatric Written Request?	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
<i>If yes, notify Pediatric Exclusivity Board RPM (pediatric exclusivity determination is required)³</i>				
Proprietary Name	YES	NO	NA	Comment
Is a proposed proprietary name submitted?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
<i>If yes, ensure that the application is also coded with the supporting document category, "Proprietary Name/Request for Review."</i>				
REMS	YES	NO	NA	Comment
Is a REMS submitted?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
<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 checked="" 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?	<input checked="" type="checkbox"/>	<input type="checkbox"/>		
<i>If no, request applicant to submit SPL before the filing date.</i>				

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

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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 checked="" type="checkbox"/>	
For applications submitted on or after June 30, 2015: Is the PI submitted in PLLR format? ⁵	<input type="checkbox"/>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	
Has a review of the available pregnancy and lactation data been included?	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
For applications submitted on or after June 30, 2015: If PI not submitted in PLLR 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/PLLR format before the filing date.</i>	<input type="checkbox"/>	<input checked="" 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 in OPQ (OBP or ONDP)?	<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? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>		

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

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

Are annotated specifications submitted for all stock keeping units (SKUs)? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
If representative labeling is submitted, are all represented SKUs defined? <i>If no, request in 74-day letter.</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
All labeling/packaging 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) <i>If yes, specify consult(s) and date(s) sent:</i>	<input checked="" type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	
Meeting Minutes/SPAs	YES	NO	NA	Comment
End-of Phase 2 meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Pre-NDA/Pre-BLA/Pre-Supplement meeting(s)? Date(s): <i>If yes, distribute minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		
Any Special Protocol Assessments (SPAs)? Date(s): <i>If yes, distribute letter and/or relevant minutes before filing meeting</i>	<input type="checkbox"/>	<input checked="" type="checkbox"/>		

ATTACHMENT

MEMO OF FILING MEETING

DATE: September 02, 2015

BACKGROUND:

REVIEW TEAM:

Discipline/Organization	Names		Present at filing meeting? (Y or N)
Regulatory Project Management	RPM:	Leila P. Hann	Y
	CPMS/TL:	Sandra L. Barnes	N
Cross-Discipline Team Leader (CDTL)	Nikolay Nikolov		Y
Division Director/Deputy	Badrul Chowdhury		Y
Office Director/Deputy			
Clinical	Reviewer:	Rachel Glaser/Gary Chiang	y/y
	TL:	Nikolay Nikolov/David Kettl	y/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:		
	TL:		
Clinical Pharmacology	Reviewer:	Yunzhao Ren	Y
	TL:	Ping Ji	Y
• Genomics	Reviewer:		
• Pharmacometrics	Reviewer:		
Biostatistics	Reviewer:	Yongman Kim/Kathleen Fritsch	Y/Y
	TL:	Greg Levin/Mohamed Alosch	Y/Y

Nonclinical (Pharmacology/Toxicology)	Reviewer:	Andrea Benedict	Y
	TL:	Marcie Wood	Y
Statistics (carcinogenicity)	Reviewer:		
	TL:		
Product Quality (CMC) Review Team:	ATL:	Marjorie Shapiro	Y
	RBPM:	Andrew Shiber	Y
• Drug Substance	Reviewer:	Peter Adams	Y
• Drug Product	Reviewer:		
• Process	Reviewer:		
• Microbiology	Reviewer:	Reyes Candau-Chacon	N
• Facility	Reviewer:	Zhong Li	N
• Biopharmaceutics	Reviewer:		
• Immunogenicity	Reviewer:	Brian Janelsins	N
• Labeling (BLAs only)	Reviewer:		
• Other (e.g., Branch Chiefs, EA Reviewer)	PQ Stats – Meiyu Shen/Yi Tsong (TL)		Y/Y
OMP/OMPI/DMPP (Patient labeling: MG, PPI, IFU)	Reviewer:		
	TL:		
OMP/OPDP (PI, PPI, MedGuide, IFU, carton and immediate container labels)	Reviewer:		
	TL:		
OSE/DMEPA (proprietary name, carton/container labels)	Reviewer:		
	TL:		
OSE/DRISK (REMS)	Reviewer:		
	TL:		
OC/OSI/DSC/PMSB (REMS)	Reviewer:		
	TL:		

Bioresearch Monitoring (OSI)	Reviewer:	Roy Blay	Y
	TL:	Janice Pohlman	N
Controlled Substance Staff (CSS)	Reviewer:		
	TL:		
Other reviewers/disciplines			
<ul style="list-style-type: none"> DPMH <p>*For additional lines, highlight this group of cells, copy, then paste: select "insert as new rows"</p>	Reviewer:	Erica Radden	Y
	TL:		
Other attendees			
*For additional lines, right click here and select "insert rows below"			

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., information to demonstrate sufficient similarity between the proposed product and the listed drug(s) such as BA/BE studies or to justify reliance on information described in published literature):</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 <input checked="" type="checkbox"/> No comments

<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: February 10, 2016 <input type="checkbox"/> NO <input type="checkbox"/> To be determined Reason:
<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>CONTROLLED SUBSTANCE STAFF</p> <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
<p>CLINICAL MICROBIOLOGY</p> <p>Comments:</p>	<input type="checkbox"/> Not Applicable <input type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE <input type="checkbox"/> Review issues for 74-day letter

<p>CLINICAL PHARMACOLOGY</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>• Clinical pharmacology study site(s) inspections(s) needed?</p>	<p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p>BIOSTATISTICS</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p>NONCLINICAL (PHARMACOLOGY/TOXICOLOGY)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input type="checkbox"/> Review issues for 74-day letter</p>
<p>PRODUCT QUALITY (CMC)</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable <input checked="" type="checkbox"/> FILE <input type="checkbox"/> REFUSE TO FILE</p> <p><input checked="" type="checkbox"/> Review issues for 74-day letter</p>
<p><u>New Molecular Entity (NDAs only)</u></p> <p>• Is the product an NME?</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Environmental Assessment</u></p> <p>• Categorical exclusion for environmental assessment (EA) requested?</p> <p>If no, was a complete EA submitted?</p> <p>Comments:</p>	<p><input type="checkbox"/> YES <input type="checkbox"/> NO</p> <p><input type="checkbox"/> YES <input type="checkbox"/> NO</p>
<p><u>Facility Inspection</u></p> <p>• Establishment(s) ready for inspection?</p> <p>Comments:</p>	<p><input type="checkbox"/> Not Applicable</p> <p><input checked="" type="checkbox"/> YES <input type="checkbox"/> NO</p>

<p>Facility/Microbiology Review (BLAs only)</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>CMC Labeling Review (BLAs only)</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 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 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 type="checkbox"/> YES <input type="checkbox"/> NO

REGULATORY PROJECT MANAGEMENT	
Signatory Authority: Badrul A. Chowdhury	
Date of Mid-Cycle Meeting (for NME NDAs/BLAs in “the Program” PDUFA V):	
21st Century Review Milestones (see attached) (listing review milestones in this document is optional):	
Comments:	
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 type="checkbox"/> No review issues have been identified for the 74-day letter. <input checked="" type="checkbox"/> Review issues have been identified for the 74-day letter. <u>Review Classification:</u> <input checked="" type="checkbox"/> Standard Review <input type="checkbox"/> Priority Review
ACTION ITEMS	
<input type="checkbox"/>	Ensure that any updates to the review priority (S or P) and classifications/properties are entered into the electronic archive (e.g., chemical classification, combination product classification, orphan drug).
<input type="checkbox"/>	If RTF, notify everyone who already received a consult request, OSE PM, and RBPM
<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"/>	If priority review, notify applicant in writing by day 60 (see CST for choices)
<input 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 applications in the Program)
<input type="checkbox"/>	Other

Annual review of template by OND ADRAAs completed: September 2014

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

/s/

LEILA P HANN
09/29/2015

**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: BLA 761042

Application Type: New BLA

Name of Drug/Dosage Form: (b) (4) (etanercept)

Applicant: Sandoz, Inc.

Receipt Date: July 29, 2015

Goal Date: May 29, 2016 (May 27, 2016)

1. Regulatory History and Applicant's Main Proposals

New BLA is proposed biosimilar to etanercept (Enbrel)

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 October 12, 2015. The resubmitted PI will be used for further labeling review.

Selected Requirements of Prescribing Information

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.

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:** *Identical to Enbrel label, a waiver will be granted.*
- YES** 3. A horizontal line must separate HL from the Table of Contents (TOC). A horizontal line must separate the TOC from the FPI.
- Comment:**
- YES** 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:**
- 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:** *Missing white space before D&A, DF & Strengths, Contraindications, W&P, AR, and Drug Interactions*
- 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

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• 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.”)
• 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

- NO** 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: *Date should match Enbrel, right?*

Boxed Warning (BW) in Highlights

- NO** 12. All text in the BW must be **bolded**.

Comment: *“See full prescribing information for complete boxed warning” not bolded.*

- 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

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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:

- NO** 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

- YES** 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:

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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

- 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

- NO** 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: *Should mention Medication Guide*

Revision Date in Highlights

- YES** 24. The revision date must be at the end of HL, and should be **bolded** and right justified (e.g., “**Revised: 9/2013**”).

Comment:

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:
- NO** 30. The section and subsection headings in the TOC must match the section and subsection headings in the FPI.
Comment: Section 16.1 doesn't match. Section 17 should not have subsections.
- 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:

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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:

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- 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: Says “predict” rather than “reflect”

- 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

- NO** 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

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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:

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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.

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/s/

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